Editorial

Distinguishing between mediators and confounders is important for the causal inference in observational studies

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Received: 20 September 2019; Accepted: 09 October 2019; Published: 09 October 2019.
doi: 10.21037/amj.2019.09.03
View this article at: http://dx.doi.org/10.21037/amj.2019.09.03

Observational studies are common in clinical literature because they are less costly and easy to perform, as compared to the randomized controlled trials (RCT). The limitation of such kind of studies is their inability to draw a causal inference due to potential bias. However, there are many approaches being proposed in recent years for the causal inference in observational studies (1-3). Although these methods cannot replace RCTs for causal inference, analysis in their framework can help to make the causal evidence more reliable. In the following discuss, I would like to discuss some of these points by using a published article.

In a recent issue of *Annals of Intensive Care*, Inkinen and colleagues conducted an interesting study (4), which showed that endothelial and glycocalyx injury biomarkers were associated with fluid administration, acute kidney injury (AKI) and mortality outcome. However, the relationship is an association due to the observational study design that the inference for causal relationship is difficult. Although casual inference can only be hypothesis-generating with observational study, I proposed that some theoretical assumptions can be tested with the observational design. First of all, it is important to distinguish between mediators and confounders in this framework. For instance, the study showed that more fluid administration was associated with vascular adhesion protein (VAP)-1 and interleukin (IL)-6. The authors can further develop the model in the framework of causal mediation analysis (5). In this context, fluid balance can be considered to have direct and indirect causes of AKI and mortality (6); and the indirect effect is mediated via the VAP-1 and IL-6. The percentage of the direct and indirect causal effects can be estimated with the observational sample. The clinical implication of such a structural model is that the causal pathway can be blocker to prohibit the development of AKI or death (7). In order to adjust for confounders, the authors included many variables in logistic regression model to investigate the independent association of biomarker scores with AKI. However, I must point out that some variables should be adjusted with caution. In the causal inference framework, a confounder is defined if a variable has direct causal effect on the outcome of interest and the variable of interest (8). In the example, a confounder should be the cause of the increase or decrease of the injury biomarkers and the AKI. The authors included lactate and vasopressor in the multivariable regression model, which is inappropriate. Since the endothelial and glycocalyx injury biomarkers were measured on ICU admission (0 h), probability preceding the use of vasopressor and lactate measurement. Thus, use of vasopressor and lactate measurement can be mediators rather than confounders. It is well known that the adjustment for mediators in the multivariable regression model will under-estimate the causal effect of the variable of interest on the clinical outcome. Thus, the odds ratios reported in the multivariable regression model (the second last column in Table 4) for the biomarker score in predicting AKI can be underestimated. Although there are many sophisticated statistical methods to establish the causal relationship between variables, the results can best be hypothesis-generating and must be verified in an RCT.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *AME Medical Journal*. The article did not undergo external peer review.

Conflicts of Interest: The author has completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/amj.2019.09.03). The author has no conflicts of interest to declare.

Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

doi: 10.21037/amj.2019.09.03

Cite this article as: Zhang Z. Distinguishing between mediators and confounders is important for the causal inference in observational studies. AME Med J 2019;4:35.

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