data suggest that there is a need for systematic reassessment of the indication for anticoagulation in these patients, either by considering initiation of this therapy around age 65 years or, ideally, scheduling follow-up visits at the time patients reach that age.

## FUNDING

None.

## ETHICAL CONSIDERATIONS

We accept the responsibility outlined by the International Committee of Medical Journal Editors. The study has been approved by the local ethics committee, which, given the retrospective and anonymized nature of the research, has waived the need for consent. Potential biases related to sex and gender have been taken into account.

## STATEMENT ON THE USE OF ARTIFICIAL INTELLIGENCE

Artificial intelligence was not used.

## AUTHORS' CONTRIBUTIONS

S. Raposeiras-Roubín, E. Abu-Assi, and A. Íñiguez-Romo designed the study; S. Raposeiras-Rubín and D. González-Fernández wrote the manuscript; D. González-Fernández, A. González-García, and C. Iglesias-Otero collected the data. All authors reviewed and approved the final draft.

## CONFLICTS OF INTEREST

S. Raposeiras-Roubín has received presentation fees from the following companies: Amgen, Abbott, Sanofi, Novartis, AstraZeneca, Daichii, Pfyzer-BMS, Bayer, and Boehringer. The remaining authors declare no conflicts of interest.

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## C-reactive protein in patients with acute heart failure and preserved ejection fraction

### *Concentraciones de proteína C reactiva en pacientes con insuficiencia cardiaca aguda y fracción de eyección conservada*

**To the Editor,**

In recent years, increasing evidence has emerged to support the distinct biological behavior of patients with heart failure (HF) in the upper ranges of left ventricular ejection fraction (LVEF). Indeed, among patients with HF and preserved ejection fraction (HFpEF), those with higher LVEF have been termed as having "supranormal" ejection fraction (HFsnEF).[1–3]

There are well-known differences among patients with reduced, mid-range, and preserved ejection fraction.[1,3] However, the factors associated with those patients with higher systolic function remain poorly understood. Along this line, heightened inflammatory activity has emerged as a crucial pathophysiological mechanism and potential therapeutic target in HFpEF.[4] For instance, an ongoing trial is evaluating the efficacy of ziltivekimab vs placebo in patients with ambulatory HF, LVEF $>$ 40%, and high-sensitivity C-reactive protein (hs-CRP) $>$ 2 mg/L (NCT05636176). No prior studies have evaluated the inflammatory status profile along the continuum of LVEF, especially when LVEF $\geq$ 50%. In this study, we aimed to examine whether circulating hs-CRP at presentation differs along the continuum of LVEF in patients with acute HF (AHF) and LVEF $\geq$ 50%.

We conducted a retrospective study of an ongoing multicenter registry of patients admitted with AHF from January 2010 to January 2021 that enrolled 5246 patients. Patients with evidence of LVEF $<$ 50% during hospitalization (n = 2433), evidence of infection at admission (n = 113), missing values of hs-CRP (n = 312), early deaths without assessment of LVEF (n = 38) were excluded from this analysis. No patients received inotropes at presentation. The final study sample included 2350 patients. Clinical and biochemical characteristics, including hs-CRP, were assessed at presentation. Echocardiographic assessments, including LVEF, were performed during hospitalization (72 $\pm$ 24 hours after admission). LVEF was assessed by 2-dimensional echocardiography using the Simpson method. The association between hs-CRP and LVEF was evaluated along the continuum of LVEF or dichotomized ($<$ 65% vs

