**Name of Journal:** *World Journal of Meta-Analysis*

**Manuscript NO:** 88561

**Manuscript Type:** EDITORIAL

**Importance of well-designed meta-analyses in assessing medical and surgical treatments**

Au SCL. Importance of well-designed meta-analyses

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**Author contributions:** Au SCL designed the research study; performed the research; analyzed the data and wrote the manuscript; All authors have read and approve the final manuscript.

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**Received:** September 28, 2023

**Revised:** November 10, 2023

**Accepted:** November 29, 2023

**Published online:**

**Abstract**

When evaluating the efficacy of medical or surgical treatments, the most robust study design is often considered to be the high-quality randomized clinical trial (RCT). However, the true answer lies in the meta-analysis of high-quality RCTs. While RCTs have their merits, meta-analyses possess two crucial qualities that make them superior: generalizability and the ability to verify replicability across different trials. A well-designed meta-analysis, defined here as a systematic review that pools data, holds significant advantages over individual RCTs. Retrospective and observational surgical research is prone to biases that are not mutually offsetting; instead, they accumulate. Selection bias, transfer bias, and assessment bias all taint retrospective studies more than randomized trials, making the novel treatment appear more effective than it truly is. Pooling studies suffering from these limitations in a meta-analysis amplifies these biases, causing an overestimation of treatment benefits. This becomes particularly concerning when the treatment itself carries substantial risks, as is often the case in surgical journals. The consequences can result in harm or even death for patients. While a well-designed meta-analysis is the best tool for assessing medical and surgical treatments, a weak meta-analysis amplifies biases and promotes flawed data. Thoughtful readers must become proficient in honing their methodological toolkits, delving deeper into topics like heterogeneity and publication bias. It is essential to avoid wasting time on meta-analyses drawing data from retrospective or observational research regarding surgical treatments.

**Key Words:** Meta-analysis; Systematic review; Methodology; Research; Journal; Academic

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**Core Tip:** It is crucial to differentiate between well-designed and poorly designed meta-analyses. Not all meta-analyses are conducted equally, and identifying their quality is vital to avoid misleading conclusions that can potentially harm patients. Meta-analyses concerning medical or surgical treatment outcomes should ideally include only randomized, controlled trials or high-quality prospective studies as source material. While reputable journals adhere to this research ethics, caution must be exercised when exploring studies that pool data without maintaining strict criteria.

**INTRODUCTION**

Dear Editor, When evaluating the efficacy of medical or surgical treatments, the most robust study design is often considered to be the high-quality randomized clinical trial (RCT)[1]. However, the true answer lies in the meta-analysis of high-quality RCTs[2]. While RCTs have their merits, meta-analyses possess two crucial qualities that make them superior: generalizability and replicability[3,4].

The limitation of relying solely on individual RCT is that what works at one institution may not necessarily work in others[5]. By pooling data from multiple high-quality RCTs, a meta-analysis provides a broader perspective, enhancing generalizability. This is essential as treatments that prove effective in prestigious institutions may not yield similar results elsewhere. Furthermore, a meta-analysis verifies the replicability of the findings observed in the source trials. These factors contribute to the credibility and reliability of the conclusions drawn from a meta-analysis.

**Meta-analyses and Systematic reviews**

It is crucial to differentiate between well-designed and poorly designed meta-analyses. Not all meta-analyses are conducted equally, and identifying their quality is vital to avoid misleading conclusions that can potentially harm patients[6]. Good meta-analysis involves several key elements: clear research objective, precise research questions, comprehensive literature search *via* different scientific databases as well as the reference lists of included articles, well-defined inclusion and exclusion criteria, objective quality assessment with standard tools (*e.g.* Cochrane Risk of Bias Tool or the Newcastle-Ottawa Scale), meticulous data extraction and statistical analysis, and thoughtful consideration of publication bias. These elements are actually defined in the widely recognized PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses)[7]. It plays a vital role in promoting transparency, consistency, and quality in the development of meta-analyses. However, it is important to acknowledge that adherence to these guidelines does not guarantee the quality or validity of a meta-analysis. Proper implementation and interpretation of these guidelines rest on the expertise and judgment of the researchers involved.

Meta-analyses concerning medical or surgical treatment outcomes should ideally include only randomized, controlled trials or high-quality prospective studies as source material. While reputable journals adhere to this research ethics[8,9], caution must be exercised when exploring studies that pool data without maintaining strict criteria[10]. Such practices can lead to severe discrepancies and mislead both readers and those affected by the treatments under scrutiny.

Retrospective and observational surgical research is prone to biases that are not mutually offsetting[11,12]; in contrast, they accumulate. Selection bias, transfer bias, and assessment bias all taint retrospective studies more than randomized trials[13,14], making the novel treatment appear more effective than it truly is. Pooling studies suffering from these limitations in a meta-analysis amplifies these biases, causing an overestimation of treatment benefits. This becomes particularly alarming when the treatment itself carries substantial risks, as is often the case in surgical journals. The consequences can result in harm or even mortality for patients.

