

Original Research

Plasma Steroids as Biomarkers of Congestion and Predictors of Prognosis in Acute Heart Failure During the Vulnerable PhaseYangkai Fan^{1,2,†}, Jing Cui^{1,2,†}, Lu Ren^{1,2}, Xin Tan^{1,2}, Weiyao Chen³,
Yuan Wang^{1,2,*}¹Beijing Collaborative Innovation Centre for Cardiovascular Disorders, The Key Laboratory of Remodeling-Related Cardiovascular Disease, Ministry of Education, Beijing Anzhen Hospital, Capital Medical University, 100029 Beijing, China²Beijing Institute of Heart, Lung, and Blood Vessel Diseases, 100029 Beijing, China³Department of Nutrition, The First Affiliated Hospital of Sun Yat-sen University, 510080 Guangzhou, Guangdong, China*Correspondence: wangyuan980510@163.com (Yuan Wang)

†These authors contributed equally.

Academic Editor: Jan Slezak

Submitted: 28 April 2026 Revised: 6 June 2026 Accepted: 15 June 2026 Published: 21 July 2026

Abstract

Background: Patients with heart failure (HF) are at high risk of mortality and readmission during the 90-day “vulnerable phase” post-discharge, often because of persistent congestion. However, tools effective for assessing risk are lacking. Thus, this study aimed to develop a steroid-based congestion score from the plasma steroid profile and determine the associated prognostic value during the vulnerable phase in patients with acute HF. **Methods:** Plasma levels of 18 steroids were measured by liquid chromatography–tandem mass spectrometry in patients from the Registry Study of Biomarkers in Heart Failure. Patients were divided into a discovery cohort for biomarker screening and model development ($n = 691$), a cohort for validation of prognostic value (validation cohort 1, $n = 267$), and a cohort with paired discharge and 90-day plasma samples available for assessment of dynamic changes in biomarkers (validation cohort 2, $n = 46$). Steroids independently associated with the clinical congestion score (CCS) were identified by correlation analysis and multivariable logistic regression and were used to construct the “steroid-based” congestion score (SCS). The 90-day prognostic value of the SCS was assessed using Cox regression, and the incremental predictive ability of the SCS was quantified using integrated discrimination improvement. **Results:** The SCS included cortisol, dehydroepiandrosterone sulfate, and pregnenolone. In the discovery cohort, an $SCS \geq -0.563$ was associated with a 2.02-fold increase in the risk of the 90-day composite endpoint of all-cause death and HF readmission (95% confidence interval, 1.42–2.88). Adding the SCS to clinical, B-type natriuretic peptide, and clinical congestion score model increased the integrated discrimination improvement by 1.2%, 0.8%, and 1.0%, respectively (all $p < 0.05$). The prognostic value of the SCS for 90-day and long-term outcomes was confirmed in validation cohort 1. In validation cohort 2, a higher baseline SCS was associated with higher 90-day congestion rates, and SCS dynamics paralleled congestion progression. **Conclusions:** The SCS independently predicts adverse outcomes during the vulnerable phase in patients with HF, offering incremental prognostic value beyond traditional indicators and potentially supporting dynamic monitoring for individualized management.

Keywords: heart failure; prognosis; steroids**1. Introduction**

Heart failure (HF) remains a major public health challenge, imposing a significant burden on healthcare systems worldwide owing to its high mortality and readmission rates [1,2]. Studies have shown that within 60–90 days post-discharge, all-cause mortality and readmission rates can reach as high as 15% and 30%, respectively. This period is recognized as the “vulnerable phase” for patients with HF and is characterized by a peak incidence of adverse clinical outcomes [3,4,5,6].

Although in-hospital treatment can alleviate the acute symptoms of HF, many patients are discharged with persistent hemodynamic abnormalities, namely, ongoing or subclinical congestion [6,7]. This hemodynamic disturbance is considered a core pathophysiological mechanism driving death and readmission rates during the vulnerable phase

[6]. Elevated left ventricular filling pressure, a hallmark of congestion, can lead directly to recurrence or worsening of symptoms such as dyspnea and edema. Therefore, accurate identification of individuals at high risk for adverse events as a result of residual hemodynamic congestion upon discharge is necessary for implementation of effective interventions during this critical window and to improve the patient’s prognosis.

However, routine clinical assessment (e.g., physical examination) has limited sensitivity for detecting subclinical congestion. While classical biomarkers such as B-type natriuretic peptide (BNP) are widely used, their interpretation can be influenced by age, renal function, and obesity; moreover, they primarily reflect myocardial wall stress and may not fully capture the complex neurohormonal and metabolic disturbances underlying congestion [8,9,10,11].



Therefore, there is a need for novel biomarkers that better reflect the hemodynamic state during the vulnerable phase in patients with HF.

Steroid hormones are a class of fat-soluble molecules that are synthesized from cholesterol through a series of enzymatic reactions and form a complex and tightly regulated network [12]. Clinical and basic research suggests that dysregulation of steroid hormone metabolism is closely linked to hemodynamic alterations in HF. In cardiometabolic risk states such as obesity and diabetes, local glucocorticoid metabolism may be altered through dysregulated steroid-converting enzymes, particularly 11 β -hydroxysteroid dehydrogenase type 1 [13]. Dysregulation of mineralocorticoids (e.g., aldosterone) and glucocorticoids (e.g., cortisol) can promote sodium and water retention, increase plasma volume, thereby exacerbating cardiac load [14,15]. Furthermore, corticosteroid receptors on vascular smooth muscle can influence ion channels, mediating left ventricular systolic and diastolic dysfunction [16]. Androgens can also directly impact ventricular remodeling and function through receptors on cardiomyocytes [17]. Collectively, these mechanisms may ultimately contribute to or worsen hemodynamic deterioration in patients with HF.

We hypothesized that the plasma steroid hormone profile could better reflect the hemodynamic state during the vulnerable phase of HF than any single hormone, enabling early identification of high-risk individuals. In this study, we used a metabolomics approach to identify specific steroid hormones associated with the clinical congestion score (CCS) and constructed a steroid-based congestion score (SCS). We then evaluated the prognostic value of the SCS for all-cause mortality and readmission for HF, both individually and as a composite endpoint, within 90 days post-discharge (the vulnerable phase) in a discovery cohort and two independent validation cohorts. We also explored the incremental prognostic value of the SCS over traditional clinical parameters and BNP. Our findings indicate that the SCS is an independent and robust prognostic marker, potentially offering a novel strategy for risk stratification and personalized management during the vulnerable phase of HF.

2. Materials and Methods

2.1 Study Design and Population

This study prospectively enrolled consecutive patients hospitalized with acute heart failure (AHF) at Beijing Anzhen Hospital, Capital Medical University, from May 2017 to November 2022, who were part of the BIOMS-HF cohort (NCT03784833, <https://clinicaltrials.gov/study/NCT03784833>). Written informed consent was obtained from all participants prior to enrollment. The study protocol was approved by the ethics committee of Beijing Anzhen Hospital, Capital Medical University (approval number: [2016037X]), and all procedures were conducted in accordance with the

Declaration of Helsinki. The study inclusion criteria were based on current guidelines for the diagnosis and management of AHF and our previously published registry cohort (BIOMS-HF) [18,19,20]. The study inclusion criteria were as follows: age ≥ 18 years; diagnosis of AHF based on symptoms and signs of dyspnea at rest or on minimal exertion (orthopnea, paroxysmal nocturnal dyspnea, acute pulmonary edema), pulmonary rales, peripheral edema, and/or elevated jugular venous pressure, with pulmonary congestion confirmed by chest radiography; and plasma BNP ≥ 100 pg/mL or N-terminal proBNP ≥ 300 pg/mL. In the present study, all enrolled patients had BNP measured at admission; NT-proBNP was not used. The patients were divided according to the phase of the study into a discovery cohort ($n = 691$) for biomarker screening and model development and two validation cohorts (validation cohort 1, $n = 267$ and validation cohort 2, $n = 46$) for validation of prognostic value and assessment of dynamic changes in biomarker levels, respectively. CCS was assessed at admission based on physical examination findings. Blood samples were collected after an overnight fast on the morning after admission in all cohorts. In validation cohort 2, additional blood samples were obtained at discharge and at the 90-day follow-up. The plasma was stored at -80°C until analysis. Discharge CCS was recorded but was not included in the primary prognostic models, as the main analysis focused on admission CCS, it was used only to describe reconnection dynamics in validation cohort 2.

2.2 Clinical Congestion Score and Outcomes

The CCS was calculated based on findings on physical examination at admission. This score ranges from 0 to 3 (<1 , no/mild congestion; 1 to <2 , moderate congestion; ≥ 2 , significant congestion) [21,22]. The primary outcomes were all-cause mortality and readmission for HF individually and as the composite endpoint during the 90-day vulnerable phase of HF. Readmission for HF was defined as an unplanned emergency department visit or hospitalization related to worsening HF. Patient outcomes were ascertained by telephone follow-up or from information in the electronic medical records. The median follow-up for validation cohort 1 was 376 days [interquartile range 38, 567], which allowed assessment of the prognostic value of the SCS for long-term outcomes.