**Table 1**
Baseline characteristics across LVEF quartiles

| Variable | 50%-56% (n = 587) | 56%-61% (n = 588) | 61%-67% (n = 588) | 67%-88% (n = 587) | Total (n = 2350) | *P* |
|---|---|---|---|---|---|---|
| *Demographics and medical history* | | | | | | |
| Age, y | 76.4 (9.8) | 76.7 (9.9) | 76.3 (9.9) | 77.3 (9.1) | 76.7 (9.7) | .245 |
| Female sex | 324 (55.2) | 372 (63.3) | 374 (63.6) | 388 (66.1) | 1458 (62.0) | .001 |
| First HF admission | 399 (68.0) | 402 (68.4) | 392 (66.7) | 370 (63.0) | 1563 (66.5) | .198 |
| ADHF | 461 (78.5) | 467 (79.4) | 479 (81.5) | 477 (81.3) | 1884 (80.2) | .521 |
| Acute pulmonary edema | 92 (15.7) | 89 (15.1) | 85 (14.5) | 75 (12.8) | 341 (14.5) | .149 |
| NYHA III-IV | 92 (15.7) | 86 (14.6) | 102 (17.4) | 120 (20.4) | 400 (17.0) | .045 |
| DM | 243 (41.4) | 238 (40.5) | 247 (42.0) | 230 (39.2) | 958 (40.8) | .777 |
| Hypertension | 471 (80.2) | 497 (84.5) | 478 (81.3) | 495 (84.3) | 1941 (82.6) | .127 |
| Dyslipidemia | 308 (52.5) | 303 (51.5) | 315 (53.6) | 304 (51.8) | 1230 (52.3) | .899 |
| Ischemic heart disease | 196 (33.4) | 148 (25.2) | 133 (22.6) | 110 (18.7) | 587 (25.0) | < .001 |
| Charlson index | 2.2 ± 1.9 | 2.1 ± 1.9 | 2.1 ± 1.7 | 2.0 ± 1.7 | 2.1 ± 1.8 | .345 |
| *Vital signs and electrocardiogram* | | | | | | |
| Heart rate, bpm | 98 ± 28.6 | 95.0 ± 29.0 | 93.1 ± 28.6 | 90.5 ± 29.0 | 94.3 ± 28.9 | .001 |
| SBP, mmHg | 140 [124-160] | 144 [125-166] | 140 [126- 162] | 141 [124-164] | 141 [125-164] | .320 |
| DPB, mmHg | 78 [69-90] | 77 [66-91] | 74[64-90] | 74 [63-87] | 75 [65-90] | < .001 |
| Atrial fibrillation | 329 (56) | 312 (53.1) | 279 (47.4) | 318 (54.2) | 1238 (52.7) | .061 |
| *Blood tests* | | | | | | |
| Leukocytes, $x10^9$ /L | 9015 [7200-11 600] | 9015 [7200-11 600] | 9015 [7200- 11 600] | 9015 [7200- 11 600] | 9015 [7200- 11 600] | .482 |
