



## Comments to “Neutrophil-to-lymphocyte ratio compared to N-terminal pro-brain natriuretic peptide as a prognostic marker of adverse events in elderly patients with chronic heart failure”

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We have read the article which entitled “Neutrophil-to-lymphocyte ratio compared to N-terminal pro-brain natriuretic peptide as a prognostic marker of adverse events in elderly patients with chronic heart failure” published in *Journal of Geriatric Cardiology* with great interest.<sup>[1]</sup> However, we have some comments regarding this study.

First of all, it has not been stated that any inflammatory marker was analyzed in study patients. The authors reported that patients with known evidence of infection, chronic inflammatory conditions were excluded. But there is no data to support it in any way. At least C-reactive protein (CRP) or hypersensitive CRP could have been examined. Thus, the relationship between neutrophil-to-lymphocyte (N/L) ratio and CRP could be investigated.

Secondly, in the study, it is highlighted that heart failure and AF often coexist and each condition can promote the other, with an associated increase in overall morbidity and mortality.<sup>[2]</sup> So a higher N/L ratio was associated with an increased risk of AF which may make the prognosis of heart failure become worse in the elderly with CHF. Although the N/L ratio was higher in the major cardiovascular events (MCEs) group, AF was reported as lower at this study.<sup>[1]</sup> How do you explain this contradiction? At the same time, the contribution of N/L ratio to NYHA III-IV group is limited because it is known that there is already more MCE in

NYHA III-IV patients. In addition NYHA class IV patients are still considered unsuitable for survival studies and have been systematically excluded from clinical trials because of the expectation of a much shortened lifespan.<sup>[3]</sup> In the present study 51.9% of the major cardiovascular events (MCEs) group was composed of NYHA III-IV patients. It might be better to investigate the predictive power of N/L ratio for MCE in patients with NYHA I-II.

As the third NYHA was mistakenly written as HYHA in all parts of the text.

Future studies should be directed towards larger randomized trials with more emphasis on long term clinical endpoints.

### References

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### Authors' reply

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We thank the authors of this letter for their thoughtful comments. The first topic concerns inflammatory markers analyzed in study patients. We did not include information on inflammatory markers, such as CRP, tumor necrosis factor- $\alpha$ , or interleukin-6, partly because such inflammatory markers are more expensive and difficult to obtain in a clinical practice compared to the N/L ratio. That lack of information is one of our study's limitations. To study the relationship between the N/L ratio and CRP level, we added the CRP data. The CRP levels in the total study cohort, in patients who had MCEs, and in patients who did not have MCEs, were  $0.387 \pm 0.347$ ,  $0.443 \pm 0.372$  and  $0.362 \pm 0.332$ , respectively ( $P < 0.001$ ). We used the receiver operating characteristic (ROC) curve based on a univariate model to examine the ability of CRP levels to predict MCEs; the area under the curve was 0.564 ( $P < 0.001$ , 95% CI: 0.531–0.597). The CRP level and N/L ratio exhibited a positive correlation ( $r = 0.261$ ,  $P < 0.001$ ) using the Spearman correlation test.

Secondly, patients with concomitant heart failure (HF) and atrial fibrillation (AF) indeed have a worse prognosis.<sup>[1]</sup> However, numerous prognostic markers, such as AF, hypertension, smoking, obesity, diabetes, renal impairment, sleep apnea, and coronary artery disease and/or HF hospitalization, have been identified in patients with HF.<sup>[2]</sup> Although AF was lower in the MCE group in our study, certain prognostic factors with high hazard ratios that we did not include might affect the prognosis of HF when combined with those we did include in the multivariate Cox model. Thus, AF may make the prognosis of HF worse in the multivariate

Cox model. In addition, the reader's observation that NYHA class IV patients are unsuitable for survival studies because of the expectation of a much-shortened lifespan is very relevant. Even though our study had very few NYHA class IV patients (9.1% in the total study cohort and 14.2% in the patients who had MCE), we will focus our attention primarily on NYHA I-II patients in the future.

Thirdly, we are sorry to have mistakenly written NYHA as HYHA. We express our sincere apologies for this mistake.

Finally, we agree that multicenter randomized trials with large sample sizes and long-term follow-up should be conducted in the future, as larger trials would make our conclusions more reliable. Our investigation is still underway. We hope that more markers, such as the N/L ratio, that are inexpensive and can be readily obtained at the time of admission for every HF patient will be observed and that the relationship between N/L ratio and poor prognosis in HF will be confirmed in more research populations.

## References

- 1 Kotecha D, Piccini JP. Atrial fibrillation in heart failure: what should we do? *Eur Heart J* 2015; 36: 3250–3257.
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