LETTER

REPLY TO PAN ET AL.:

Whole blood metabolome analysis combined with comprehensive frailty assessment

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As frailty patients are vulnerable to stressors, due to declined physiological capacity of organs during aging, comprehensive frailty assessment efficiently predicts health risk of elderlies (1). First, Pan et al. raise concerns about the definition of frailty (2). Currently, there are three major approaches to defining "frailty": 1) the physical frailty model by Fried Cardiovascular Health Study Index (CHS), 2) the deficit accumulation model covering multimorbidity by Rockwood Frailty Index, and 3) the Edmonton Frailty Scale (EFS) or Tilburg Frailty Indicator, as mixed physical and psychosocial models (3). Thus, EFS is recognized as a valid and reliable measurement tool for the identification of frailty (4) and widely recommended in the clinical guidelines (3). Our study is designed to cover multidomains of frailty, by the application of EFS, the Japanese version of the Montreal Cognitive Assessment, and Timed Up & Go Test as diagnostic tools (5).

Second, we agree regarding the discrepancy between our study (5) and several other related works (6–8). Moreover, these reports on frailty metabolome were based on larger sample sizes than our study. However, their large sample sizes notwithstanding, these papers drew conflicting, nonoverlapping conclusions. Our study by EFS identified blood metabolites involved in antioxidation, cognition, and mobility as frailty markers (5), while the studies based on Fried CHS reported blood metabolites mainly on physical or sarcopenic frailty (6). While gas chromatography–mass spectrometry (GC-MS) effectively detects nonpolar metabolites such as lipids and vitamins (7), our whole blood metabolome by liquid chromatography (LC)-MS unraveled the involvement of antioxidants, enriched in cellular components. We agree that the simultaneous evaluation of metabolites in serum and whole blood would give us additional information (9). Thus, a plausible explanation for the discrepancy is not the sample size but the difference in study design: EFS vs. Fried CHS, GC-MS vs. LC-MS, and serum vs. whole blood analysis. Indeed, many other metabolomic analyses with small sample sizes succeeded in reaching valid conclusions (10).

Third, we agree regarding the importance of longitudinal studies on these frailty markers, as recent findings on longitudinal study consistently support our notion that antioxidative defenses are much involved in pathogenesis of frailty (6).

Finally, it is conceivable that women could have an intrinsic risk of frailty due to their inherently lower lean mass and strength than those of age-matched men (11). We noticed a significant difference in skeletal muscle index (SMI) between male and female (average 7.49 vs. 5.31, $P = 0.00003$) in our study (5). It would be worthwhile to analyze our samples, regarding SMI and muscle strength, in the future. As shown in the results of clinical blood tests (table S1 in ref. 5), our study carefully excluded the patients with cancer, rheumatic diseases, diabetes, or any other relevant diseases, by the interviews (5). Although the average ages of both frail and nonfrail populations were more than 80 y old in our study, 5 frailty related metabolites among 15 were overlapped with aging markers (9), indicating the intriguing link of metabolites between frailty and human aging.

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Author contributions: M.K., T.T., M.Y., and H.K. wrote the paper.

The authors declare no competing interest.

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Published December 22, 2020.

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