| Neutrophils, $x10^9$ /L | 6610 [5100-8650] | 6900 [5000-9210] | 6650 [5100-9020] | 6590 [4750-8780] | 6700 [5000-8900] | .661 |
| Lymphocytes, $x10^9$ /L | 1250 [900-1830] | 1290 [935-1820] | 1250 [890-1790] | 1255 [910-1780] | 1260 [900-1800] | .783 |
| Neutrophils/lymphocytes | 5.0 [3.2-8.2] | 4.9 [3.3-7.9] | 5.1 [3.4-8.0] | 5.1 [3.1-8.2] | 5.1 [3.1-8.2] | .662 |
| eGFR, mL/min/1.73 $m^2$ | 61.3 ± 24.7 | 62.0 ± 26.3 | 61.3 ± 33.5 | 61.1 ± 26.4 | 61.4 ± 27.9 | .948 |
| eGFR < 60 mL/min/1.73 $m^2$ | 299 (50.9) | 294 (50.0) | 317 (46.1) | 305 (52.0) | 1215 (51.7) | .576 |
| Sodium, mEq/L | 138 ± 4.6 | 138 ± 4.6 | 138 ± 4.6 | 138 ± 4.6 | 138 ± 4.6 | .163 |
| RDW | 15.5 (2.2) | 15.3 (1.9) | 15.6 (2.2) | 15.5 (2.2) | 15.5 (2.1) | .182 |
| Hemoglobin, g/dL | 12.1 ± 1.9 | 12.2 ± 1.9 | 11.9 ± 1.9 | 12.1 ± 1.9 | 12.1 ± 1.9 | .072 |
| hs-CRP, mg/dL | 17.3 [9.7-34] | 18.3 [10.3-38.9] | 19.7 [9.8-38.1] | 20.2 [11.0-39.4] | 21.7 [11.5-37.9] | .031 |
| NT-proBNP, pg/mL | 3852 [2173-7141] | 2826 [1624-4988] | 2769.7 [1552- 5144] | 2397 [1320- 4508] | 2947.4 [1617-5447] | < .001 |
| *Echocardiography* | | | | | | |
| LVEF, % | 53 ± 2.0 | 58.9 ± 1.5 | 64.2 ± 1.5 | 72.1 ± 4.0 | 62.0 ± 7.5 | < .001 |
| TAPSE, mm | 18.7 ± 3.3 | 19.4 ± 3.2 | 20.1 ± 3.6 | 20.2 ± 3.9 | 19.6 ± 3.5 | < .001 |
| Septum, mm | 12.1 ± 3.0 | 12.4 ± 2.8 | 12.4 ± 2.3 | 12.5 ± 2.9 | 12.4 ± 2.8 | .147 |
| LVEDD, mm | 52.5 ± 6.4 | 49.7 ± 7.1 | 48.4 ± 6.6 | 47.4 ± 6.3 | 49.5 ± 6.8 | < .001 |
| *Treatment at admission* | | | | | | |
| RASi | 234 (39.9) | 237 (40.3) | 244 (41.5) | 228 (38.8) | 943 (40.1) | .828 |
| Beta-blockers | 237 (40.4) | 212 (36.1) | 252 (42.9) | 213 (36.3) | 914 (38.9) | .044 |
| MRA | 74 (12.6) | 75 (12.8) | 83 (14.1) | 67 (11.4) | 299 (12.7) | .585 |
| Statins | 256 (43.6) | 239 (40.6) | 252 (42.9) | 233 (39.7) | 980 (41.7) | .485 |
| Diuretics | 370 (63) | 353 (60) | 371 (63.1) | 385 (65.6) | 1479 (62.9) | .272 |