Meta-analyses hold significant influence in subsequent research and are cited more frequently than any other study design across scientific research[15,16]. Consequently, the repercussions of a poorly designed observational study are overshadowed by those of a sloppy meta-analysis. Therefore, it is imperative to exercise caution and delve deeper into methodology to avoid being misled. Topics such as heterogeneity and publication bias are essential components of understanding meta-analyses comprehensively[17-19]. While they may seem intimidating at first, learning about these issues is crucial in critically evaluating the reliability and validity of meta-analyses.

It is important to distinguish between systematic reviews and meta-analyses[20]. Systematic reviews utilize reproducible approaches to search available evidence and explicitly outline parameters that determine which papers are included or excluded[21,22]. Unlike meta-analyses, systematic reviews do not pool data, resulting in more qualitative conclusions[23]. While well-done retrospective work may be included to provide a snapshot of existing knowledge, its source material is not as strong as that of meta-analyses, thus necessitating careful interpretation. Occasionally, meta-analyses may focus on complications, risk factors, or unusual endpoints that cannot be randomized[24]. Journals should exercise caution when presenting such information, always providing suitable caveats.

**CONCLUSION**

“Garbage in, garbage out”[25]. In conclusion, while a well-designed meta-analysis is the best tool for assessing medical and surgical treatments, a weak meta-analysis amplifies biases and promotes flawed data. Researchers and scientists should be proficient in honing their methodological toolkits.

**ACKNOWLEDGEMENTS**

Dr. Lam Wai Yan polished the professional English language as a native English-speaking expert.

**REFERENCES**

1 **Hariton E**, Locascio JJ. Randomised controlled trials - the gold standard for effectiveness research: Study design: randomised controlled trials. *BJOG* 2018; **125**: 1716 [PMID: 29916205 DOI: 10.1111/1471-0528.15199]

2 **Leopold SS**. Editorial: When to Trust a Meta-analysis or Systematic Review About a Surgical Treatment, and Why. *Clin Orthop Relat Res* 2022; **480**: 437-438 [PMID: 35014979 DOI: 10.1097/CORR.0000000000002117]

3 **Delgado-Rodríguez M**, Sillero-Arenas M. Systematic review and meta-analysis. *Med Intensiva (Engl Ed)* 2018; **42**: 444-453 [PMID: 29169792 DOI: 10.1016/j.medin.2017.10.003]

4 **Braver SL**, Thoemmes FJ, Rosenthal R. Continuously Cumulating Meta-Analysis and Replicability. *Perspect Psychol Sci* 2014; **9**: 333-342 [PMID: 26173268 DOI: 10.1177/1745691614529796]

5 **Chan PY**, Tang SM, Au SC, Rong SS, Lau HH, Ko ST, Ng DS, Chen LJ, Yam JC. Association of Gestational Hypertensive Disorders with Retinopathy of prematurity: A Systematic Review and Meta-analysis. *Sci Rep* 2016; **6**: 30732 [PMID: 27491726 DOI: 10.1038/srep30732]

6 **Au SCL**. Comments on Stroke as a Neurological Complication of COVID-19: A Systematic Review and Meta-Analysis of Incidence, Outcomes and Predictors. *J Stroke Cerebrovasc Dis* 2021; **30**: 105863 [PMID: 34059440 DOI: 10.1016/j.jstrokecerebrovasdis.2021.105863]

7 **Page MJ**, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, Chou R, Glanville J, Grimshaw JM, Hróbjartsson A, Lalu MM, Li T, Loder EW, Mayo-Wilson E, McDonald S, McGuinness LA, Stewart LA, Thomas J, Tricco AC, Welch VA, Whiting P, Moher D. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021; **372**: n71 [PMID: 33782057 DOI: 10.1136/bmj.n71]

8 **Kum E**, Patel M, Diab N, Wahab M, Zeraatkar D, Chu DK, O'Byrne PM, Guyatt GH, Satia I. Efficacy and Tolerability of Gefapixant for Treatment of Refractory or Unexplained Chronic Cough: A Systematic Review and Dose-Response Meta-Analysis. *JAMA* 2023; **330**: 1359-1369 [PMID: 37694849 DOI: 10.1001/jama.2023.18035]

9 **Zeymer U**, Freund A, Hochadel M, Ostadal P, Belohlavek J, Rokyta R, Massberg S, Brunner S, Lüsebrink E, Flather M, Adlam D, Bogaerts K, Banning A, Sabaté M, Akin I, Jobs A, Schneider S, Desch S, Thiele H. Venoarterial extracorporeal membrane oxygenation in patients with infarct-related cardiogenic shock: an individual patient data meta-analysis of randomised trials. *Lancet* 2023; **402**: 1338-1346 [PMID: 37643628 DOI: 10.1016/S0140-6736(23)01607-0]

