



Blood urea nitrogen-to-creatinine ratio and prognosis of acute heart failure: more confounding factors should be considered

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As blood urea nitrogen (BUN) and creatinine (Cr) are well-recognized biomarkers for estimation of glomerular filtration rate (GFR) since they are freely filtered at the glomerulus due to their small size. Cr is more preferred in clinical practice for this purpose because it is not reabsorbed in the renal tubules of the nephron, while approximately half of the BUN is reabsorbed after filtration (1). The magnitude of BUN reabsorption is greatly affected by neurohormonal activity. Therefore, BUN to Cr ratio (BUN/Cr) is usually regarded as a metric of neurohormonal activity. Since neurohormonal activity is associated with prognosis of acute heart failure (AHF) (2), it is reasonable to hypothesize that BUN/Cr is a potential prognostic factor for AHF.

Recently, Matsue *et al.* (3) performed a study to investigate the prognostic value of BUN/Cr for AHF in two large cohorts. Using a general population based cohort named the Prevention of Renal and Vascular End-stage Disease (PREVEND) (4), they established an age- and gender-specified reference interval for BUN/Cr. An AHF based cohort named Treatment Effect on Congestion and renal function (PROTECT) (5) was used to explore the prognostic value of BUN/Cr. The authors found that AHF patients have significantly higher BUN/Cr than general population. In patients with AHF, baseline BUN/Cr was associated with several laboratory tests, including albumin, brain natriuretic peptide (BNP), glucose and uric acid (UA). Based on the reference interval derived from PREVEND study, the authors categorized the PROTECT cohort

into three groups: higher, lower and normal range BUN/Cr. The subjects in PROTECT cohort were followed for 180 days to investigate the association between baseline BUN/Cr and outcomes of AHF. Using Kaplan-Meier curve, the authors found that BUN/Cr is significantly associated with all-cause mortality. In a multivariable Cox regression model, higher BUN/Cr was independently associated with all-cause mortality with a hazard ratio (HR) of 1.86. Furthermore, using net reclassification improvement (NRI) and integrated discrimination improvement (IDI), the authors found that BUN/Cr can provide additional prognostic information beyond clinical model.

Some previous studies showed that increased BUN/Cr is associated with poor clinical outcomes of HF patients (6-8). The work of Matsue *et al.* (3) has its strengths. First, the sample size in this study is relatively large (n=1,956); therefore, the results are more robust. Second, the criteria used to categorize subjects are based on the reference interval derived from the general population. Therefore, results are more reliable. Third, this study indicated that BUN/Cr is able to provide additional prognostic information beyond clinical characteristics including albumin, blood pressure and sodium. Taken together, this study indicates that BUN/Cr may represent a promising laboratory test for estimating the prognosis of AHF up to 180 days.

Prognostic estimation is the basis of personal intervention, and thus can greatly affect the treatment approach selection. The work performed by Matsue

et al. provides a new evidence on the association between BUN/Cr and the prognosis of HF, thus supporting the use of BUN/Cr for stratifying patients and facilitating the management of HF. Nevertheless, the study has some limitations, which have been clearly addressed by the authors. Despite this, we have some concerns with the statistical methods used in this study. As indicated by the authors, many factors are associated with BUN/Cr, such as age, UA, albumin, BNP, glucose, hypertension and blood pressure. Some of these factors have been widely used in clinical practice and proven useful in estimating the prognosis of HF, such as UA (9,10) and BNP (11,12). These factors can interfere with the relationship between BUN/Cr and the prognosis of HF, and their effects should be adjusted by using multivariable analysis. However, these factors are not completely adjusted in a multivariable analysis. In the past, other easily obtainable hematological parameters such as red blood cell distribution width (RDW), has been proven as strong prognostic factors for HF (13,14). Therefore, authors should have adjusted data for the effects of these factors, especially these widely used and easily attainable. Almost 31% of patients with higher than normal Bun/Cr died within 180 days, which is an unusually high mortality in this group compared to New York Heart Association (NYHA) class IV patients (15). Because of the retrospective nature of the study, it is almost impossible to establish whether the majority of these patients were also affected by other conditions other than HF, which could be a cause for unusually high mortality. We also know that decreased muscle mass is commonplace in patients with HF, so ultimately lowering serum Cr values and increasing the BUN/Cr ratio, which could skew the results.

Taken together, the work performed by Matsue *et al.* covers an interesting topic and provides new evidences on the relationship between BUN/Cr and prognosis of HF. However, additional studies should be done to know if this ratio can be added to our armamentarium of other HF prognostic factors such as BNP, NYHA classification and others. As some of the well-recognized factors were not considered when analyzing data, further prospective cohort studies with data analysis using full-adjusted model are needed to validate the findings of this study.

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Footnote

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/jlpm.2017.03.05>). Zhi-De Hu serves as an unpaid Executive Editor of *Journal of Laboratory and Precision Medicine* from November 2016 to October 2021. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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