ADHF, acute decompensated heart failure; DM, diabetes mellitus; DPB, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HF, heart failure; hs-CRP, high-sensitivity C-reactive protein; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; RASi, renin-angiotensin-system inhibitors; RDW, red cell distribution width; SBP, systolic blood pressure; TAPSE, tricuspid annular plane systolic excursion.
Data presented as No. (%), mean ± standard deviation, or median [Q1-Q3].

≥ 65%). Continuous variables are presented as mean ± standard deviation or median (percentile 25% to percentile 75%), and their differences across LVEF quartiles were tested using ANOVA or Kruskal-Wallis tests. Discrete variables were presented as numbers (percentages), and differences were examined using the chi-square test. The multivariable relationship between hs-CRP along the continuum of LVEF and < 65% vs ≥ 65% was examined through multivariate linear regression analysis and logistic regression, respectively. Candidate covariates included in the multivariate models were based on biological plausibility. The linearity assumption for all continuous variables was simultaneously tested, and the variable transformed, if appropriate, with fractional polynomials. The contribution of the covariates to the variability of the linear regression model was evaluated by R-square, and the discriminative ability of the multivariate model was assessed by the area under the receiver operating characteristic curve. The final models included the

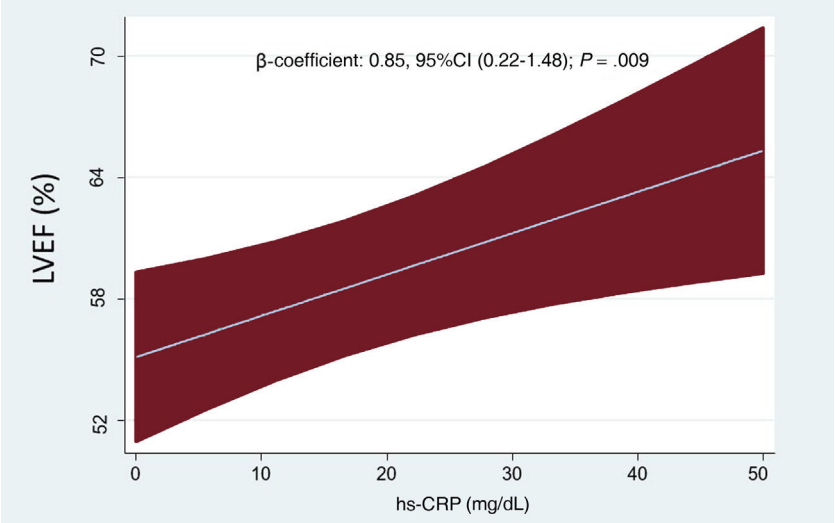


**Figure 1.** Relationship between hs-CRP and LVEF. 95%CI, 95% confidence interval; hs-CRP, high-sensitivity C-reactive protein, LVEF, left ventricular ejection fraction.

following covariates: age, sex, first admission, prior stable New York Heart Association (NYHA) class, ischemic heart disease, Charlson comorbidity index, systolic and diastolic blood pressure, heart rate, atrial fibrillation, creatinine, N-terminal pro-B-type natriuretic peptide (NT-proBNP), left atrial diameter, left ventricular end-diastolic diameter, and tricuspid annular plane systolic excursion (TAPSE).

The mean age was 76.7 ± 9.7 years, and 1458 patients (62%) were women. The proportion of patients with ischemic heart disease was 25%. The mean LVEF was 62 ± 7%, and 876 (37.3%) showed LVEF ≥ 65%. The median of hs-CRP on admission was 19.7 mg/dL (10.5-37.9). Baseline characteristics across LVEF quartiles are presented in table 1. Patients in the upper quartiles of LVEF were more frequently women and were less likely to have a history of ischemic heart disease. Likewise, they showed lower heart rate, diastolic blood pressure, NT-proBNP, and left ventricular end-diastolic diameters. Conversely, these patients showed a higher proportion of NYHA class III/IV before admission, higher TAPSE, and higher hs-CRP values. Inferential multivariate linear regression analysis confirmed the significant and positive association between higher hs-CRP and LVEF. This relationship was linear (figure 1). The logistic multivariate regression analysis also confirmed higher hs-CRP as a predictor of LVEF ≥ 65%. Indeed, per each 1 mg/dL increase of hs-CRP, the odds increased by 22% (odds ratio [OR], 1.22, 95% confidence interval [95%CI], 1.01-1.48; *P* = .046). The R-square (linear regression) and the area under the receiving operating curve (logistic regression) were 0.33 and 0.706, respectively.

Following the comorbidity-inflammation paradigm in HFpEF, the current work shows a significant association between higher LVEF levels and higher hs-CRP values in AHF. This paradigm postulates that a greater comorbidity burden will induce systemic vascular inflammation, leading to endothelial dysfunction, myocardial fibrosis, high diastolic stiffness, and clinical HF.[4] We postulate that the greater comorbidity burden and immunoinflammatory activation increases oxygen demand and that the heart will initially compensate by increasing systolic function. As the situation advances, encompassing increased myocardial fibrosis, this compensatory mechanism will prove insufficient, leading to progression of HF.

Our study has several limitations. First, this is a retrospective single-center study and extrapolation of the current findings to other scenarios requires confirmation. Second, we did not explore the association between higher HFsnEF and hs-CRP values and adverse clinical outcomes. Third, we excluded patients with infections on admission; however, we cannot exclude subclinical infection or other proinflammatory confounders. Fourth, we had no data on weight, height, cytokines, other acute-phase reactants, liver function, coagulation, or troponins in any of the patients. Finally, with the current data, we cannot infer causality or unravel the biological mechanisms behind it.

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## ETHICAL CONSIDERATIONS

The study conformed to the principles outlined in the Declaration of Helsinki and was approved by the local ethics committee (*Hospital Clínico Universitario de Valencia*). All patients previously gave informed consent. SAGER guidelines have been considered.

## STATEMENT ON THE USE OF ARTIFICIAL INTELLIGENCE

No artificial intelligence tool was used in the preparation of this work.

## AUTHORS' CONTRIBUTIONS

The authors have no other funding, financial relationships, or conflicts of interest to disclose relative to this work.

