Frequency and Predisposing Factors for Drug-Induced Hypoglycemia in Patients with Type-2 Diabetes Mellitus: A Comment

Dear Editor,

We read with great interest the paper by Shariff *et al*. that reported frequency and predisposing factors for drug-induced hypoglycemia in patients with type 2 diabetes.[1] Despite the importance of the study topic, we faced issues in the methodology.

Identification of hypoglycemia using patient reports in real-world studies is a common method; however, it suffers from recall bias. Although the period for which the history was taken in this study was not long, the accuracy of patient-reported hypoglycemia could have been affected when the symptoms were mild. In addition, some patients might have been unable to differentiate between real and pseudo hypoglycemia.[2] Determination of blood glucose levels seems necessary to ascertain the reliability of patient-reported hypoglycemia in such cases. However, for 13% of patients with a history of hypoglycemia in this study, blood glucose levels were not available.

Hypoglycemia was classified in this study using the American Diabetes Association (ADA) 2005 definition.[3] In 2017, the ADA changed previous definitions and classified hypoglycemia in three levels to detect patients who need timely clinical management.[4] Hence, using recent classification could have provided a more informative picture in this study. The number of hypoglycemic symptoms in the study patients does not seem to be an appropriate surrogate of event importance. Nocturnal hypoglycemia, which is a clinically significant event, was not investigated either.

One of the study objectives was to investigate the factors predisposed patients to hypoglycemia. The study results should have been interpreted more cautiously due to lacked representative sample. Factors including those related to diabetes complexity, multimorbidity, pharmacotherapy, patient context, and environment were necessary to be considered.[2] However, few demographic and clinical characteristics have been focused in this study with questionable logic behind some of them (e.g., number of antidiabetic agents).

The final point is that relative risk seems to be an inappropriate statistical measure in this study. This measure has been estimated in representative population-based studies that do not suffer from selection bias. However, in this study, no robust sampling strategy was used. Moreover, it seems that the estimator of relative risk has been biased due to the presence of sparse data. Some of the wide 95% confidence intervals reported in Table 3 signal the bia.[1] To overcome this limitation, the firth penalization and data augmentation method of bias adjustment could have been considered.[5]

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Conflicts of interest

There are no conflicts of interest.

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