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Prognostic role of anemia in heart failure with preserved ejection fraction: A systematic review and meta-analysis

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Nearly half of heart failure patients present with preserved ejection fraction. The prevalence of anemia in heart failure with preserved ejection fraction (HFpEF) varies from 19% to 68%. Anemia portends poor outcomes in heart failure with reduced ejection fraction (HFrEF), but its prognostic role in HFpEF is controversial. Currently, there is no specific treatment that improves mortality in HFpEF, and few evidence-based treatment strategies are associated with improvement in morbidity. Comorbidities contribute majorly to the morbidity and mortality in HFpEF, and anemia being one among them. However, the effect of anemia on outcomes in HFpEF patients is not well-established. A post-hoc analysis of the Candesartan Cilexietil in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM)-Preserved trial and patient-level meta-analysis by the MAGGIC group demonstrated that anemia was associated with higher mortality.[1,2] However, several other studies demonstrated inconsistent results.[3,4] Hence, the present meta-analysis aimed at analyzing the prognostic role of anemia in patients with HFpEF.

The PubMed and Cochrane databases were electronically searched for studies that reported the effect of anemia on patients with HFpEF using a pre-specified list of terms to locate studies. Two authors (AK and MM) independently screened searched citations for relevant studies and performed data extraction from included studies. Any disparity was solved by mutual consensus and after consultation with other authors through a video conference to reach a unanimous decision. The systematic search was performed in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) requirements. We only included studies which used the WHO definition for anemia, which is Hgb <13 g/dL in male adults and Hgb <12 g/dL in female adults. HFpEF was defined as clinical features suggestive of heart failure with ejection fraction >50%. The adjusted effect size was pooled wherever available. Corresponding authors of studies were contacted for information otherwise not reported in the manuscript. The primary outcome of the study was all-cause mortality, and the secondary outcome was all-cause hospitalization. Among ten studies, one study was included after the information required for analysis was provided by the corresponding author of the study, one was a patient-level meta-analysis by the MAGGIC group, two were post-hoc analysis of randomized controlled studies, and the remainder of the seven studies were either retrospective or prospective cohort studies.[4] Of the ten included studies, four studies reported unadjusted hazard ratios, while six studies reported adjusted hazard ratios. We used the inverse variance method with the Paule-Mandel (PM) estimator of Tau with Hartung-Knapp-Sidik-Jonkman adjustment to calculate the pooled hazard ratio (HR) with 95% confidence interval (CI). P curve analysis was used to assess publication bias and the possibility of P hacking. P curve analysis assumes that publication bias is not only because a researcher is not publishing non-significant results, but also because the researcher is trying and manipulating the data to achieve statistical significance. All statistical analysis was carried out using R version 3.6.2.

Ten studies constituting 28,735 patients were included in the final analysis.[2–11] Of 28,735 patients, 13,584 (47.27%) patients were anemic. The follow-up period across studies varied from 1.5 years to 12 years. The weighted mean age of patients included in the meta-analysis was 75.58 years. Anemia among patients with HFpEF was associated with statistically significant higher rates of all-cause mortality [HR: 1.44; 95% CI: 1.26–1.65; χ^2 – 16.24; χ^2 P-value – 0.06; I^2 – 45%] [Fig. 1**, PANEL A],** which was the primary outcome of this study. Additionally, anemia in HFpEF patients was associated with statistically significant higher rates of all-cause hospitalization [HR: 1.32; 95% CI: 1.03–1.68; χ^2 – 11.53; χ^2 P-value – 0.009; I^2 – 74%] [Fig. 1, PANEL B]. Since the I^2 value was 74%, heterogeneity was moderately high for this outcome. P curve analysis for all-cause mortality did not report publication bias or P hacking [Fig. 2]. Seven of the included studies had a P-value of <0.025. The P curve was right-skewed, with the power of the analysis estimated as 94% (95% CI - 79%–99%).

