Letter to the Editor

Neutrophil-to-lymphocyte ratio: A crucial determinant of reverse remodeling in patients with heart failure undergoing transcatheter aortic valve implantation?

Over the past years, certain indices of inflammatory cells including neutrophil-to-lymphocyte ratio (NLR) have been extensively studied as simple measures of systemic inflammation in the clinical setting. On the other hand, systemic inflammation is well known to be associated with a variety of life-threatening conditions including acute coronary syndromes, cardiac arrhythmias, and new onset or worsening heart failure (HF). In their recently published article, Khalil et al have demonstrated the particular clinical value of NLR in predicting major cardiovascular events, HF admissions along with all-cause mortality at one-year after transcatheter aortic valve implantation (TAVI). Accordingly, a pre-TAVI NLR value of ≥4 was identified as significantly predictive of these adverse events in the post-TAVI setting. The authors should be congratulated for further substantiating the association between systemic inflammation (as demonstrated with high NLR values) and poor cardiovascular outcomes specifically in a subset of high-risk and fragile subjects. However, I would like to focus on the converse perspective in this setting and make a few comments regarding the auspicious consequences of low NLR values including left ventricular reverse remodeling (LVRR) among TAVI recipients with HF.

In clinical practice, LVRR, unlike adverse myocardial remodeling, has been considered as an auspicious sign probably with the highest prognostic benefit among patients with systolic HF. In this setting, it is universally defined as a gradual improvement in left ventricular ejection fraction values (as demonstrated with an increment of ≥15% or an increment of ≥10% accompanied by a substantial diminution of end-systolic diameter or volume index within one-year as compared with baseline values). Within this context, LVRR might potentially emerge spontaneously particularly in the presence of proper systemic milieu harboring a blunted inflammatory and mitogenic response or might more commonly arise after hemodynamic relief of certain valvular pathologies including aortic stenosis (AS), and so on. However, it is also well known that LVRR might not be encountered even after correction of the culprit valvular pathology in a significant portion of subjects with left ventricular (LV) systolic dysfunction (even with favorable features including moderate LV impairment with a short duration, etc) suggesting the potential impact of an inadvertent milieu with high systemic inflammatory burden in this setting: accordingly, elevation of certain cytokines including hematocyte growth factor (HPG) at baseline were recently reported to be associated with reduced recovery of LV functions (as measured with a variety of more sensitive echocardiographic indices including global longitudinal strain (LGS), etc.) at 1-year following TAVI.

Given the high prevalence of systolic HF (with high- or occasionally low-gradient AS) among TAVI recipients (for e.g., approximately one-third of the whole study population in the study by Khalil et al), evolution of LVRR in these patients might also have important implications that might potentially be addressed by the present study.

First, as expected, a portion of TAVI recipients with systolic HF might incur LVRR after correction of transaortic gradient, particularly if the AS substantially accounts for the evolution of systolic dysfunction. Accordingly, what was the incidence of LVRR at one year in patients with a baseline systolic HF in the study?

Second, low systemic inflammation as measured with low NLR values, on top of the impact of mechanical relief of AS, might create a significant proclivity for the emergence of LVRR (and possibly in a more striking manner) among TAVI recipients with a preexisting systolic HF. Accordingly, was there an association between LVRR and NLR values in the study? Was there a certain cutoff value of pre-TAVI NLR, below which it is feasible to highly predict LVRR at one year?

And finally, LVRR is well known to be associated with a substantial prognostic benefit, regardless of the underlying cause of systolic HF. Therefore, how was the prognosis among HF patients with LVRR as compared with those without LVRR at one year? Did LVRR serve as an independent favorable prognostic factor (if so) or appear to be dependent, at least to some extent, on certain factors including low NLR values in the study?

In conclusion, LVRR has been considered to yield a substantial prognostic benefit in the setting of systolic HF that is generally encountered in a substantial portion of TAVI candidates as well. Mechanistically, evolution of this auspicious phenomenon following TAVI might not only be attributable to the mechanical relief of transaortic gradient but might also be strongly associated with the coexistence of a proper milieu characterized by reduced systemic inflammation (as measured with certain cytokine levels and NLR values at baseline, etc) in these patients. This potentially implies that an existing low NLR value in this setting might serve as a potential predictor of LVRR evolution following TAVI. On the other hand, favorable prognostic impact of LVRR among TAVI recipients to some extent, seems to be dependent on low NLR values, and vice versa. However, the potential association between low NLR and LVRR (as well as their independent impacts on prognosis) in the setting of TAVI yet remains to be established.
References

1. Khalil C, Pham M, Sawant AC, et al. Neutrophil to lymphocyte ratio predicts heart failure readmissions and outcomes in patients undergoing transcatheter aortic valve replacement. *Indian Heart J*. 2018. https://doi.org/10.1016/j.ihj.2018.08.002.