2.3 Measurement of Steroid Hormones and Score Construction

The plasma concentrations of 18 steroid hormones were quantified using liquid chromatography–tandem mass spectrometry. The LC-MS/MS system consisted of a Waters Xevo TQ-S system (Waters Corporation, Milford, MA, USA), equipped with an ACQUITY UPLC[®] Peptide BEH C8 column (1.7 μm , 2.1 mm $\times$ 100 mm; Waters Corporation, Milford, MA, USA). Steroid standards (18 analytes) and internal standards (testosterone- $^{13}\text{C}_3$,

DHEAS-d₆, 11-deoxycortisol-d₅, dihydrotestosterone-d₄, and DHEA-d₅) were purchased from Sigma (St. Louis, MO, USA). Internal standards (androstenedione-¹³C₃, cortisol-d₄, pregnenolone-d₄, 17-hydroxypregnenolone-¹³C₂-d₂, progesterone-d₉, estrone-d₄, estradiol-d₄, and aldosterone-d₈) were obtained from Cambridge Isotope Laboratories (Tewksbury, MA, USA). Internal standards (17-hydroxypregnenolone-d₈, cortisone-d₈, estriol-d₃, corticosterone-d₈, and deoxycorticosterone-d₇) were from Toronto Research Chemicals (Toronto, ON, Canada). For samples below the lower limit of detection, the concentration was imputed as the limit of detection value. The proportion of such imputed values for each steroid in the discovery cohort is reported in **Supplementary Table 1**. To assess the impact of this single imputation approach, we performed sensitivity analyses using four different strategies: (1) limit of detection (LOD) imputation (primary); (2) LOD/2; (3) LOD/√2; and (4) complete-case analysis (excluding all samples below the LOD). The LOD/2 and LOD/√2 methods are common ad-hoc substitution approaches that have been recommended for handling non-detects in biomarker studies [23,24]. Congestion-related steroid hormones were screened for in the discovery cohort using (1) Spearman correlation analyses of steroid hormone levels, CCS, and key clinical parameters (e.g., BNP, creatinine, heart rate) and (2) multivariable logistic regression analysis with CCS category as the dependent variable. Steroids with a Spearman $p < 0.05$ versus continuous CCS were selected for further analysis. Three hormones met this criterion: dehydroepiandrosterone sulfate (dehydroepiandrosterone sulfate (DHEAS); $\rho = -0.13$, $p = 0.001$), pregnenolone ($\rho = 0.12$, $p = 0.001$), and cortisol ($\rho = 0.11$, $p = 0.004$). The level of each hormone was normalized to the Z-score. The weight of association (regression coefficient) of each hormone with congestion status (CCS ≥ 1) was obtained from the logistic regression model. The SCS was calculated using the following formula:

$$\text{SCS} = -0.7716 + (0.2686 \times Z_{\text{cortisol}}) - (0.2004 \times Z_{\text{DHEAS}}) - (0.0131 \times Z_{\text{pregnenolone}}).$$

2.4 Statistical Analysis

Continuous variables are expressed as the mean $\pm$ standard deviation or median [interquartile range] and were compared between cohorts using analysis of variance or the Kruskal–Wallis test. Categorical variables are shown as the frequency (percentage) and were compared between cohorts using the chi-squared test. To evaluate the prognostic value of the SCS, we used Cox proportional hazards regression models to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for 90-day outcomes, with the SCS treated as a continuous variable or categorized by its optimal cut-off value. The optimal cut-off value was determined using “maximally selected rank statistics” based on its performance as a predictor of the 90-day composite endpoint [25]. Kaplan–Meier curves were generated,

and differences in survival were examined using the log-rank test. Four baseline models were constructed to assess the incremental prognostic value of the SCS: (1) a clinical model using variables selected by stepwise regression; (2) a BNP model comprising log-transformed BNP only; (3) a CCS model based on CCS category; and (4) a high-sensitivity troponin I (hs-TnI) model. For the baseline clinical model, variable selection was performed using akaike information criterion (AIC)-based bidirectional stepwise regression from a candidate variable pool. The final model included the following covariates: age, male sex, systolic blood pressure (SBP), heart rate, body mass index (BMI), creatinine (Cr), angiotensin-converting enzyme (ACE) inhibitor/angiotensin receptor blocker (ARB) use, and diuretic use. Improvement in model performance upon adding the SCS was quantified by changes in the area under the curve, net reclassification improvement, and integrated discrimination improvement (IDI). Subgroup analyses of factors that included age, sex, comorbidities, left ventricular ejection fraction (LVEF), and use of diuretics were performed in pre-defined subgroups, and interactions between the SCS and these subgroups were tested. Decision curve analysis was used to evaluate the net clinical benefit of the SCS. To assess the risk of overfitting and correct for optimism, we performed internal validation within the discovery cohort, including 500 iterations of bootstrap resampling and 10-fold cross-validation. In each bootstrap iteration, the optimal cut-off was re-estimated using maximally selected rank statistics, and the 95% confidence interval was derived from the bootstrap distribution. For 10-fold cross-validation, the discovery cohort was randomly split into 10 equal folds; in each round, 9 folds were used for model training and the remaining fold for evaluating out-of-fold log-rank p values and C-index. Calibration was assessed by plotting predicted versus observed event probabilities, with optimism correction using bootstrap. The optimism-corrected C-index was calculated as the apparent C-index minus the mean optimism estimated from 500 bootstrap resamples. All statistical analyses were performed using R (version 4.0.2; R Foundation for Statistical Computing, Vienna, Austria). All tests were two-sided, and a p -value of < 0.05 was considered statistically significant.

3. Results

3.1 Baseline Characteristics

The study flow diagram is shown in Fig. 1. The 691 patients with AHF in the discovery cohort were categorized by CCS into three groups: $0 \leq \text{CCS} < 1$ (no/mild congestion, $n = 470$), $1 \leq \text{CCS} < 2$ (moderate congestion, $n = 195$), and $\text{CCS} \geq 2$ (significant congestion, $n = 26$). Higher CCS grades were associated with significantly greater severity of HF and characterized by higher proportions of New York Heart Association functional class III/IV, higher BNP, more prevalent signs and symptoms of con-

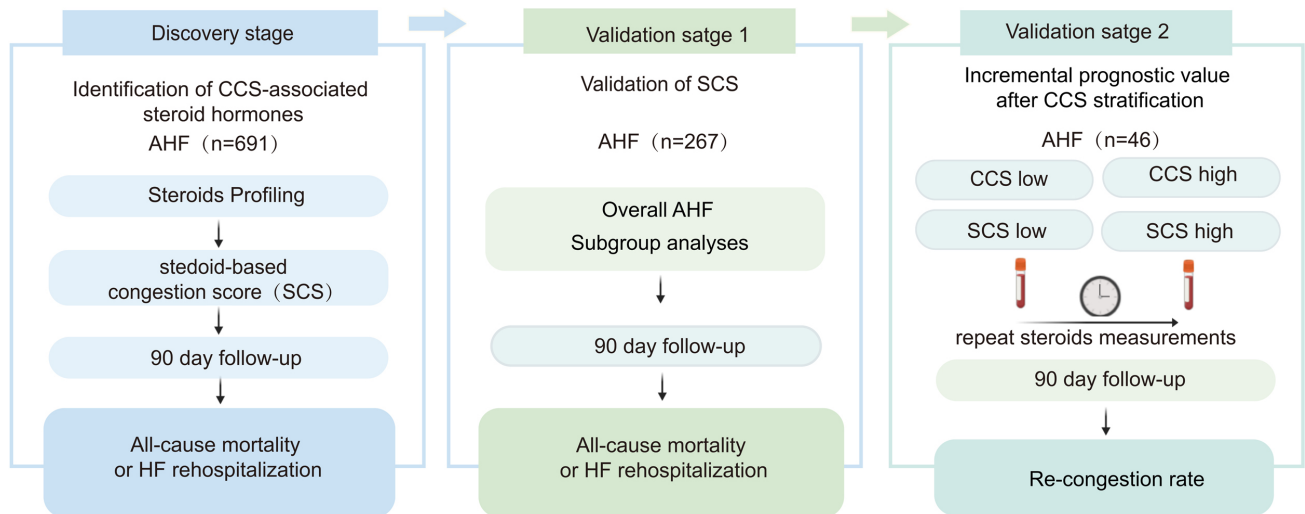


Fig. 1. Study design and flow chart. The study was divided into three stages. The first was a discovery stage ($n = 691$), in which steroid hormones associated with the clinical congestion score (CCS) were identified and used to construct the steroid-based congestion score (SCS). The second was a validation stage 1 ($n = 267$), in which the prognostic value of the SCS for 90-day and long-term outcomes was evaluated. The third was a validation stage 2 ($n = 46$), during which the association between the SCS at baseline and the re-congestion rate at 90 days was assessed by repeated steroid measurements. AHF, acute heart failure.

gestion (orthopnea, edema, hepatomegaly, ascites, elevated jugular venous pressure), worse renal function (higher creatinine, lower estimated glomerular filtration rate), and more pronounced electrolyte imbalance, including hyponatremia and hyperkalemia (all $p < 0.05$, Table 1). Baseline medications at admission in the discovery cohort are also summarized in Table 1; the most commonly prescribed drugs were diuretics (70.8%), β -blockers (61.9%), spironolactone (50.4%), and ACEi/ARB (26.6%).

Among the 18 steroids measured in plasma, cortisol levels increased significantly with higher CCS, while DHEAS levels decreased significantly ($p < 0.05$), suggesting a monotonic relationship between these two hormones and severity of congestion. Notably, pregnenolone levels showed a non-linear pattern, increasing from 1.43 ng/mL to 2.10 ng/mL in the group with no/mild or moderate congestion ($\text{CCS} < 2$) and decreasing to 1.00 ng/mL in the group with significant congestion ($\text{CCS} \geq 2$). This initial increase followed by a decrease suggests that pregnenolone, as a precursor for all steroid hormones, may be elevated in the early stages of congestion in a compensatory manner but becomes depleted as a result of synthetic exhaustion when congestion becomes severe.

3.2 Steroid Hormones Associated with the Clinical Congestion Score

Correlation analysis in the discovery cohort revealed that several steroid hormones were significantly associated with the CCS (Fig. 2). As shown in **Supplementary Table 1**, the three steroids comprising the SCS had very low proportions of values below the LOD (cortisol 0.72%, DHEAS 0.43%, pregnenolone 0%). Notably, cortisol showed a sig-

nificant positive correlation with the CCS ($r = 0.11$, $p = 0.004$) and the DHEAS demonstrated a significant negative correlation ($r = -0.13$, $p = 0.001$). These findings are consistent with the monotonic trends observed in Table 1. Pregnenolone showed a significant positive correlation with the CCS ($r = 0.12$, $p = 0.001$), primarily reflecting the progression from no/mild to moderate congestion; however, the decrease in the significant congestion group may not have been fully captured in the linear correlation analysis because of the small sample size ($n = 26$). There was a potential non-linear relationship between pregnenolone and the severity of congestion, consistent with the pattern of an initial increase followed by a decrease observed in Table 1.

