## LETTER TO THE EDITOR





# Response to the letter by Buldukoglu et al. regarding our manuscript "Body mass index and survival among patients with advanced biliary tract cancer: a single-institutional study with nationwide data-based validation"

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#### Abbreviations

BMIBody mass indexNWONormal-weight obesity

We appreciate the comments by Dr. Buldukoglu and colleagues on our study [1]. Despite the plausible tumorprompting property of adiposity, our study failed to demonstrate a positive association of body mass index (BMI) with the risks of tumor progression and overall mortality among patients diagnosed with advanced biliary tract cancer. BMI has been widely used as a surrogate for the levels of systemic body fatness. However, this metric cannot distinguish the weights of fat, muscles, or bones, nor provide any information on the body composition (e.g., fat distribution).

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As Buldukoglu et al. noted, normal-weight obesity (NWO) is the status of high-level body fatness in individuals within the normal range of BMI, which warrants further investigation in the context of prognostication of patients with advanced biliary tract cancer. Compared to individuals with obesity, those with NWO may have similarly elevated risks for metabolic syndrome, cardiovascular diseases, and other obesity-related disorders due to chronic systemic inflammation and increased levels of insulin, hormones, adipokines, etc. [2]. Therefore, simply categorizing patients based on BMI levels (including patients with NWO to a reference group) might have underestimated the risk of unfavorable survival outcomes associated with adiposity. In our previous investigation, we utilized a specific imaging processing platform to estimate the volume and density of skeletal muscles and characterized the clinical outcomes by the skeletal muscle status [3]. Through a similar platform, we can annotate the visceral and subcutaneous adipose tissue areas on computed tomography images and investigate the prognostic roles of adipose tissue and its distribution in patients with the same level of BMI. Given the complementary properties of various metrics in profiling body adipose tissue, prospective research is desired based on other analytical techniques, such as bioelectrical impedance analysis, dual-energy X-ray absorptiometry, or skinfold measurements to quantify body fat percentage. In addition, sarcopenic obesity and osteosarcopenia may be additional research areas for dysregulated body balance in patients with adiposity-related cancer [4, 5].

In summary, despite the null findings in our study, further research is warranted incorporating more detailed body composition metrics to explore the prognostic role of adiposity and provide evidence for potential target conditions for better outcomes of patients with advanced biliary tract cancer. **Funding** This work was partly supported by grants from the Ministry of Health, Labour, and Welfare, Japan (22AA2003 to K. Fushimi and 23AA2003 and 22AA2003 to HY). TH was supported by Japan Society for the Promotion of Science (JSPS) KAKENHI grants (JP19K08362 and JP22H02841) and by grants from Takeda Science Foundation and Daiichi Sankyo Company. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

### Declarations

**Conflict of interest** The authors declare that they have no conflicts of interest.

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