## CONFLICTS OF INTEREST

None.

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## Assessing the accuracy of ChatGPT as a decision support tool in cardiology

### *Evaluación de la fiabilidad de ChatGPT como herramienta de soporte a la toma de decisiones en cardiología*

**To the Editor,**

ChatGPT, an artificial intelligence dialogue-based language model, has generated strong expectations worldwide due to its surprising ability to convincingly answer complex queries formulated in plain natural language. It has been used in a wide variety of fields, including education, computer programming, and journalism, with potentially paradigm-shifting results. The medical community is no exception. ChatGPT has successfully passed the exams required to obtain a medical license,[1] draft scientific abstracts,[2] and compose complete medical reports.[3] In cardiology, the bot has provided appropriate cardiology-related assistance for common cardiovascular conditions in simulated patients[4] and has outperformed medical students in standardized cardiovascular tests.[5]

In light of the above, there is a strong temptation to try ChatGPT out as a decision-support tool in real-world clinical data. However, it is important to ask whether ChatGPT is able to process real-world medical records and suggest appropriate treatment. Most of the current literature focuses on its application in "synthetic" databases with highly preprocessed, curated texts, and/or multiple-choice answers.[1–6] Real-world accuracy cannot be directly inferred from those settings. To answer this question, we assessed the agreement between ChatGPT and a heart team consisting of cardiologists and cardiac surgeons in a specific use case: the decision-making process in patients with severe aortic stenosis.

We performed a descriptive retrospective analysis of the medical records of 50 consecutive patients with aortic stenosis presented at a heart team meeting of our institution between January 1, 2022 and February 14, 2022 (these dates were chosen to guarantee that information on the patients' eventual treatment was available). Depending on a wide variety of variables, the treatment of these patients consisted of the following options: *a)* surgical valve replacement; *b)* percutaneous valve implant; or *c)* medical treatment. The management strategies of the heart team were compared with those recommended by ChatGPT. An anonymized summary of each patient's status was produced by a cardiologist, who copy-pasted together the following sections from the electronic health record: demographics, past medical history, echocardiogram, coronary angiogram, symptoms, and diagnosis. During the second half of February 2023, this information was entered 3 times as a prompt in ChatGPT (GPT-3.5, 13 February 2023 version) as part of an enquiry about the optimal treatment. Initially, the question was "What is the best treatment for this patient?", but the responses of ChatGPT were too comprehensive and included medications and interventions for any concurrent comorbidities in the test patient. Therefore, the final prompt used for the experiments was "What is the best treatment for the aortic stenosis in the following patient?" to elicit a focused response that would facilitate data interpretation, labeling, classification, and processing. No further changes to the prompt were necessary to obtain meaningful answers. Responses were codified as *a)* surgery; *b)* transcatheter aortic valve implantation (TAVI); *c)* medical treatment; *d)* undefined intervention (ChatGPT recommended aortic valve replacement but did not specify whether the approach should be surgical or percutaneous); or *e)* inconclusive. The results were classified according to the following definitions:

- *Fully consistent*: all 3 responses recommended exactly the same treatment.
- *Partially consistent*: all 3 responses recommended a similar approach (intervention vs medical treatment).
- *Full agreement*: fully consistent response that matched the heart team's assessment.
- *Agreement on approach*: fully or partially consistent response that matched the heart team's "intervention vs medical treatment" assessment.

Figure 1 shows the results in detail. The mean age was 78 years, and 41% were men. The heart team's decision was TAVI in 56%, surgery in 40%, and medical treatment in 4% of cases. Of 150 responses generated by ChatGPT, 14 (9%) were inconclusive. A total of 70% of ChatGPT's recommendations were at least partially consistent and 38% were fully consistent. There was *agreement on approach* in 58% of the cases but *full agreement* in only 18% of cases. Fifteen recommendations were inconsistent and 6 recommendations that were consistent diverged from the heart team's decision, representing a total of 21 errors. Of these 21 cases, 10 (48%) had other concomitant valve or coronary artery disease requiring intervention, 4 (19%) were cases in which the indications