2. Yalta T, Yalta K. Systemic inflammation and arrhythmogenesis: a review of mechanistic and clinical perspectives. *Angiology*. 2018;69(4):288–296.

3. Van Lintouth S, Tschöpe C. Inflammation – cause or consequence of heart failure or both? *Curr Heart Fail Rep*. 2017;14(4):251–265.

4. Yilmaz A, Yalta K, Turgut OO, et al. Clinical importance of elevated CK-MB and troponin I levels in congestive heart failure. *Adv Ther*. 2006;23(6):1060–1067.

5. Yalta K, Svni N, Yalta T, Geyik B, Aksoy Y, Yetkin E. Copeptin (C-terminal pro-vasopressin): a promising marker of arrhythmogenesis in arrhythmia prone subjects? *Int J Cardiol*. 2011;148(1):105.

6. Yalta K, Zorkun C. Soluble ST2 biomarker and reverse remodeling in patients with systolic heart failure. *Indian Heart J*. 2018;70(1):196.

7. Lupon J, Gaggin HK, de Antonio M, et al. Biomarker-assist score for reverse remodeling prediction in heart failure: the ST2-R2 score. *Int J Cardiol*. 2015;184:337–343.

8. Yalta K. Reverse remodeling in systolic heart failure: a puzzle yet to be solved? *Int J Cardiol*. 2015;187:46–47.

9. Sato K, Kumar A, Jones BM, et al. Reversibility of cardiac function predicts outcome after transcatheter aortic valve replacement in patients with severe aortic stenosis. *J Am Heart Assoc*. 2017 Jul 11;6(7). https://doi.org/10.1161/JAHA.117.005798, pii: e005798.

10. Kim JB, Kobayashi Y, Kuznetsova T, et al. Cytokines profile of reverse cardiac remodeling following transcatheter aortic valve replacement. *Int J Cardiol*. 2018;270:83–88.

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In the letter to the editor in response to our recently published article, the authors discuss the association of high systemic inflammatory burden and left ventricular reverse remodeling (LVRR) defined as an improvement in left ventricular systolic function ≥ 15% in patients with heart failure (HF) undergoing transcatheter aortic valve replacement (TAVR). The authors propose that LVRR can be considered as a prognostic marker after TAVR in patients with systolic HF and is associated with low neutrophil-to-lymphocyte ratio (NLR) and consequently low inflammatory state after the procedure. We completely agree with the authors that inflammatory milieu indeed plays a critical role not only in acute coronary syndrome but also after undergoing TAVR in the setting of underlying HF.

In our study cohort, 82 (28%) patients had systolic HF and experienced NYHA Class II and higher HF symptoms. Among these patients, 78 (95%) patients had a follow-up echocardiogram (ECHO) after TAVR. There were 54 (66%) patients who experienced LVRR during the follow-up and had a significantly lower median NLR than those who did not experience LVRR after TAVR (3.68 vs. 4.67, p = 0.02). Next, those patients with a NLR cut-off value < 4.0 were more likely to experience LVRR (61% vs. 39%, p = 0.05). Finally, patients experiencing LVRR were also less likely to have major adverse cardiac events (MACE) during the follow-up (20% vs. 80%, p = 0.03). However, our study lacked the power (n = 82) to address if LVRR could be identified as an independent prognostic factor for MACE after adjusting for other variables including NLR.

In conclusion, our study confirms the important role of LVRR in patients undergoing TAVR. In addition, we also found that patients experiencing LVRR had significantly lower NLR, which is suggestive of a lower inflammatory state. We thus agree with the authors that LVRR may indeed be influenced by underlying inflammatory milieu, but given the limited number of patients, our study lacked the power to identify LVRR as an independent prognostic indicator of MACE after TAVR. Future prospective studies addressing this important issue are thus warranted.

Disclosures

There are no additional disclosures.

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References

1. Khalil C, Pham M, Sawant AC, et al. Neutrophil-to-lymphocyte ratio predicts heart failure readmissions and outcomes in patients undergoing transcatheter aortic valve replacement. Indian Heart J. 2018. https://doi.org/10.1016/j.ihj.2018.08.002.

2. Sato K, Kumar A, Jones BM, et al. Reversibility of cardiac function predicts outcome after transcatheter aortic valve replacement in patients with severe aortic stenosis. J Am Heart Assoc. 2017 Jul 11;6(7). https://doi.org/10.1161/JAHA.117.005798. pii: e005798.

3. Sawant AC, Adhikari P, Narra SR, et al. Neutrophil to lymphocyte ratio predicts short- and long-term mortality following revascularization therapy for ST elevation myocardial infarction. Cardiol J. 2014;21(5):500–508. https://doi.org/10.5603/CJ.a2013.0148. Epub 2013 Oct 21.