10 **Chan EOT**, Chan VWS, Tang TST, Cheung V, Wong MCS, Yee CH, Ng CF, Teoh JYC. Systematic review and meta-analysis of ketamine-associated uropathy. *Hong Kong Med J* 2022; **28**: 466-474 [PMID: 36464318 DOI: 10.12809/hkmj209194]

11 **Yu IT**, Tse SL. Workshop 11-sources of bias in studies of systematic reviews with or without meta-analysis. *Hong Kong Med J* 2013; **19**: 156-158 [PMID: 23535676]

12 **Yu IT**, Tse SL. Clinical Epidemiology Workshop 12--Appraising a systematic review with meta-analysis. *Hong Kong Med J* 2013; **19**: 249-250 [PMID: 23732430]

13 **Lin L**, Chu H. Quantifying publication bias in meta-analysis. *Biometrics* 2018; **74**: 785-794 [PMID: 29141096 DOI: 10.1111/biom.12817]

14 **McShane BB**, Böckenholt U, Hansen KT. Adjusting for Publication Bias in Meta-Analysis: An Evaluation of Selection Methods and Some Cautionary Notes. *Perspect Psychol Sci* 2016; **11**: 730-749 [PMID: 27694467 DOI: 10.1177/1745691616662243]

15 **Au SC**, Tang SM, Rong SS, Chen LJ, Yam JC. Association between hyperglycemia and retinopathy of prematurity: a systemic review and meta-analysis. *Sci Rep* 2015; **5**: 9091 [PMID: 25766465 DOI: 10.1038/srep09091]

16 **Lei C**, Duan J, Ge G, Zhang M. Association between neonatal hyperglycemia and retinopathy of prematurity: a meta-analysis. *Eur J Pediatr* 2021; **180**: 3433-3442 [PMID: 34114080 DOI: 10.1007/s00431-021-04140-w]

17 **Lin L**. Comparison of four heterogeneity measures for meta-analysis. *J Eval Clin Pract* 2020; **26**: 376-384 [PMID: 31234230 DOI: 10.1111/jep.13159]

18 **Spineli LM**, Pandis N. Exploring heterogeneity in meta-analysis: Meta-regression analysis. *Am J Orthod Dentofacial Orthop* 2020; **158**: 623-625 [PMID: 32988571 DOI: 10.1016/j.ajodo.2020.07.002]

19 **Phua QS**, Lu L, Harding M, Poonnoose SI, Jukes A, To MS. Systematic Analysis of Publication Bias in Neurosurgery Meta-Analyses. *Neurosurgery* 2022; **90**: 262-269 [PMID: 35849494 DOI: 10.1227/NEU.0000000000001788]

20 **Siddaway AP**, Wood AM, Hedges LV. How to Do a Systematic Review: A Best Practice Guide for Conducting and Reporting Narrative Reviews, Meta-Analyses, and Meta-Syntheses. *Annu Rev Psychol* 2019; **70**: 747-770 [PMID: 30089228 DOI: 10.1146/annurev-psych-010418-102803]

21 **Scheidt S**, Vavken P, Jacobs C, Koob S, Cucchi D, Kaup E, Wirtz DC, Wimmer MD. Systematic Reviews and Meta-analyses. *Z Orthop Unfall* 2019; **157**: 392-399 [PMID: 30399626 DOI: 10.1055/a-0751-3156]

22 **Page MJ**, Moher D, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, Chou R, Glanville J, Grimshaw JM, Hróbjartsson A, Lalu MM, Li T, Loder EW, Mayo-Wilson E, McDonald S, McGuinness LA, Stewart LA, Thomas J, Tricco AC, Welch VA, Whiting P, McKenzie JE. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. *BMJ* 2021; **372**: n160 [PMID: 33781993 DOI: 10.1136/bmj.n160]

23 **Knight SR**. The Value of Systematic Reviews and Meta-Analyses in Surgery. *Eur Surg Res* 2021; **62**: 221-228 [PMID: 34710877 DOI: 10.1159/000519593]

24 **Stroup DF**, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA* 2000; **283**: 2008-2012 [PMID: 10789670 DOI: 10.1001/jama.283.15.2008]

25 **Rocco G**. Garbage in, garbage out. *Eur J Cardiothorac Surg* 2022; **61**: 1020-1021 [PMID: 34849672 DOI: 10.1093/ejcts/ezab504]

**Footnotes**

**Conflict-of-interest statement:** All authors have disclosed no conflicts of interest.

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**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review started:** September 28, 2023

**First decision:** November 2, 2023

**Article in press:**

**Specialty type:** Methodology

**Country/Territory of origin:** China

**Peer-review report’s scientific quality classification**

Grade A (Excellent): A

Grade B (Very good): 0

Grade C (Good): C

Grade D (Fair): D

Grade E (Poor): 0

**P-Reviewer:** Moreno-Gómez-Toledano R, Spain; Vlachopanos G, Greece; Maslennikov R, Russia **S-Editor:** Liu JH **L-Editor:** A **P-Editor:**