Meta-analysis: a cornerstone of clinical research?

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Keywords: meta-analysis, research

Introduction: The increasing volume of scientific publications leads, sometimes, to contradictory conclusions. Meta-analysis is a quantitative, formal and epidemiological study design used to assess data from a systematic review, in order to derive conclusions about that body of research. [1] The benefits of meta-analysis include a consolidated and quantitative review of several studies, often complex and sometimes conflicting. [1] Its main disadvantage is that it can not compensate for the inherent limitations of the studies on which it is based. [1, 2] The specification of the outcome and of the hypotheses that are tested is critical to the conduction of meta-analysis, as is a sensitive literature research. [1, 3] This study aims to explore the role of a meta-analysis and its inherent biostatistical tests on clinical research advances.

Materials and Methods: The authors used the meta-analysis "The use of Procalcitonin (PCT) for diagnosis of sepsis in burn patients: a meta-analysis" [4] to evaluate the importance of a meta-analysis as a summary of clinical research published in the literature on a specific theme.

Results: The previously stated meta-analysis [4] included articles written in English focusing on burn patients and on the evaluation of PCT role on the diagnosis and monitoring of septic episodes. PubMed, Scopus and Web of Science databases were used. A study was considered eligible for inclusion in the meta-analysis if it provided area under the curve (AUC) on serum PCT for diagnosis of sepsis or the serum PCT levels by sepsis and non-sepsis groups in burn patients. After reviewing titles and/or abstracts for the eligibility criteria and excluding duplicates, 14 articles were included. Studies differed in the PCT cut-off defined for sepsis definition. Using the different cut-offs for sepsis diagnosis proposed in each study, the weight average of all PCT cut-offs for sepsis was computed and the resulting cut-off was 1.59ng/mL. Homogeneity among studies was evaluated using the Cochran's Q statistic and the I^2 statistic. For all effect sizes under analysis, the included studies showed significant heterogeneity ($p< 0.01$, $I^2> 50\%$), thus a random-effects model for meta-analysis was used (DerSimonian-Laird method). AUC plays a central role in evaluating diagnostic ability of tests, in particular of PCT biomarker. Meta-DiSc 1.4 (XI Cochrane Colloquium, Barcelona, Spain) was used to calculate the summary receiver operating characteristics (SROC) and the pooled AUC. The publication bias associated with the AUC on diagnostic sepsis effect was analysed by the funnel plot and the Egger test. The result of Egger's test was significant ($p<0.001$). To find out sources of heterogeneity, a subgroup analysis was done, using the random effect model, according to different criteria used for sepsis determination in the works of the sample, namely clinical evaluation, Baltimore Sepsis Scale, American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM) definition

and the more recent and specific one from the American Burn Association (ABA). Another subgroup analysis, excluding retrospective studies, was also conducted and achieved an AUC of 0.86 (95%CI=0.78 to 0.93). Sensitivity analysis to show the impact of each study or subgroup studies on the results was also held. MetaXL 2.0 (Epi-Gear International Pty Ltd, Wilston, Queensland, Australia) was used to calculate the pooled Cohen's d effect sizes (difference of PCT levels between sepsis and non-sepsis groups, the pooled AUC and pooled mean effects). Due to the significant heterogeneity, the overall mean estimate was obtained assuming the random effects model: 4.68 ng/mL (95% CI = 2.5 to 91.1) for sepsis group and 0.9ng/mL (95% CI= 0.1 to 1.6) for non-sepsis group. This analysis is useful to evaluate the strength of the PCT concentration for each group, and a statistically significant mean difference was found between sepsis and non-sepsis group. Doing a subgroup analysis based on the sepsis definition, the resulting values for Cohen's d were 3.69 (95% CI= 0.45 to 6.92) when ACCP/SCCM classification was employed; 0.64 (95% CI= 0.02 to 1.26) according to ABA classification and 3.38 for the rest (95% CI = 0.90 to 5.87).

Conclusion: This meta-analysis showed that PCT may be considered as a biomarker with strong diagnostic ability to discriminate between the septic from the non-septic burn patients. Rigorously conducted meta-analyses are useful tools in evidence-based medicine. Meta-analyses have made and continue to make major contributions to medical research and clinical decision making.

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