Notably, aldosterone showed a weak correlation with CCS that was not statistically insignificant. From the perspective of the steroid metabolic network, the hormones significantly associated with CCS, namely, pregnenolone (a synthetic precursor), cortisol (a glucocorticoid), and DHEAS (an androgen precursor), represent key nodes in different branches of the steroidogenesis pathway. This finding suggested that metabolic reprogramming of steroids in the congestive state may involve a dynamic imbalance between the synthetic reserve upstream and the stress/sex hormone axes downstream.

Furthermore, the levels of these CCS-related hormones correlated consistently with the values for other markers of severity of HF. For example, the cortisol level correlated positively with heart rate ($r = 0.18$, $p < 0.001$) and negatively with serum sodium ($r = -0.11$, $p = 0.003$), pregnenolone correlated positively with hemoglobin ($r = 0.33$, $p < 0.001$), and DHEAS correlated positively with both heart rate ($r = 0.22$, $p < 0.001$) and hemoglobin ($r = 0.36$, $p < 0.001$).

Table 1. Baseline clinical characteristics in the discovery cohort according to the clinical congestion score.

	No/mild congestion 0 ≤ CCS < 1 (n = 470)	Moderate congestion 1 ≤ CCS < 2 (n = 195)	Significant congestion CCS ≥ 2 (n = 26)	<i>p</i> value
Demographics				
Age, years	62.5 (14.2)	63.1 (14.3)	59.8 (15.5)	0.532
Male sex (n, %)	300 (63.8%)	131 (67.2%)	17 (65.4%)	0.711
BMI, kg/m ²	24.4 (5.81)	25.2 (5.54)	25.2 (4.39)	0.305
NYHA class III/IV (n, %)	314 (66.8%)	168 (86.2%)	25 (96.2%)	<0.001
Smoking (n, %)	115 (24.5%)	64 (32.8%)	3 (11.5%)	0.018
Vital signs				
Heart rate, beats/min	80.8 (18.8)	83.9 (18.6)	82.5 (18.3)	0.146
SBP, mm Hg	123 (20.1)	124 (21.5)	129 (21.2)	0.304
DBP, mm Hg	72.7 (13.2)	74.4 (14.3)	71.4 (12.0)	0.273
Clinical profile (n, %)				
Orthopnea	0 (0.00%)	162 (83.1%)	23 (88.5%)	<0.001
Oedema	76 (16.2%)	72 (36.9%)	22 (84.6%)	<0.001
Cardiac murmur	137 (29.1%)	58 (29.7%)	11 (42.3%)	0.361
Hepatomegaly	16 (3.40%)	14 (7.18%)	6 (23.1%)	<0.001
Ascites	7 (1.49%)	6 (3.08%)	3 (11.5%)	0.009
Rales	113 (24.0%)	95 (48.7%)	13 (50.0%)	<0.001
Jugular venous pressure	0 (0.00%)	16 (8.21%)	13 (50.0%)	<0.001
Echocardiography				
LVEF, %	46.5 (14.8)	41.3 (14.1)	46.0 (15.7)	<0.001
E/A	1.42 (1.18)	1.62 (1.19)	1.69 (1.13)	0.099
IVST, mm	10.1 (3.99)	10.2 (2.63)	11.7 (12.0)	0.195
LVEDD, mm	55.7 (10.8)	58.4 (11.7)	55.3 (9.81)	0.015
LVESD, mm	41.7 (12.2)	45.4 (13.2)	41.0 (11.0)	0.002
Laboratory				
BNP, pg/mL	566 [330; 1088]	833 [439; 1518]	881 [569; 1632]	<0.001
Hemoglobin, g/L	131 (24.0)	131 (23.3)	119 (27.8)	0.05
HDL, mmol/L	1.09 (0.72)	1.02 (0.77)	1.04 (0.39)	0.499
LDL, mmol/L	2.50 (0.87)	2.44 (0.87)	2.29 (0.76)	0.38
Na, mmol/L	139 (3.85)	138 (4.56)	137 (5.71)	0.001
K, mmol/L	4.21 (0.53)	4.22 (0.62)	4.58 (0.63)	0.005
Cr, μmol/L	83.6 [67.7; 113]	99.7 [76.8; 135]	99.1 [79.6; 206]	<0.001
Medical history (n, %)				
Diabetes	146 (31.1%)	83 (42.6%)	7 (26.9%)	0.013
Hypertension	249 (53.0%)	117 (60.0%)	16 (61.5%)	0.204
Hyperlipidemia	172 (36.6%)	83 (42.6%)	10 (38.5%)	0.354
Coronary artery disease	230 (48.9%)	105 (53.8%)	14 (53.8%)	0.484
Valvular disease	220 (46.8%)	78 (40.0%)	9 (34.6%)	0.162
Baseline medications (n, %)				
ACEi/ARB	123 (26.2%)	54 (27.7%)	7 (26.9%)	0.921
Beta-blockers	286 (60.9%)	126 (64.6%)	16 (61.5%)	0.66
Spironolactone	232 (49.4%)	108 (55.4%)	8 (30.8%)	0.046
Diuretics	337 (71.7%)	134 (68.7%)	18 (69.2%)	0.732
Digoxin	116 (24.7%)	53 (27.2%)	6 (23.1%)	0.768
ARNI	65 (13.8%)	39 (20.0%)	3 (11.5%)	0.122
Steroids(ng/mL)				
Estrone	0.005 [0.005; 0.054]	0.005 [0.005; 0.063]	0.005 [0.005; 0.062]	0.38
Estradiol	0.02 [0.01; 0.03]	0.02 [0.01; 0.03]	0.01 [0.01; 0.02]	0.544
Estriol	0.005 [0.005; 0.009]	0.005 [0.005; 0.010]	0.005 [0.005; 0.020]	0.059
17-hydroxypregnenolone	0.44 [0.23; 1.13]	0.48 [0.20; 1.23]	0.27 [0.19; 0.51]	0.168
Dehydroepiandrosterone	0.98 [0.51; 2.10]	0.97 [0.48; 1.92]	0.49 [0.38; 1.25]	0.098

Table 1. Continued.

	No/mild congestion 0 ≤ CCS < 1 (n = 470)	Moderate congestion 1 ≤ CCS < 2 (n = 195)	Significant congestion CCS ≥ 2 (n = 26)	p value
Androstenedione	0.53 [0.34; 0.86]	0.63 [0.40; 1.11]	0.49 [0.30; 0.78]	0.011
Testosterone	1.27 [0.18; 3.30]	1.84 [0.25; 3.59]	0.68 [0.15; 2.97]	0.054
Dihydrotestosterone	0.18 [0.06; 0.38]	0.18 [0.07; 0.38]	0.14 [0.03; 0.44]	0.908
Pregnenolone	1.43 [0.51; 4.19]	2.10 [0.72; 5.88]	1.00 [0.37; 4.23]	0.003
Progesterone	0.06 [0.04; 0.12]	0.08 [0.05; 0.15]	0.09 [0.04; 0.15]	0.16
11-deoxycorticosterone	0.04 [0.02; 0.09]	0.04 [0.03; 0.10]	0.05 [0.02; 0.08]	0.667
17-hydroxyprogesterone	0.50 [0.26; 0.88]	0.57 [0.28; 0.89]	0.49 [0.18; 1.01]	0.744
Corticosterone	2.46 [1.11; 5.05]	2.58 [1.17; 5.97]	3.04 [1.27; 4.76]	0.727
11-deoxycortisol	0.24 [0.11; 0.55]	0.23 [0.12; 0.70]	0.18 [0.12; 0.40]	0.569
Cortisone	16.7 [12.4; 20.5]	16.5 [11.6; 21.6]	17.1 [13.0; 22.1]	0.966
Cortisol	145 [103; 211]	176 [118; 261]	189 [114; 245]	0.003
DHEAS	704 [302; 1410]	652 [292; 1230]	372 [116; 572]	0.001
Aldosterone	0.08 [0.03; 0.21]	0.07 [0.03; 0.22]	0.08 [0.03; 0.21]	0.92

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; BMI, body mass index; BNP, B-type natriuretic peptide; Cr, creatinine; DBP, diastolic blood pressure; DHEAS, dehydroepiandrosterone sulfate; E/A, E/A ratio; HDL, high-density lipoprotein; LVEF, left ventricular ejection fraction; IVST, interventricular septal thickness; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LDL, low-density lipoprotein; NYHA, New York Heart Association; SBP, systolic blood pressure; CCS, clinical congestion score.

0.001) (Fig. 2, **Supplementary Table 2**). BNP showed weak correlations with most of the steroid hormones, indicating that steroid levels may provide pathophysiological information distinct from BNP.

3.3 Prognostic Value of the SCS for 90-Day Outcomes

After 90 days of follow-up, 161 (23.3%) composite endpoint events occurred in the discovery cohort (73 deaths, 98 readmissions for HF). Using maximally selected rank statistics, the SCS had an optimal cut-off value of -0.563 for prediction of the 90-day composite endpoint.

