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LETTER TO THE EDITOR

Comment on: "Association between triglyceride-glucose index and gastric carcinogenesis: a health checkup cohort study. Gastric cancer, 2021 Aug 5" by Kim et al.

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Dear Editor,

We have read with interest the recent paper entitled "Association between triglyceride-glucose index and gastric carcinogenesis: a health checkup cohort study" [1]. In this study, Kim et al. observed that the extent of the increase in the triglyceride–glucose (TyG) index between the baseline and follow-up tests was significant in gastric cancer, and recommended that monitoring the TyG index using routine laboratory tests could be useful for early detection of gastric cancer in clinical practice. Their results seemed reliable and inspiring with appropriate statistical methods applied in a large-scale cohort. We congratulate the authors for this pioneering study that established a predictive biomarker for gastric carcinogenesis. However, there are some issues raised in this study that are worthy of attention and comment.

The TyG index was firstly proposed by Simental-Mendía et al. to estimate insulin resistance in healthy subjects [2], and also applied to predict the development of cardiovascular events [3]. In this study, the TyG index was calculated as a natural logarithm (ln) using ln[fasting triglycerides (mg/dL) × fasting glucose (mg/dL)/2], which reflected the average serum level of triglyceride (TG) and glucose. However, in this study, patients with a current medication for TG-lowering agents or with an elevated TG level (≥ 400 mg/dL) were excluded, whereas the population with an elevated glucose level, a current medication for glucose-lowering agents or diagnosed with diabetes mellitus (DM) were not excluded. This exclusion criteria introduced the selective bias from the researchers into this study, leading to the unbalanced distribution of TG and glucose level in the population. For example, in a patient diagnosed with DM, high TyG index might be mainly resulted from the high level of glucose with regardlessness of TG. Although the authors adopted the statistical method to reduce the bias, we still raise the concern that which population is adequate for the application of the TyG index in clinical practice, due to the non-negligible bias from the included criteria in this study.

In addition, the authors also found that precancerous conditions group and cancer group both harbored more advanced age than control group in the univariate analysis. Besides, the mean TyG index between the baseline and follow-up tests was elevated in both the cancer and control groups. The authors explained that the elevated TyG index was associated with the aging process over time. Taken together, considering the significant association between age and TyG index, it would be validated if age could be adopted as one of the variables in the multivariate analysis.

Besides, the authors described that patients who were diagnosed with dysplasia, atrophic gastritis (AG), and/or intestinal metaplasia (IM) were included in the precancerous group. However, the term "adenoma" was included in the precancerous lesions in the Figure. Currently, the term "dysplasia" has been reintroduced for adenomas in the 2019 World Health Organization (WHO) classification [4]. The term "adenoma" was recommended to be replaced using the term "dysplasia" in this paper.

In summary, this is the first study to demonstrate the direct association between the TyG index and gastric carcinogenesis, and provide a promising predictive biomarker for early detection of gastric cancer. In future, prospective studies would help to validate the role of the TyG index in gastric cancer. Nevertheless, a clarification of the above issues by the authors would provide further insights and a

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better understanding for this predictive biomarker for gastric carcinogenesis in real clinical practice.

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