Prognostic Markers and Valve Therapy
To Pause or Not to Pause*

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Due to ongoing improvements in oncology care, the number of adult patients with cancer survivorship continues to grow significantly. Importantly, in comparison to patients without cancer, those with an oncologic history are excessively vulnerable to age-related cardiovascular disease, owing to the pathophysiological effects of the malignancy (e.g., inflammation), its treatment (e.g., radiation, chemotherapy), and accompanying morbidity (e.g., hypertension). For patients with valvular heart disease, ~20% have a current or prior cancer, which may be overt or discovered incidentally during clinical evaluation, such as cardiac computed tomography imaging for transcatheter aortic valve replacement (TAVR). Indeed, the common overlap of oncological issues and valvular heart disease poses a frequent vexing clinical challenge, especially when decision-making for therapeutic intervention is required.

For patients with aortic stenosis who may be TAVR candidates, prognostication is elementary to decision-making for therapy. Certainly, when there are not procedure impediments, the clinical benefit is greatest when longevity is seemingly unthreatened by morbidity, save for the presence of severe aortic stenosis. A history of cancer or any life-threatening illness (e.g., severe lung, kidney, or liver disease), is a common reason for pause in the therapeutic path. Excessive frailty, cognitive impairment, and limited mobility also are examples of cautionary conditions. Concerted efforts have been made to streamline the clinical algorithms for prognostication, with an increasing focus on simplified, bedside approaches that meaningfully impact the management of patients with aortic stenosis. One example of such an approach is the essential frailty toolkit (i.e., appropriate drawing of a clock, the number of chair rises that can be completed, hemoglobin, and albumin), whose prognostic capability has been validated in a cohort of 1,020 patients undergoing TAVR or surgery (1).

In this light, the report by Tabata et al. (2) in this issue of JACC: CardioOncology is a welcomed contribution to the field of cardio-oncology and aortic stenosis. In their findings, the platelet-to-lymphocyte ratio (PLR) was found to be an independent prognostic marker for survival among patients with TAVR, with or without a history of cancer. Overall, the prevalence of cancer among those treated with TAVR was 19.9% (i.e., 240 of 1,204 patients). Certainly, patients with cancer would be expected to have relatively poorer survival, as observed in the present study (3-year mortality, 49.2% vs. 36.8%; p < 0.001). However, the use of PLR was associated with further stratification, both by relative risk as measured with adjusted hazard ratio (1.07 per 100 increase in PLR; p = 0.006 for patients with cancer; 1.20 per 100 increase in PLR; p = 0.004 for patients without cancer), and by binary analyses with a PLR of 216 as the cutoff value. The 3-year mortality was nearly 2-fold greater for patients with cancer and a high PLR (57.9%), compared with patients without cancer with a low PLR (31.0%). Moreover, those patients with cancer and a low PLR had survival that was similar to
patients without cancer with high PLR (3-year mortality, 37.7% vs. 41.8%). Importantly, these observations were made among patients with cancer in whom most patients (208 of 240 or 86.7%) had a prior, but not current, history of cancer. Taken together, these results suggest that PLR, which is easily available with a differentiated blood cell count, could be considered in the prognostication of patients undergoing TAVR.

An attractive quality for the use of PLR is the potential link to underlying pathophysiology, specifically chronic inflammation. Both elevated platelet count and low lymphocytes have each been associated with impaired survival in a variety of cardiovascular disorders, and PLR further magnifies this association as a pooled marker. However, like many markers, the link to underlying pathophysiology is seemingly more associative than causative. In the present study, the prognostic ability of PLR was independent in multivariable models, yet it does correlate with Logistic EuroSCORE, EuroSCORE II, and STS score. Although these correlations were relatively weak ($R = 0.11$ to 0.15), these scoring systems are comprehensive amalgamations of many patient risk factors, including age and severe morbidities. Moreover, the data of Tabata et al. [2] show prognostic ability of PLR in a patient cohort with a variety of cancers, but this ability, as also demonstrated in the current report, is not necessarily specific to patients with cancer. The impact of PLR might be different in cancers treated with cardiotoxic medications (e.g., adriamycin). Interestingly, cardiac death occurred in patients with past cancer, but not current malignancy, highlighting the importance of survivorship follow-up in a multidisciplinary fashion.

The present work is a single-center report, and further validation of PLR in larger cohorts, with comparison to other simplified scoring systems (e.g., Essential Frailty Toolset) is needed. Such validation is especially important when conclusions are based on relatively small sample sizes. In the present study, the differences in PLR between the survivors and nonsurvivors was only ~45, with broad, overlapping confidence intervals for the 2 groups, leading to challenges in applying the data for any individual patient. Another example of the limited power to predict mortality with PLR is that survival curves in patients with a cancer diagnosis, stratified by high versus low PLR crossed twice in the first year (Figure 4 in Tabatha et al. [2]).

For any prognostic marker, with or without extensive validation, the greatest challenge is knowing the exact boundary to use to decline therapy in a given patient. Clearly, such decisions should not be based on a single or even a few prognostic markers, such as PLR. Defining clinical futility is an art form that requires a careful, holistic approach, with consideration of physical, psychological, and social factors. Such definitions have become even more challenging with the evolution of TAVR into a procedure that has become relatively facile and with low rates of complications. When a chance of clinical benefit, even if small, is possible in a suffering patient, there certainly is temptation to offer potentially life-saving therapy, such as TAVR, despite relatively higher probability of a poor outcome or futility. Further work on helping to define, validate, and examine the impact of the boundaries proposed by our prognostic tools in these patients is still needed.

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