Kaplan–Meier analysis showed that the cumulative incidences of 90-day all-cause mortality, readmission for HF, and the composite endpoint were significantly higher in patients with an SCS of ≥ -0.563 than in those with an SCS of < -0.563 (Model 1, $p < 0.05$, log-rank test, Fig. 3A). Multivariable Cox regression confirmed that the SCS was an independent predictor of adverse 90-day outcomes, both as a continuous variable and as a categorical variable. After adjusting for age and sex, patients in the high SCS group (≥ -0.563) had a 2.02-fold higher risk of the composite endpoint (Model 2, 95% CI: 1.42–2.88, $p < 0.001$), a 1.96-fold higher risk of all-cause mortality (Model 2, 95% CI: 1.16–3.31, $p = 0.011$), and a 1.95-fold higher risk of readmission for HF (Model 2, 95% CI: 1.24–3.07, $p = 0.004$) than those in the low SCS group. Multivariable Cox regression with progressive adjustment demonstrated that the high SCS group remained independently associated with the composite endpoint after adjustment for established HF risk factors (Model 3: HR = 1.69, 95% CI: 1.18–2.41, p

= 0.004; Model 4: HR = 1.68, 95% CI: 1.17–2.41, $p = 0.005$). For HF rehospitalization, the high SCS group also remained significant in adjusted models (Model 3: HR = 1.66, 95% CI: 1.05–2.61, $p = 0.029$; Model 4: HR = 1.62, 95% CI: 1.02–2.56, $p = 0.041$). However, for all-cause mortality, the association was no longer significant after full adjustment (Model 3: HR = 1.49, 95% CI: 0.87–2.55, $p = 0.144$; Model 4: HR = 1.60, 95% CI: 0.93–2.75, $p = 0.091$), possibly reflecting the limited number of deaths ($n = 73$) or a closer link between SCS and HF rehospitalization (Fig. 3B, **Supplementary Table 3**). Internal validation via bootstrap and 10-fold cross-validation confirmed the stability of the cut-off (**Supplementary Fig. 1A, B**) but showed limited reproducibility of the prognostic signal across subsamples (**Supplementary Fig. 1C**). Calibration was good in apparent analysis (**Supplementary Fig. 1D**) and after bootstrap correction (**Supplementary Fig. 1E**), although out-of-fold calibration indicated mild overfitting (**Supplementary Fig. 1F**). The apparent C-index of 0.680 was optimism-corrected to 0.649 (**Supplementary Fig. 1G**), suggesting genuine but modestly optimistic prognostic value.

3.4 Incremental Predictive Value of the SCS

Fig. 3C demonstrates the incremental predictive value of the SCS beyond the four baseline models. Adding SCS to the baseline clinical model (which includes multiple clinical risk factors) increased the risk of 90-day all-cause mortality, readmission for HF, and the composite endpoint by 51%, 112%, and 88%, respectively, with a significant improve-

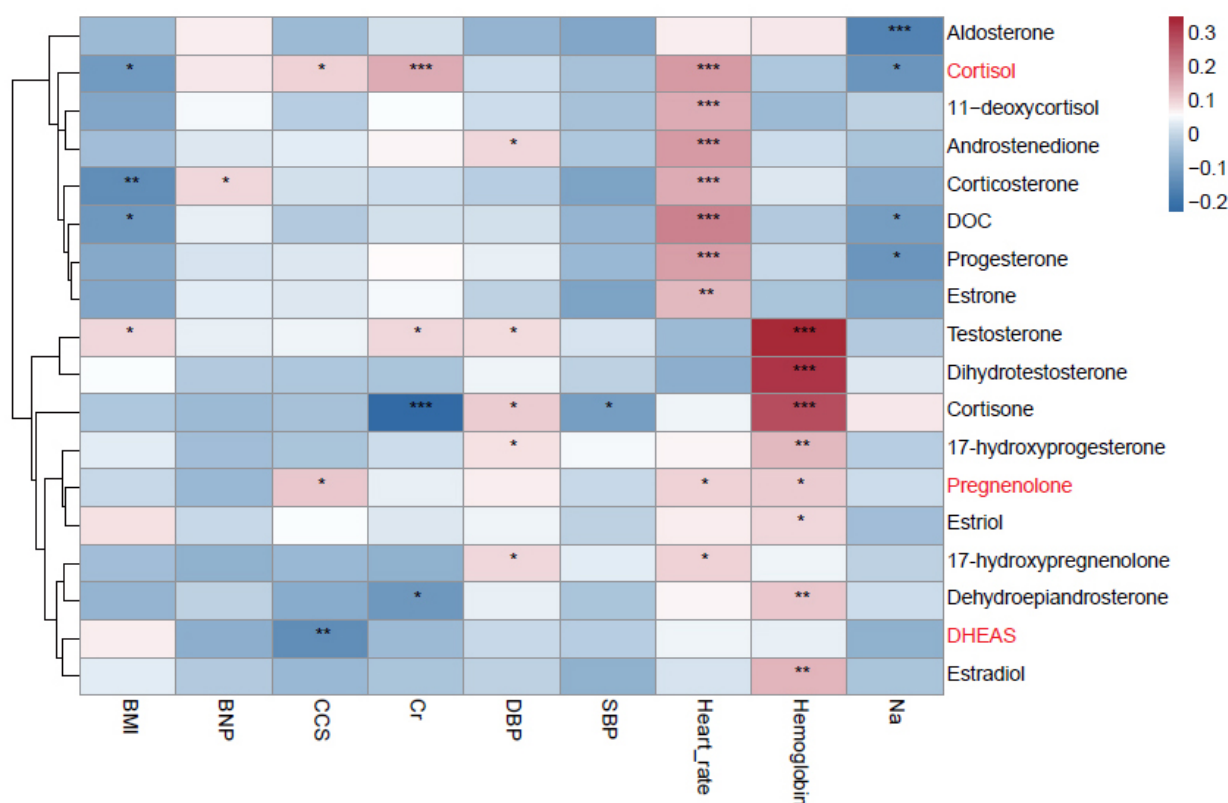


Fig. 2. Correlations of steroid hormones with the clinical congestion score and key clinical parameters in the discovery cohort. Heatmap showing Spearman correlation coefficients for plasma steroid hormones (rows) and selected clinical variables (columns), including the CCS, BNP, Cr, BMI, blood pressure, heart rate, hemoglobin, and sodium. The color scale represents the magnitude and direction of correlation. Asterisks indicate statistical significance (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$). Steroid hormones that were significantly correlated with the CCS (cortisol, DHEAS, and pregnenolone) are in red text. BMI, body mass index; BNP, B-type natriuretic peptide; CCS, clinical congestion score; Cr, creatinine; DBP, diastolic blood pressure; DHEAS, dehydroepiandrosterone sulfate; DOC, 11-deoxycorticosterone; SBP, systolic blood pressure.

ment in the IDI value of 1.2% ($p < 0.05$) and an increase in the Nagelkerke R^2 value from 0.038 to 0.047. Adding SCS to the BNP model increased the risk of readmission for HF and the composite endpoint by 96% and 66%, respectively, with a significant increase in the IDI value of 0.8% ($p < 0.05$). Addition of the SCS to the CCS model increased the risk of readmission for HF and the composite endpoint by 121% and 81%, respectively, with a significant increase in the IDI value of 1.0% ($p < 0.05$). Furthermore, adding SCS to the hs-TnI model increased the risk of the 90-day composite endpoint by 162%, with an IDI of 0.017 (95% CI: 0.013–0.020, $p < 0.001$) and an increase in Nagelkerke R^2 from 0.026 to 0.041. Correlation analysis showed a very weak correlation between SCS and log-hs-TnI (Spearman's $\rho = 0.004$) and a weak correlation between SCS and log-BNP ($\rho = 0.114$), whereas hs-TnI and BNP had a modest correlation ($\rho = 0.211$). These results indicated that the SCS provides incremental prognostic information beyond traditional clinical factors, BNP, and physical examination.

3.5 Validation of the Prognostic Value of the SCS

These findings were successfully validated in validation cohort 1 ($n = 267$). During the 90-day follow-up, 87 (32.6%) composite endpoint events occurred. As in the discovery cohort, patients with an SCS of ≥ -0.563 had significantly higher risks of the 90-day composite endpoint (HR 1.39, 95% CI 1.14–1.70) and all-cause mortality (HR 1.64, 95% CI 1.32–2.04) than those with a low SCS (Fig. 4A, **Supplementary Table 4**). Subgroup analysis confirmed that the prognostic value of the SCS was consistent when stratified by age, sex, hypertension, and diabetes ($p_{\text{interaction}} > 0.05$ for all) (Fig. 4B, **Supplementary Table 4**).

Decision curve analysis demonstrated that addition of the SCS to the baseline clinical model was associated with a greater net clinical benefit across a wide range of threshold probabilities when compared with the baseline clinical model alone (Fig. 4C). Furthermore, incorporating the SCS into the baseline clinical model significantly improved the discriminative ability of the model for the 90-day composite endpoint, with the area under the curve increasing from

