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Critical considerations, including overfitting in regression models and confounding in study designs for delirium follow-up

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To the Editor:

We read the article by Kaneko et al. with interest [1]. The authors reported a single-center retrospective study in patients after transcatheter aortic valve implantation. The results showed that remimazolam was associated with less delirium within 3 days postoperatively compared with propofol. While we thank the authors for their contributions, we have some concerns with this study. First, the authors' logistic regression model included many covariates despite the small sample size, which is likely to have resulted in overfitting and incorrect effect estimates. The remimazolam group had 3/40 delirium patients, which allowed only one covariate to be entered into the logistic regression analysis; however, the authors entered as many as five. As evidence of incorrect effect estimation, although the history of stroke is a confounding factor for delirium, as demonstrated in previous reports [2,3], the history of stroke in this study did not differ significantly, with an odds ratio of 3.74 and a 95% confidence interval of 0.52-26.84 (Table 5 in Ref. [1]). Additionally, propensity score analysis produces more correct effect estimates than regression analysis when the sample size is small [4]. Therefore, the authors need to justify the analysis method used in this study. Second, it is likely that this study did not successfully identify all patients with postoperative delirium. Although 13/18 (72.2%) delirium patients were diagnosed at postoperative day 0, few delirium patients could be determined in the general ward after postoperative day 1. Interviews would have been necessary to accurately determine which patients developed delirium [5]. Third, the authors' primary endpoint was the incidence of delirium within 3 days postoperatively, although several previous studies reported 5 days after cardiac surgery as a reasonable period of cognitive recovery [6-8]. The authors should explain why the

duration was limited to 3 days, considering previous studies, in the Discussion section. Fourth, unmeasured delirium confounders remain in this study. For example, betablockers, statins, and benzodiazepines have been reported to affect postoperative delirium [9]. In particular, patients taking benzodiazepines may develop remimazolam tolerance [10]. Collectively, we await additional studies to verify the conclusions by Kaneko et al. [1].

Declarations

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Conflict of interest: The authors have no conflicts of interest to declare.

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