The current pooled meta-analysis included ten articles and assessed the prognostic role of anemia in patients with HFpEF. Our meta-analysis extrapolated that anemia is associated with statistically significant higher all-cause mortality and hospitalization, supporting anemia as an adverse prognostic comorbid condition in patients with HFpEF. Albeit, our secondary outcome was associated with high heterogeneity. Our results were consistent with a post-hoc analysis of the CHARM-Preserved trial by O'Meara et al. in HFpEF patients, which demonstrated that anemic patients had a higher risk of mortality and hospitalization.[1] Furthermore, former patient-level meta-analysis by the MAGGIC group demonstrated analogous results as of the current study.[2]

The pathogenesis of anemia among heart failure patients is not well elucidated, but former studies have proposed hemodilution,

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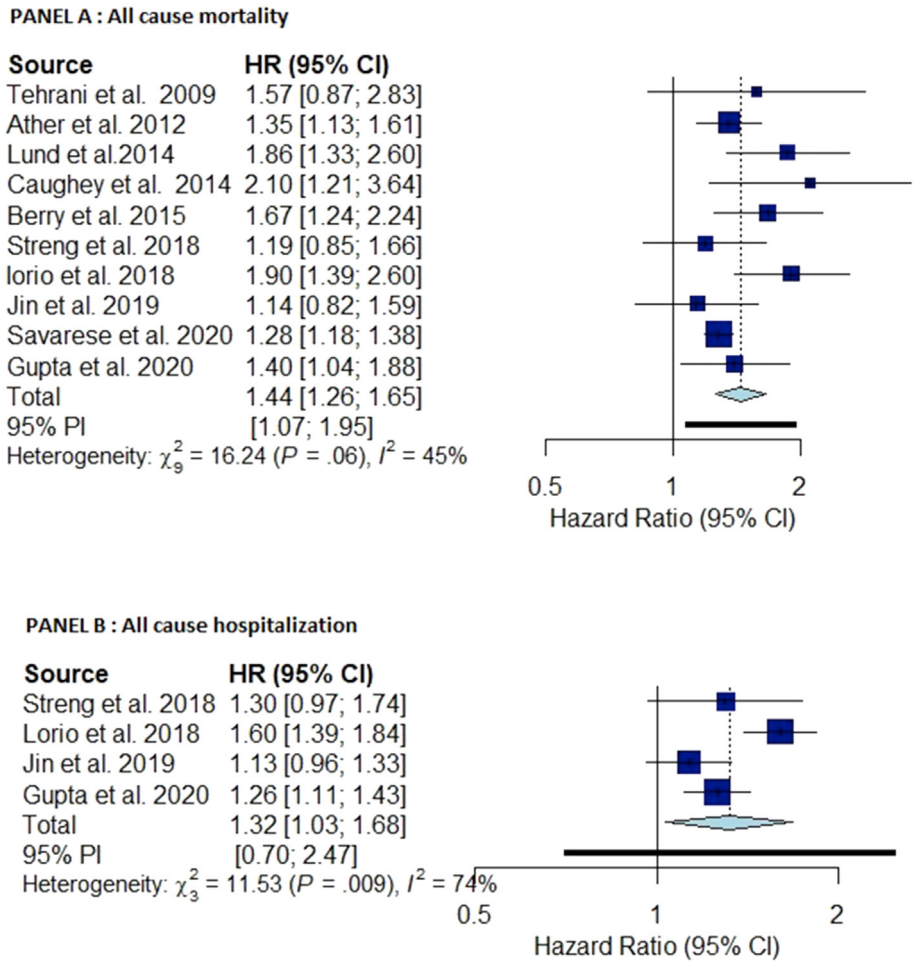

Fig. 1. PANEL A: Forest plot for all-cause mortality, anemia among patients with HFpEF was associated with statistically significant higher rates of all-cause mortality; PANEL B: Forest plot for all-cause hospitlaization, anemia in HFpEF patients was associated with statistically significant higher rates of all-cause hospitalization; HR- Hazard ratio.