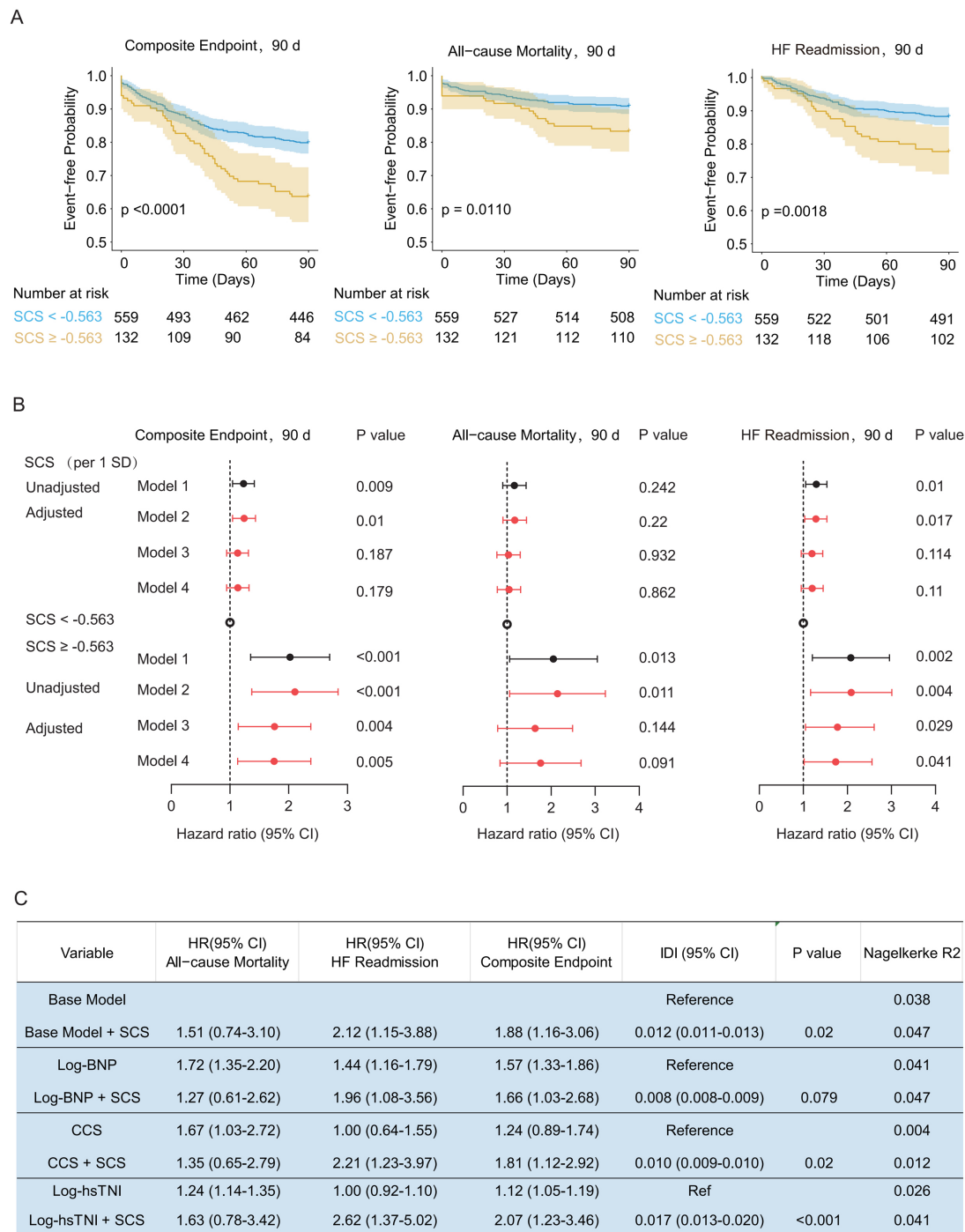


Fig. 3. Prognostic value of the steroid-based congestion score for 90-day outcomes in the discovery cohort. (A) Kaplan–Meier curves for the composite endpoint (all-cause mortality and readmission for HF) according to SCS category (low, SCS <−0.563; high, SCS ≥−0.563). (B) Multivariable Cox regression for 90-day outcomes in the discovery cohort. Model 1: unadjusted. Model 2: adjusted for age and sex. Model 3: adjusted for age, sex, log-transformed BNP, eGFR, sodium, LVEF, NYHA class III/IV, diabetes, loop diuretics, ACEi/ARB, beta-blockers, and spironolactone. Model 4: further adjusted for coronary artery disease, valvular disease, and ARNI. (C) Table showing the increase in risk (i.e., an increase in the HR) for the composite endpoint, all-cause mortality, and readmission for HF, along with improvements in the IDI and Nagelkerke R² values when the SCS is added to the baseline clinical model, BNP model, CCS model and hs-TnI model. BNP, B-type natriuretic peptide; CCS, clinical congestion score; CI, confidence interval; HF, heart failure; HR, hazard ratio; IDI, integrated discrimination improvement; SCS, steroid-based congestion score; hs-TnI, high-sensitivity troponin I; SD, standard deviation; eGFR, estimated glomerular filtration rate.

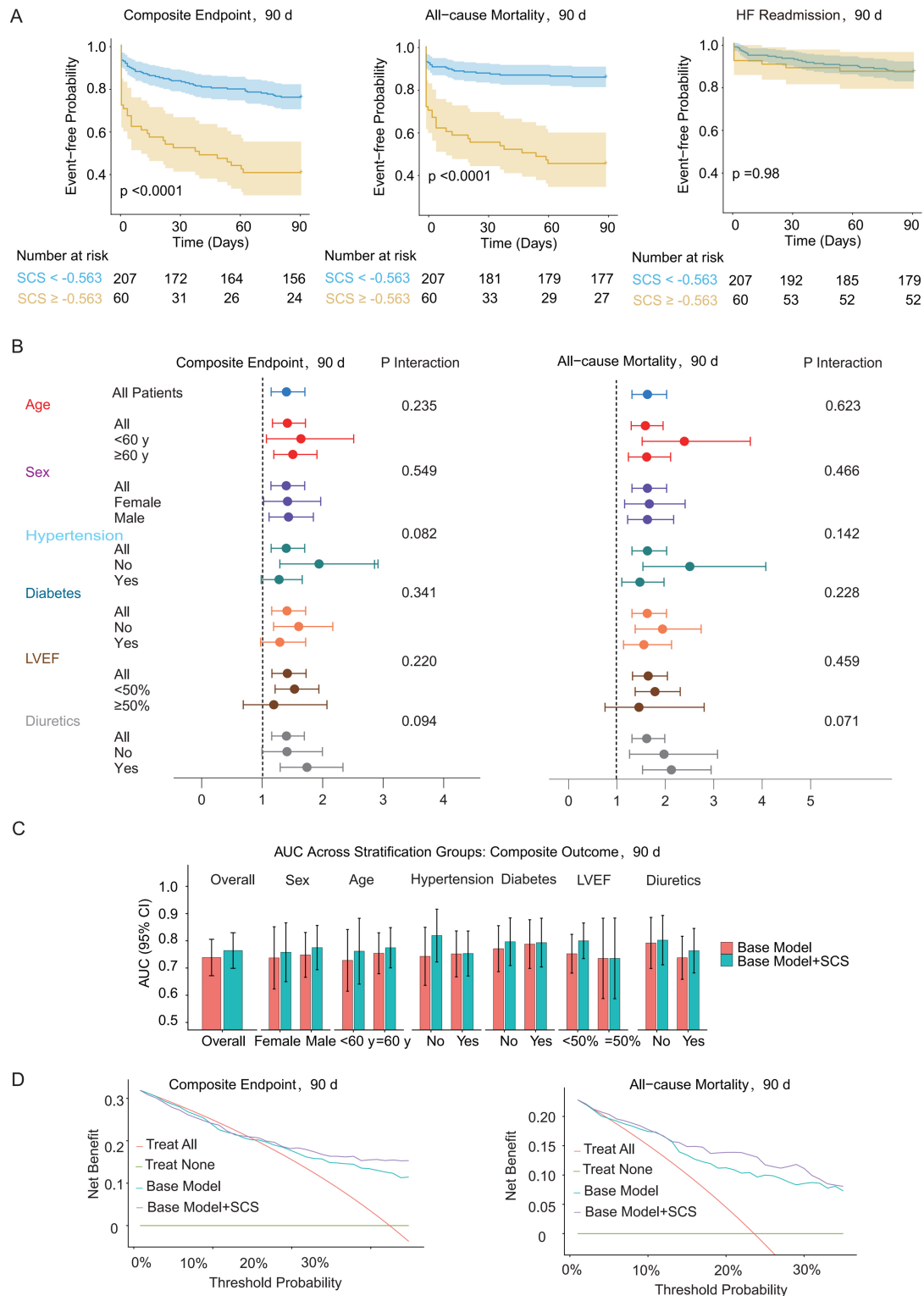


Fig. 4. Validation of the prognostic value of the SCS for 90-day outcomes in validation cohort 1. (A) Kaplan–Meier curves for the composite endpoint according to SCS category. (B) Subgroup analysis for the composite endpoint: forest plot showing hazard ratios (high vs. low SCS) across subgroups based on age, sex, hypertension, diabetes, LVEF, and use of diuretics. p -values for interaction are shown. (C) Discrimination performance (AUC) of the baseline model and the baseline model plus the SCS for the composite endpoint in the overall population and across subgroups. (D) Decision curve analysis for the composite endpoint, comparing the net clinical benefit of the clinical baseline model with and without the SCS. AUC, area under the curve; CI, confidence interval; HF, heart failure; LVEF, left ventricular ejection fraction; SCS, steroid-based congestion score.

0.73 (95% CI 0.67–0.81) to 0.76 (95% CI 0.70–0.83) and a significant IDI value ($p < 0.05$). Exploratory subgroup analyses suggested that this improvement was consistent across subgroups of sex, age, hypertension, diabetes, LVEF, and diuretic use (Fig. 4D, **Supplementary Table 4**); however, the absence of statistically significant interactions does not confirm homogeneous effects across all subgroups, particularly given the limited sample size in some strata.

As shown in **Supplementary Fig. 2** and **Supplementary Table 5**, all four imputation strategies yielded nearly identical effect estimates. In the discovery cohort, the HR (high vs. low) for the 90-day composite endpoint was 1.69 (95% CI: 1.18–2.41) for LOD, LOD/2, and LOD/ $\sqrt{2}$, and 1.75 (95% CI: 1.22–2.51) for complete-case analysis. Similarly consistent results were observed in validation cohort 1. These findings confirm that the single LOD imputation used in the primary analysis did not materially affect the robustness of the SCS.

3.6 Prognostic Value of the SCS for Long-Term Outcomes

In validation cohort 1, during a median follow-up of 376 days [interquartile range 38, 567], 151 (56.5%) composite endpoint events occurred (97 deaths, 79 readmissions for HF). The SCS also demonstrated strong prediction performance for long-term outcomes: the risk of the long-term composite endpoint was nearly double in the group with a high (≥ -0.563) SCS (HR 1.96, 95% CI 1.33–2.90), as were the risks of all-cause mortality (HR 2.02, 95% CI 1.28–3.18), and readmission for HF (HR 1.96, 95% CI 1.24–3.10) (Fig. 5A, **Supplementary Table 6**).

Subgroup analyses revealed higher HR estimates for long-term all-cause mortality in men, patients with an LVEF $< 50\%$, those using diuretics, and those without diabetes. However, all p -values for interaction were > 0.05 (range 0.054–0.419), indicating no statistically significant differences in the prediction performance of the SCS across subgroups according to age, sex, hypertension, diabetes, LVEF, and use of diuretics. These findings indicated that the prognostic value of the SCS for long-term outcomes remained largely consistent across subgroups (Fig. 5B, **Supplementary Table 6**).

