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LETTER TO THE EDITORS

Response to the Letter: "C-reactive protein-to-albumin ratio in transcatheter tricuspid valve repair: methodological concerns and inconsistencies"

Karl Finke[1] · Laura Marx[1] · Jan Althoff[1] · Thorsten Gietzen[1] · Matthieu Schäfer[1] · Jan Wrobel[1] · Philipp von Stein[1,2] · Jennifer von Stein[1,2] · Maria Isabel Körber[1] · Stephan Baldus[1] · Roman Pfister[1] · Christos Iliadis[1]

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Sirs,

We thank Zorlu et al. for their interest in our study investigating the prognostic significance of the C-reactive protein-to-albumin ratio (CAR) in patients undergoing transcatheter tricuspid valve repair (TTVr) for tricuspid regurgitation (TR) [1]. We welcome the opportunity to address the specific points raised and hope this response deepens the understanding of the manuscript.

As discussed in our manuscript (p. 901), high-CAR patients demonstrated higher mortality during the 2 year follow-up (Kaplan Meier estimates) and lower procedural success. Within this group, procedural success reduced mortality during follow-up (26%) compared to procedural failure (59%). Importantly, mortality remained higher than in low-CAR patients regardless of procedural success in multivariable regression analysis. However, patients with intraprocedural success in the high CAR group had significantly reduced mortality during follow-up. We elaborated on this fact already in the discussion:''*Opposingly, patients of the high CAR group with intraprocedural success had significantly reduced mortality during follow-up. This indicates that while patients with high CAR have higher mortality risk, they have a survival benefit when achieving intraprocedural success during TTVr. This effect was not observed in the low CAR group. This study therefore identifies a high-risk subgroup which may lower its mortality risk due to a successful TTVr procedure.*'' This underlines CAR as a marker of residual risk and further studies should investigate the marker as a predictor for treatment futility [1]. The author asked about the TR reduction in the different subgroups, this is covered by procedural success definition in the methods section [2]. The Procedural success was defined by TVARC criteria, including reduction of tricuspid regurgitation (TR) to mild or moderate [1].

All symptomatic endpoints remained non-significant in our study. Regarding NYHA functional class, the low CAR group showed a non-significant trend (61%) in improvement in NYHA class of I or more compared to the high CAR group (39%, $p=0.253$) [1]. This opposes the statement of the author that the symptomatic improvements where similar in both groups [2]. As highlighted in Table 2, follow-up data on symptomatic parameters was not available for all patients which could limit statistical power. The primary endpoint of this study was the mortality up to two years after TTVr [1]. Further we would like to highlight that the findings in Table 4 showed a trend of better symptomatic outcomes in the high CAR group with procedural success [1]. This subgroup might also have a symptomatic benefit from procedural success and could be a driver of the similar outcomes in both CAR groups. Future studies should investigate symptomatic outcomes and CAR in a multicenter setting.

There was an non-significant trend towards more peripheral edema in the high-CAR group at baseline (85.5% vs 76.2%, $p=0.134$). In clinical examination one day before the procedure, both groups were similarly recompensated prior to the procedure, as reflected by the absence of significant clinical differences in edema despite higher RAP in high-CAR patients [1]. Persistently elevated RAP may therefore indicate more severe TR and atrial dysfunction rather than overt volume overload.

Direct comparison of CAR and TRIVALVE was not feasible due to diverging endpoints and populations, as discussed in our manuscript. Further studies should explore CAR together with the TRI-VALVE score. In direct comparison,

✉ Karl Finke
Karl.finke@uk-koeln.de

[1] Department III of Internal Medicine, Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany

[2] Cardiovascular Research Foundation, New York, NY, USA

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TRI-SCORE outperformed CAR. However, adding CAR to TRI-SCORE improved prognostic accuracy, suggesting complementary roles. The TRI-SCORE is a multiparametric score and CAR as a biomarker not included in the TRI-SCORE, which explains why adding CAR to the multiparametric score leads to a better area under the curve (AUC). The aspect of chronic inflammation is neglected in the original TRI-SCORE and CAR includes this novel aspect of TR pathophysiology [1].

The author claims that there were methodological flaws in the Cox regression analysis and the cofounder renal function was neglected [2]. As stated in the Methods section, only variables tested significant in univariable analysis were entered into multivariable analysis. Chronic kidney disease was non-significant and therefore excluded, eGFR was included as a continuous objective marker of renal function [1]. NYHA functional class was excluded due to its subjective nature, in line with our strategy to use objective variables [1]. Thus, renal and functional parameters were not neglected, as suggested by the author [2].

Patients with any sign of pre-procedural infections were excluded. Infections were evaluated using routine clinical, laboratory, and if appropriate imaging protocols as established in our daily clinical practice at a tertiary university hospital. Sensitivity analyses excluding CRP outliers confirmed robustness of findings and showed a low rate of postprocedural infections. The limitation of using standard CRP versus high-sensitivity CRP (hs-CRP) and the potential value of hs-CRP were already discussed in our manuscript (p. 902). As discussed in the manuscript CRP is more readily available in clinical routine and less expensive than hs-CRP. Right heart failure with intestinal congestion and bacterial micro translocation can contribute to systemic inflammation in the setting of TR as discussed in our manuscript [1]. This chronic low-grade inflammation could be considered as a chronic subclinical infection being part of the TR pathophysiology. Exactly this aspect is covered by the CRP in the CAR ratio, allowing the readily available CAR to monitor this aspect of TR pathophysiology [1].

We agree the threshold derived from the Youden index requires external validation [2]. External validation was not possible within the scope of our single-center study as discussed in the limitations section; however, future multicenter studies should address this question and confirm the applicability of CAR in broader clinical settings. The exploratory very high CAR subgroup (≥ 6.85) identified in exploratory analysis exhibited extremely poor survival (50% at 1 year), highlighting the need for individualized treatment strategies in this subgroup. In the discussion we recommend looking at individual patient factors in this very high-risk subgroup.

In summary, CAR represents a simple biomarker that augments risk stratification after TTVr. To our knowledge this study is the first to explore this marker in the setting TTVr and lays ground for future research. We appreciate the critique, which allowed us to further clarify our methodology and strengthen interpretation of our findings.

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Declarations

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References

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