

Pulmonary Regurgitation in Heart Failure: Causality or a Marker of Disease Severity?

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Dear Editor,

We read with great interest the article by Aydin et al.¹ which investigates the association between pulmonary valve regurgitation (PR) severity and levels of N-terminal pro-B-type natriuretic peptide (pro-BNP), six-minute walk test (6MWT) distance, and complications in 490 heart failure (HF) patients. We commend the authors for addressing this underexplored valvular pathology; however, several methodological and interpretive concerns warrant careful consideration before the conclusions can be fully accepted.

1. Severe Group Imbalance and Statistical Power

The striking disparity in group sizes—272 (No PR) and 162 (Mild PR) versus only 20 (Moderate PR) and 36 (Severe PR)—raises serious concerns about the statistical power of the multivariate models.² In a multivariate model featuring five predictors (PR severity, age, LVEF, PASP, and hemoglobin), the reliability of the derived coefficients for the smaller subgroups may be compromised by the lack of statistical power. This imbalance raises additional concerns regarding the precision and stability of the reported regression coefficients ($\beta=0.48$ for pro-BNP and $\beta=-0.39$ for 6MWT). We urge the authors to report 95% confidence intervals for all beta coefficients and to consider bootstrap-based sensitivity analyses to assess the robustness.

2. Echocardiographic Grading Reliability

The authors acknowledge that a systematic interobserver reproducibility assessment was not performed. Without kappa statistics, the reliability of the semi-quantitative PR grading cannot be verified, particularly given that vena contracta width was the only quantitative parameter available. Furthermore, the lack of other quantitative parameters—such as regurgitant volume or fraction—limits the validity of a four-grade classification system when based solely on vena contracta width.³

3. Selection Bias in 6MWT Data

The 6MWT was performed only “when available,” creating a substantial risk of ascertainment bias. Patients with the most severe functional limitation—who are more likely to be in the Moderate and Severe PR groups—may have been systematically excluded from testing, potentially underestimating functional impairment in these groups.⁴ The authors should report completion rates per PR severity group and baseline comparisons between tested and non-tested patients.

4. Unmeasured Confounders and Causal Language

The multivariate model omits key confounders—including body mass index, HF etiology, atrial fibrillation burden, and contemporary HF therapies (SGLT2 inhibitors, sacubitril/valsartan)—that independently influence both pro-BNP and 6MWT. Moreover, the discussion employs causal and mechanistic language that a cross-sectional retrospective design cannot support. It is equally plausible that advanced HF leads to secondary pulmonary hypertension, annular dilation, and consequently more PR—the reverse causal pathway. We recommend consistently replacing causal wording with associative language throughout the manuscript. Therapeutic implications should be clearly framed as hypothesis-generating rather than practice-guiding.

In summary, Aydin et al.¹ address a clinically relevant question and present findings of interest to the HF community. Addressing the statistical, methodological, and interpretive concerns outlined above would substantially enhance the validity of the manuscript's conclusions. We look forward to prospective studies that more definitively establish the prognostic role of PR severity in HF populations.

Keywords

Heart Failure; Walk Test; Natriuretic Peptides

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Manuscript received March 27, 2026, revised manuscript April 01, 2026, accepted April 01, 2026

DOI: <https://doi.org/10.36660/abc.20260265i>

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Reply

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Dear Editor,

We thank the authors of the letter for their careful reading of our work and for raising several points that allow us to clarify the design and interpretation of our study. We welcome this kind of scholarly dialogue, and we hope our response addresses each concern in turn.

Regarding group size imbalance and statistical power, we fully acknowledge the unequal distribution across PR severity categories. This reflects the real-world prevalence of pulmonary regurgitation in a general heart failure population, where moderate and severe forms are inherently less common. The purpose of our study was precisely to characterize this distribution as it exists in clinical practice, not to balance groups artificially. That said, the point concerning confidence intervals for the regression coefficients is well taken. We concede that reporting 95% confidence intervals alongside the standardized beta coefficients would strengthen transparency. Bootstrap sensitivity analyses are a reasonable suggestion for future iterations, and we welcome this guidance for prospective work.

On echocardiographic grading reliability, the commentators correctly note the absence of formal kappa statistics. We must emphasize, however, that our grading protocol was not based solely on vena contracta width. As described in the Methods section, we employed a comprehensive, multi-parameter approach that integrated color Doppler jet width relative to the pulmonary annulus, continuous-wave Doppler signal density and deceleration profile, and the presence of diastolic flow reversal in the pulmonary branches, which is fully consistent with the American Society of Echocardiography recommendations.¹ Vena contracta width was highlighted because it was the only parameter available in tabular form retrospectively; it does not capture the full scope of our classification

approach. We agree that formal interobserver analysis should be a cornerstone of any future prospective study.

The concern about ascertainment bias in the 6MWT is legitimate and is one we explicitly discussed in the Limitations section. However, we would gently push back on the framing. If patients with the most severe functional limitation were indeed unable to complete the 6MWT, the observed differences across PR severity groups would represent a conservative estimate of the true functional gradient rather than an overestimation. This would, if anything, make our findings more rather than less credible. Nevertheless, we agree that reporting completion rates per group is a valuable transparency measure, and future prospective designs should incorporate this.

Finally, we fully accept the critique regarding causal language and unmeasured confounders. Atrial fibrillation burden, body mass index, HF etiology, and the use of SGLT2 inhibitors or sacubitril/valsartan are relevant variables that our retrospective data did not consistently capture. The reverse causal pathway, in which advanced HF drives secondary pulmonary hypertension, annular dilation, and ultimately PR, is a biologically plausible and important alternative explanation.^{2,3} We did not intend to imply a unidirectional mechanism, and we agree that mechanistic language should consistently be replaced with associative framing. Our conclusions are explicitly observational, and any therapeutic implications should be read as hypothesis-generating rather than actionable guidance.^{4,5}

We are grateful to the correspondents for helping to sharpen the discussion of this underexplored valvular lesion in the context of heart failure. Their comments reinforce the need for well-designed prospective cohort studies, which we intend to pursue.

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