We also analyzed the prediction performance of the SCS in validation cohort 2 ($n = 46$) based on tertile for the risk of congestion during the vulnerable phase (Fig. 6). Among patients with no/mild congestion at discharge ($0 \leq \text{CCS} < 1$), those in the second and third SCS tertiles had a 7.1% and 22.7% greater likelihood of experiencing congestion ($\text{CCS} \geq 1$) during the 90-day follow-up, respectively, than those in the first SCS tertile. Among patients with moderate or worse congestion at discharge ($\text{CCS} \geq 1$), those in the second and third SCS tertiles had a 14.3% and 12.5% greater likelihood of persistent or recurrent congestion, respectively, than those in the first SCS tertile. Medication use in this cohort was recorded descriptively: at discharge, β -blockers, spironolactone, and diuretics were used

in 65.2%, 52.2%, and 52.2% of patients, respectively; at 3-month follow-up, the corresponding rates were 58.7%, 50.0%, and 63.0%. Given the small sample size ($n = 46$), these findings should be considered exploratory. The effect estimates were imprecise, with wide confidence intervals (e.g., OR for SCS high vs. low = 1.57, 95% CI: 0.07–35.03; **Supplementary Table 7**). Although a trend toward higher baseline SCS associated with greater rehospitalization risk was observed, these exploratory analyses do not provide confirmatory evidence and require validation in larger cohorts.

4. Discussion

In this study, we systematically profiled plasma steroid hormone levels in patients with AHF and constructed and validated a novel congestion score, the SCS, based on three hormones: cortisol, DHEAS, and pregnenolone. Our main findings can be summarized as follows: (1) in patients with AHF, the steroid hormone profile, particularly the stress and protective hormonal axes represented by pregnenolone as a synthetic precursor and cortisol and DHEAS as downstream effectors, is closely associated with clinical congestion status; (2) the SCS derived from these hormones is an independent and robust predictor of 90-day (vulnerable-phase) and long-term all-cause mortality and readmission for HF; and (3) the SCS not only provides incremental prognostic information beyond traditional clinical risk factors, BNP, and physical examination, but also demonstrates robust performance across multiple subgroups and independent internal validation cohorts, with favorable net clinical benefit. These findings suggest that the multi-hormone SCS could serve as a novel tool for assessment of the congestion burden and risk stratification in HF, particularly for identifying high-risk patients during the critical vulnerable phase post-discharge. Given the observational nature of this study, the reported associations should not be interpreted as causal, and the mechanistic interpretations proposed herein are speculative and hypothesis-generating, requiring confirmation in future experimental and translational studies.

The composition of the SCS and its underlying biological rationale are central to this study. Our results showed that the SCS is jointly constituted by cortisol (with a positive coefficient as a risk factor) and DHEAS/pregnenolone (with negative coefficients as protective factors). This combination may reflect an imbalance between catabolic (stress) and anabolic (protective) hormonal axes in patients with HF, although this interpretation remains speculative [26]. Cortisol is a classic stress hormone; in the setting of HF-related neurohormonal activation, elevated cortisol may contribute to hemodynamic compromise and ventricular remodeling through volume retention, increased vascular resistance/afterload, and myocardial fibrosis [27,28,29]. DHEAS is the most abundant circulating steroid and has potential protective effects, including vasodilatory, antioxidant, and immunomodulatory properties. A low DHEAS

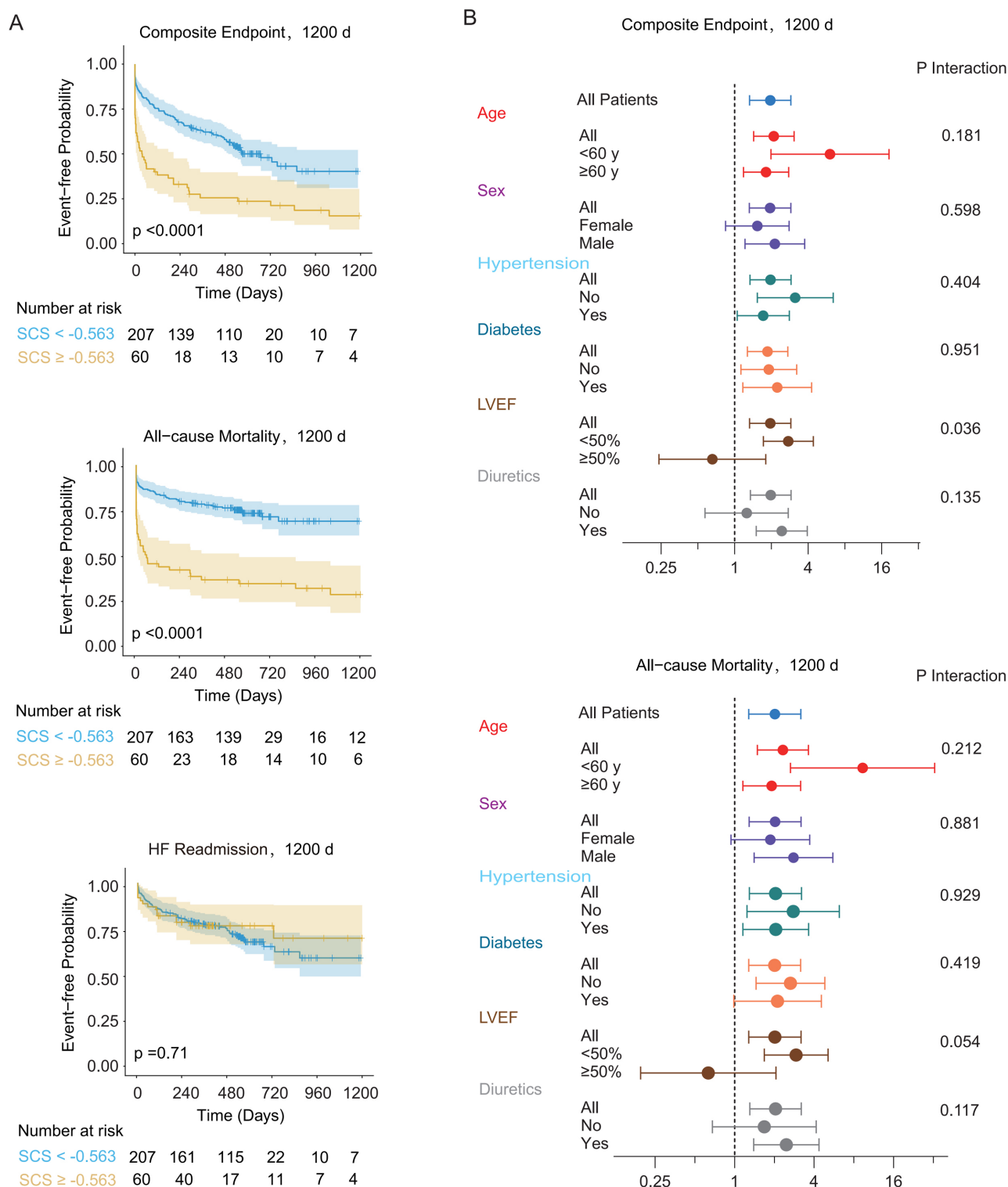


Fig. 5. Prognostic value of SCS for long-term outcomes in validation cohort 1. (A) Kaplan-Meier curves for the composite endpoint, all-cause mortality, and readmission for HF. (B) Subgroup analysis for the composite endpoint and all-cause mortality, with forest plots showing hazard ratios (high vs. low SCS) across subgroups. LVEF, left ventricular ejection fraction; SCS, steroid-based congestion score.

level has been associated with a poor prognosis in patients with HF [30,31,32,33]. Pregnenolone is the precursor for all steroid hormones, and its decline in patients with

HF and congestion may reflect overall impairment of synthesis of anabolic steroids or a shift towards production of stress hormones [34]. Therefore, by integrating these

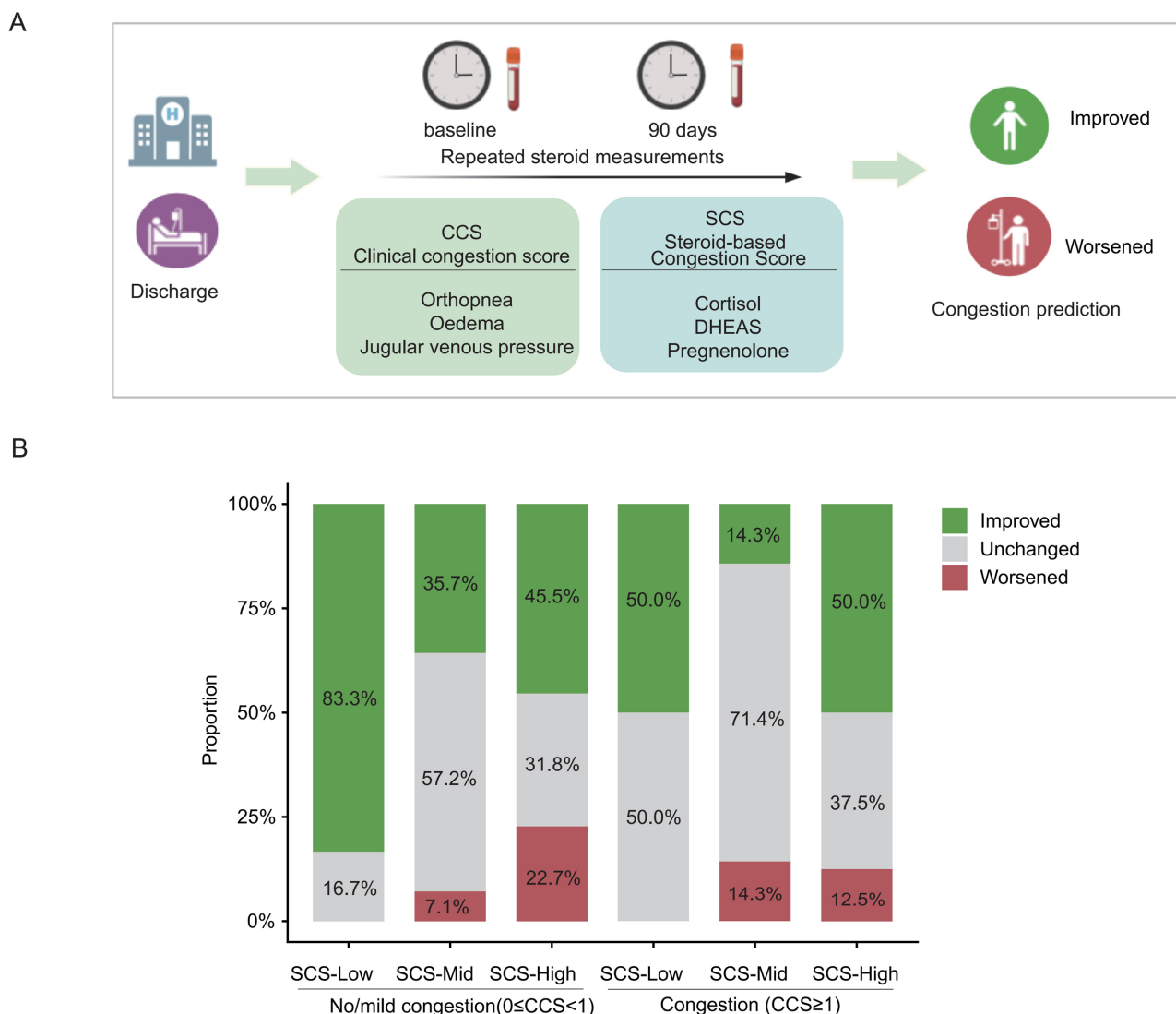


Fig. 6. Association of baseline SCS with the recongestion rate at 90 days in validation cohort 2. (A) Schematic diagram showing the study design for validation cohort 2, including collection of blood samples at discharge and at the 90-day follow-up and measurement of steroid hormones by liquid chromatography–tandem mass spectrometry. (B) Bar graphs showing the proportion of patients who had developed congestion ($\text{CCS} \geq 1$) by the 90-day follow-up when stratified by SCS tertile at baseline. CCS, clinical congestion score; SCS, steroid-based congestion score.