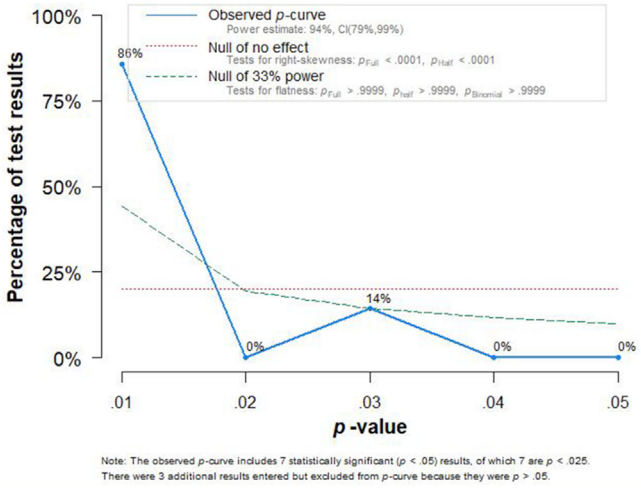

Fig. 2. P curve analysis for all-cause mortality. The P curve was right-skewed, hence opposing the possibility of publication bias and P hacking.

blunted erythropoietin production especially among patients with chronic kidney disease, and defective iron supply as the likely causes. Several mechanisms may explain the higher mortality and hospitalization in patients with anemia. In patients with HFpEF, myocardial energy efficiency is altered, that is further enhanced by anemia due to a reduction in oxygen delivery to the myocytes. Additionally, studies have shown that anemia is associated with increased cardiac mass by 25%, change in LV geometry, and impaired global longitudinal strain. Anemic patients were found to have lower systolic blood pressure and associated with neurohumoral activation. A previous study reported a strong association between anemia and preload dependent markers of diastolic dysfunction.[12] The factors mentioned above can work in conjugation leading to remodeling and decompensation that can be manifested as higher mortality and hospitalization in patients with anemia. Anemia also affects the quality of life and exercise tolerance in patients with HFpEF. However, only one study examined the effect of anemia on quality of life, which failed to demonstrate any difference in patients with anemia compared with patients without anemia.[4]

Treatment of anemia in patients with HFpEF lacks evidence. A randomized trial failed to show clinical benefit (quality of life, 6-min walk test, left ventricular mass) with erythropoietin in patients with HFpEF and anemia compared with the placebo.[13] The failure of this trial might be attributed to the existence of several distinct phenotypes of HFpEF-anemia, like iron deficiency-related, erythropoietin-dependent, inflammation-dependent, and volume-overload related. This might imply the role of a phenotype-matched approach for the treatment of anemia in HFpEF. Further, failure to exhibit clinical benefit in a randomized trial of

erythropoietin in HFpEF with anemia, might suggest that anemia could be more of a prognostic factor rather than a treatable therapeutic target in HFpEF.[13] However, larger studies in HFpEF patients with anemia are required to get an elaborated explanation and validation of erythropoietin clinical trial results. Currently, an ongoing FAIR-HFpEF (ClinicalTrials.gov Identifier: NCT03074591) and VITALITY-HFpEF (ClinicalTrials.gov Identifier: NCT03547583) trial is evaluating the effect of intravenous iron treatment on the prognosis in patients with HFpEF. This study has limitations. Four studies reported the unadjusted hazard ratio, and six studies reported the adjusted hazard ratio. Among the six studies that reported the adjusted hazard ratio, the adjustment was not similar across all the studies. Second, this was a trial level meta-analysis.

In conclusion, the current meta-analysis supported the adverse prognostic effect of anemia in patients with HFpEF. In patients with HFpEF, anemia was associated with higher all-cause mortality and all-cause hospitalization compared with patients without anemia. Perhaps, the treatment of anemia may help improve clinical outcomes in such patients.

Declaration of competing interest

The authors declare they have no conflict of interest.

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