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Letters to the Editor

Epidemiology and risk factors for *Clostridium difficile*-associated diarrhea in adult inpatients in a university hospital in China: Methodological issues

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To the Editor:

We read with interest the article recently published in the *American Journal of Infection Control* by Tang and colleagues.[1] The authors investigated the risk factors for *Clostridium difficile*-associated diarrhea at a university hospital in eastern China.[1] Although the study reported several interesting findings, several methodological issues must be considered.

First, the article does not mention which method was used to select the predictors included in the multivariable analysis. As shown in Table 2,[1] the authors included only length of hospital stay (≥6 days), comorbidity (e.g., diabetes), and treatment type (e.g., coloclysis and proton-pump inhibitor) in the multivariable analysis. This is puzzling, as their univariable analysis showed statistically significant ($P < .05$) associations for other predictors, such as the use of different types of antibiotics (e.g., cephalosporin and fluoroquinolones). Investigators normally conduct multivariable analyses using a stepwise method, selecting the variables to retain using statistical criteria, or they select predictors according to their clinical relevance.[2] However, the approach used by Tang and colleagues[1] is not clear.

Second, the differences in odds ratios between the univariable and multivariable models for some predictors (e.g. comorbidity with diabetes) were relatively small. Generally, it has been reported that the unadjusted exposure-outcome should be changed by a certain percentage (e.g., 10%) in the multivariable analysis. When this is not the case, it is likely to be caused by the degree of residual confounding.[3]

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Conflict of interest: None to report.

Regarding "Epidemiology and risk factors for *Clostridium difficile*-associated diarrhea in adult inpatients in a university hospital in China: Methodologic issues"

To the Editor:

We appreciate the interest in our study and would like to respond to the methodology-related issues raised by Safiri and Sullman in their letter to Editor. The letter concerned 2 statistics questions, mainly variable selection in the multivariable analysis and confounder identification.

VARIABLE SELECTION IN THE MULTIVARIABLE ANALYSIS

The forward selection method was used in our study and we apologize if not mentioning that in our article made Safiri and Sullman confused. We did mention that "some well-acknowledged factors had no significant difference in the study, such as age >64 years and nasogastric tube feeding, but they were also included for multivariate logistic regression alone

with significant ones" in risk factors for *Clostridium difficile*-associated disease described as part of the Results section. Additionally, this was explained in the notes for Table S1. Specifically, blank cells in the multivariate analysis indicate $P > .05$, which has no statistical significance, and data not used for multivariate logistic regression.

CONFOUNDER IDENTIFICATION

Confounding is usually referred to as a distortion of estimation of the true relationship between an exposure and a given outcome when the effect of primary exposure of interest are mixed in with the effects of an additional factor.[1,2] It usually has 3 major characteristics: a true confounding factor should be associated with the exposure of interest and the outcome simultaneously, the confounding factor is usually distributed unequally among the groups being compared, and a confounder cannot be involved in the causal pathway from the exposure of interest to the outcome. We used χ^2 tests to exclude the possibility of diabetes as a confounding factor. Diabetes is not associated with any other of the 3 independent risk factors; that is, length of stay ($P = .185$), coloclysis ($P = .563$), and proton pump inhibitor ($P = .224$).

To our knowledge, there are usually 3 methods used to identify confounding in clinical research. First of all, a clinically meaningful relationship among the variable, the risk factor, and the outcome is the key point of confounder identification, regardless of whether that relationship reaches statistical significance. Second, some formal tests of hypothesis, such as χ^2 test, could be used to assess whether the variable is associated with the exposure of interest and with the outcome. Finally, a cut-off of 10% in the risk ratio, mentioned in the letter, is commonly used for the change-in-estimate criterion of confounder identification. In a previous clinical study,[3] diabetes mellitus was confirmed as a risk factor for recurrence of *C difficile* infection in an acute care hospital setting. Further analysis with the χ^2 test mentioned above showed that diabetes mellitus was not a confounder. Last but not least, cut-off points for the change-in-estimate criterion varied according to the effect size of the exposure-outcome relationship, sample size, standard deviation of the regression error, and exposure-confounder correlation.[4] A 10% cut-off point is not the sole criterion. In many published articles, the differences in unadjusted odds ratios between the univariable and multivariable models is smaller than 10% but statistical significance was still recognized. For example, in a study about the risk factors for bronchiectasis in children with cystic fibrosis,[5] data in Table S2 draw a conclusion that neutrophil elastase activity in bronchoalveolar lavage fluid at age 3 months was the major predictor of persistent bronchiectasis at age 3 years, whereas the odds ratio in multivariate and univariate analysis was 4.21.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ajic.2018.01.021.

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