three hormones, which represent stress (cortisol), protection (DHEAS), and synthetic reserve (pregnenolone), the SCS captures the complex neurohormonal and metabolic derangements underlying congestion in HF more comprehensively than any single hormone. This hypothesized mechanism explains its incremental value over traditional markers.

Neurohormonal activation and renal–cardiac/metabolic perturbations are increasingly recognized as key components of HF congestion beyond natriuretic peptide elevation [35,36,37]. In this context, our findings suggest that SCS may capture a steroid-related vulnerability dimension that is less directly reflected by BNP. BNP is released primarily by cardiomyocytes in

response to stretch and is a direct marker of ventricular wall stress [38]. Our correlation analysis found weak associations between BNP and most steroids, which supports the notion that SCS and BNP represent different but complementary dimensions of the pathophysiology in HF [39,40]. Furthermore, we observed a very weak correlation between SCS and high-sensitivity troponin I, whereas hs-TnI and BNP showed a modest correlation, suggesting that SCS captures pathophysiological information distinct from both myocardial stretch (BNP) and myocyte injury (hs-TnI). Specifically, the integration of cortisol, DHEAS, and pregnenolone in the SCS may reflect neurohormonal activation (hypothalamic–pituitary–adrenal axis dysregulation) and metabolic reprogramming (catabolic/anabolic

imbalance), which are not directly assessed by natriuretic peptides or troponins. The incremental prognostic value of the SCS, particularly over the BNP model and over the hs-TnI model, further reinforces this notion. Moreover, unlike the CCS, which is derived from physical examination, the SCS can identify high-risk patients with “subclinical” congestion, whose persistent hemodynamic abnormalities may not be detected by routine examination but still contribute significantly to adverse outcomes [41,42,43]. From a clinical perspective, the SCS may guide intensified follow-up, optimization of diuretic and neurohormonal antagonist dosing, and closer hemodynamic monitoring for such high-risk patients during the vulnerable post-discharge phase. Therefore, as a blood-based multi-hormone marker, the SCS provides clinicians with an objective tool for quantitative assessment of the overall congestion burden.

The SCS is a continuous score and relatively simple to calculate, so has potential for adoption in clinical settings. This tool could be used for refinement of risk stratification when managing the vulnerable phase in patients who have been discharged [44]. Patients with a high SCS, even if symptomatically improved, should be considered high-risk, warranting intensified follow-up, consideration of more aggressive medical therapy (e.g., optimized diuresis, upward titration of neurohormonal antagonists), and possibly closer hemodynamic monitoring [45].

Subgroup analyses demonstrated that the prognostic value of the SCS was generally consistent regardless of age, sex, comorbidities, and cardiac functional status (all *p*-values for interaction were >0.05), confirming its generalizability and robustness as a risk stratification tool. Although higher point estimates for HRs were observed in patients with reduced LVEF, those who were male, and those with diabetes, the interaction tests did not reach statistical significance. Therefore, it is possible that these subgroup differences may result from random variation and that it is too early to conclude that the SCS has stronger prognostic value in these populations. Future studies in larger prospective cohorts are needed to confirm the predictive efficacy of the SCS across various clinical subgroups and to explore its value in guiding personalized treatment.

5. Limitations

This study has several limitations. First, all patients were enrolled from a single institution, and internal validation suggested mild overfitting of the SCS. Therefore, the generalizability of our findings requires confirmation in multicenter cohorts with diverse populations. Second, measurement of the SCS currently relies on liquid chromatography–tandem mass spectrometry, which may limit its accessibility in resource-limited settings. However, the cost and time required for this method are decreasing with technological advances. Third, validation cohort 2 included only 46 patients with paired samples, and the analyses of re-congestion dynamics are therefore exploratory. Fu-

ture studies should investigate the longitudinal trajectory of the SCS and its value in guiding adjustments to treatment. Finally, as an observational study, causality cannot be inferred from the observed associations. The proposed mechanistic interpretations should therefore be considered hypothesis-generating and require experimental validation.

6. Conclusion

This study constructed and validated a novel steroid-based congestion score, known as the SCS, which incorporates cortisol, DHEAS, and pregnenolone. This score is an independent predictor of adverse outcomes during the 90-day vulnerable phase and long-term follow-up in patients with AHF, offering incremental prognostic information beyond traditional clinical factors, BNP, and physical examination. The SCS is a biomarker that integrates neurohormonal and metabolic information and may provide a novel strategy for risk stratification and personalized management during the critical vulnerable post-discharge phase in HF.

Availability of Data and Materials

The datasets generated and analyzed during the current study are available from the corresponding author upon reasonable request.

Author Contributions

YW developed the concept, designed the study, and revised the manuscript. YF and JC analyzed the data and drafted the manuscript. LR, WC and XT contributed to the acquisition and interpretation of clinical data. They also participated in critical revision of the manuscript for important intellectual content. The order of co-first authors was determined by the volume of work each contributed to the study. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of Beijing Anzhen Hospital, Capital Medical University (approval number: [2016037X]), and conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent prior to enrollment. The informed consent process included a detailed explanation of the study purpose, blood sample collection procedures, potential risks and benefits, data confidentiality measures, and the right to withdraw at any time.

Acknowledgment

Not applicable.

Funding

This work was supported by the Noncommunicable Chronic Diseases-National Science and Technology Major Project (Grant No. 2023ZD0503100), the Beijing Municipal Natural Science Foundation (Grant No. 7264239) and the National Natural Science Foundation of China (NSFC) Major Program (Grant No. 91939303).

Conflicts of Interest

The authors declare no conflicts of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at <https://doi.org/10.31083/RCM53378>.

References

- [1] Virani SS, Alonso A, Aparicio HJ, Benjamin EJ, Bittencourt MS, Callaway CW, et al. Heart Disease and Stroke Statistics-2021 Update: A Report From the American Heart Association. *Circulation*. 2021; 143: e254–e743. <https://doi.org/10.1161/CIR.0000000000000950>
- [2] Savarese G, Becher PM, Lund LH, Seferovic P, Rosano GMC, Coats AJS. Global burden of heart failure: a comprehensive and updated review of epidemiology. *Cardiovascular Research*. 2023; 118: 3272–3287. <https://doi.org/10.1093/cvr/cvac013>
- [3] Rosano GMC, Vitale C, Adamo M, Metra M. Roadmap for the management of heart failure patients during the vulnerable phase after heart failure hospitalizations: how to implement excellence in clinical practice. *Journal of Cardiovascular Medicine (Hagerstown, Md.)*. 2022; 23: 149–156. <https://doi.org/10.2459/JCM.0000000000001221>
- [4] Abidin A, Anker SD, Butler J, Coats AJS, Kindermann I, Lain-scak M, et al. ‘Time is prognosis’ in heart failure: time-to-treatment initiation as a modifiable risk factor. *ESC Heart Failure*. 2021; 8: 4444–4453. <https://doi.org/10.1002/ehf2.13646>
- [5] Kitakata H, Kohno T, Kohsaka S, Shiraishi Y, Parizo JT, Niimi N, et al. Prognostic Implications of Early and Midrange Readmissions After Acute Heart Failure Hospitalizations: A Report From a Japanese Multicenter Registry. *Journal of the American Heart Association*. 2020; 9: e014949. <https://doi.org/10.1161/JAHA.119.014949>
- [6] Greene SJ, Fonarow GC, Vaduganathan M, Khan SS, Butler J, Gheorghiade M. The vulnerable phase after hospitalization for heart failure. *Nature Reviews. Cardiology*. 2015; 12: 220–229. <https://doi.org/10.1038/nrcardio.2015.14>
- [7] Gheorghiade M, Filippatos G, De Luca L, Burnett J. Congestion in acute heart failure syndromes: an essential target of evaluation and treatment. *The American Journal of Medicine*. 2006; 119: S3–S10. <https://doi.org/10.1016/j.amjmed.2006.09.011>
- [8] Boersma EM, Ter Maaten JM, Damman K, Dinh W, Gustafsson F, Goldsmith S, et al. Congestion in heart failure: a contemporary look at physiology, diagnosis and treatment. *Nature Reviews. Cardiology*. 2020; 17: 641–655. <https://doi.org/10.1038/s41569-020-0379-7>
- [9] Nishikimi T, Nakagawa Y. Potential pitfalls when interpreting plasma BNP levels in heart failure practice. *Journal of Cardiology*. 2021; 78: 269–274. <https://doi.org/10.1016/j.jjcc.2021.05.003>
- [10] Singh S, Pandey A, Neeland JJ. Diagnostic and prognostic considerations for use of natriuretic peptides in obese patients with heart failure. *Progress in Cardiovascular Diseases*. 2020; 63: 649–655. <https://doi.org/10.1016/j.pcad.2020.09.006>
- [11] Tsutsui H, Albert NM, Coats AJS, Anker SD, Bayes-Genis A, Butler J, et al. Natriuretic peptides: Role in the diagnosis and management of heart failure: A scientific statement from the Heart Failure Association of the European Society of Cardiology, Heart Failure Society of America and Japanese Heart Failure Society. *European Journal of Heart Failure*. 2023; 25: 616–631. <https://doi.org/10.1002/ehf.2848>
- [12] Gomez-Sanchez CE, Gomez-Sanchez EP. Cholesterol Availability and Adrenal Steroidogenesis. *Endocrinology*. 2024; 165: bqae032. <https://doi.org/10.1210/endo/bqae032>
- [13] Kupczyk D, Studzińska R, Kołodziejka R, Baumgart S, Modrzejewska M, Woźniak A. 11 β -Hydroxysteroid Dehydrogenase Type 1 as a potential treatment target in cardiovascular diseases. *Journal of Clinical Medicine*. 2022; 11: 6190. <https://doi.org/10.3390/jcm11206190>
- [14] Ferreira JP, Pitt B, Zannad F. Mineralocorticoid Receptor Antagonists in Heart Failure: An Update. *Circulation. Heart Failure*. 2024; 17: e011629. <https://doi.org/10.1161/CIRCHEARTF.124.011629>
- [15] Verma S, Pandey A, Pandey AK, Butler J, Lee JS, Teoh H, et al. Aldosterone and aldosterone synthase inhibitors in cardiorenal disease. *American Journal of Physiology. Heart and Circulatory Physiology*. 2024; 326: H670–H688. <https://doi.org/10.1152/ajpheart.00419.2023>
- [16] Camarda ND, Ibarrola J, Biwer LA, Jaffe IZ. Mineralocorticoid receptors in vascular smooth muscle: Blood pressure and beyond. *Hypertension*. 2024; 81: 1008–1020. <https://doi.org/10.1161/HYPERTENSIONAHA.123.21358>
- [17] Schafstedde M, Nordmeyer S. The role of androgens in pressure overload myocardial hypertrophy. *Frontiers in Endocrinology*. 2023; 14: 1112892. <https://doi.org/10.3389/fendo.2023.1112892>
- [18] National Clinical Guideline Center. National Institute for Health and Care Excellence: Clinical Guidelines Acute Heart Failure: Diagnosing and Managing Acute Heart Failure in Adults. National Institute for Health and Care Excellence (UK): London. 2014.
- [19] Ke B, Tan X, Ren L, Fan Y, Zhang Y, Li F, et al. Aldosterone dysregulation predicts the risk of mortality and rehospitalization in heart failure with a preserved ejection fraction. *Science China. Life Sciences*. 2022; 65: 631–642. <https://doi.org/10.1007/s11427-021-1945-6>
- [20] Ren L, Li F, Tan X, Fan Y, Ke B, Zhang Y, et al. Abnormal plasma ceramides refine high-risk patients with worsening heart failure. *Frontiers in Cardiovascular Medicine*. 2023; 10: 1185595. <https://doi.org/10.3389/fcvm.2023.1185595>
- [21] Ter Maaten JM, Kremer D, Demissei BG, Struck J, Bergmann A, Anker SD, et al. Bio-adrenomedullin as a marker of congestion in patients with new-onset and worsening heart failure. *European Journal of Heart Failure*. 2019; 21: 732–743. <https://doi.org/10.1002/ehf.1437>
- [22] Lozano-Jiménez S, Vela-Martín P, Martín-Centellas A, de Castro D, Mitroi C, Hernández-Pérez FJ, et al. Clinical and Subclinical Congestion in Acute Heart Failure: A Multimodal Prognostic Assessment. *Journal of Clinical Medicine*. 2026; 15: 2601. <https://doi.org/10.3390/jcm15072601>
- [23] Balalian AA, Liu X, Siegel EL, Herbstman JB, Rauh V, Wapner R, et al. Predictors of Urinary Pyrethroid and Organophosphate Compound Concentrations among Healthy Pregnant Women in New York. *International Journal of Environmental Research and Public Health*. 2020; 17: 6164. <https://doi.org/10.3390/ijerph17176164>
- [24] Fu P, Hughes J, Zeng G, Hanook S, Orem J, Mwanda OW, et al. A comparative investigation of methods for longitudinal data with limits of detection through a case study. *Statistical*

- tical Methods in Medical Research. 2016; 25: 153–166. <https://doi.org/10.1177/0962280212444800>
- [25] Lausen B, Schumacher M. Maximally selected rank statistics. *Biometrics*. 1992; 48: 73–85. <https://doi.org/10.2307/2532740>
- [26] Anker SD, Chua TP, Ponikowski P, Harrington D, Swan JW, Kox WJ, et al. Hormonal changes and catabolic/anabolic imbalance in chronic heart failure and their importance for cardiac cachexia. *Circulation*. 1997; 96: 526–534. <https://doi.org/10.1161/01.cir.96.2.526>
- [27] Manolis AA, Manolis TA, Manolis AS. Neurohumoral Activation in Heart Failure. *International Journal of Molecular Sciences*. 2023; 24: 15472. <https://doi.org/10.3390/ijms242015472>
- [28] Morbach C, Detomas M, Sahiti F, Hoffmann K, Kroiss M, Gelbrich G, et al. Cardiovascular status in endogenous cortisol excess: the prospective CV-CORT-EX study. *European Journal of Endocrinology*. 2024; 191: 604–613. <https://doi.org/10.1093/endo/lvae145>
- [29] Włochacz A, Krzesiński P, Uziębło-Życzkowska B, Witek P, Zieliński G, Kazimierzczak A, et al. Impaired cardiac pumping function and increased afterload as determinants of early hemodynamic alterations in Cushing disease. *Scientific Reports*. 2025; 15: 233. <https://doi.org/10.1038/s41598-024-84888-x>
- [30] Wu TT, Chen Y, Zhou Y, Adi D, Zheng YY, Liu F, et al. Prognostic Value of Dehydroepiandrosterone Sulfate for Patients With Cardiovascular Disease: A Systematic Review and Meta-Analysis. *Journal of the American Heart Association*. 2017; 6: e004896. <https://doi.org/10.1161/JAHA.116.004896>
- [31] Güder G, Frantz S, Bauersachs J, Allolio B, Ertl G, Angermann CE, et al. Low circulating androgens and mortality risk in heart failure. *Heart (British Cardiac Society)*. 2010; 96: 504–509. <https://doi.org/10.1136/hrt.2009.181065>
- [32] Di Lodovico E, Facondo P, Delbarba A, Pezzaioli LC, Maffezzoni F, Cappelli C, et al. Testosterone, Hypogonadism, and Heart Failure. *Circulation. Heart Failure*. 2022; 15: e008755. <https://doi.org/10.1161/CIRCHEARTFAILURE.121.008755>
- [33] Jankowska EA, Biel B, Majda J, Szklarska A, Lopuszanska M, Medras M. Anabolic deficiency in men with chronic heart failure: prevalence and detrimental impact on survival. *Circulation*. 2006; 114: 1829–1837. <https://doi.org/10.1161/CIRCULATIONAHA.106.649426>
- [34] Fan Y, Li F, Tan X, Ren L, Peng X, Yu J, et al. Abnormal circulating steroids refine risk of progression to heart failure in ischemic heart disease. *European Journal of Clinical Investigation*. 2024; 54: e14156. <https://doi.org/10.1111/eci.14156>
- [35] Brann A, Selko S, Krauspe E, Shah K. Biomarkers of hemodynamic congestion in heart failure. *Current Heart Failure Reports*. 2024; 21: 541–553. <https://doi.org/10.1007/s11897-024-00684-8>
- [36] Kataoka H. Neurohormonal Activation and Renal Chloride Avidity in Acute Heart Failure: Clinical Evidence Supporting the “Chloride Theory”. *Cardiorenal Medicine*. 2024; 14: 94–104. <https://doi.org/10.1159/000536293>
- [37] Noels H, van der Vorst EPC, Rubin S, Emmett A, Marx N, Tomaszewski M, et al. Renal-Cardiac Crosstalk in the Pathogenesis and Progression of Heart Failure. *Circulation Research*. 2025; 136: 1306–1334. <https://doi.org/10.1161/CIRCRESAHA.124.325488>
- [38] Suci H, Călborean PA, Huțanu A, Oprica M, Opriș DR, Scurtu AC, et al. Natriuretic Peptides and Soluble ST2 Improve Echocardiographic and Invasive Long-Term Survival Prediction in Patients Evaluated for Diastolic Dysfunction. *International Journal of Molecular Sciences*. 2025; 26: 3713. <https://doi.org/10.3390/ijms26083713>
- [39] Yamaji M, Tsutamoto T, Kawahara C, Nishiyama K, Yamamoto T, Fujii M, et al. Serum cortisol as a useful predictor of cardiac events in patients with chronic heart failure: the impact of oxidative stress. *Circulation*. 2009; 2: 608–615. <https://doi.org/10.1161/CIRCHEARTFAILURE.109.868513>
- [40] Abusedera O, Sherif J, Karar L, Arekat D. Cardiac markers for risk stratification and prognosis in elderly patients with HFrEF. *Frontiers in Medicine*. 2026; 13: 1754295. <https://doi.org/10.3389/fmed.2026.1754295>
- [41] Metra M, Adamo M, Tomasoni D, Mebazaa A, Bayes-Genis A, Abdelhamid M, et al. Pre-discharge and early post-discharge management of patients hospitalized for acute heart failure: A scientific statement by the Heart Failure Association of the ESC. *European Journal of Heart Failure*. 2023; 25: 1115–1131. <https://doi.org/10.1002/ehf.2888>
- [42] Grigore M, Nicolae C, Grigore AM, Balahura AM, Păun N, Urscoiu G, et al. Contemporary Perspectives on Congestion in Heart Failure: Bridging Classic Signs with Evolving Diagnostic and Therapeutic Strategies. *Diagnostics (Basel, Switzerland)*. 2025; 15: 1083. <https://doi.org/10.3390/diagnostics15091083>
- [43] Lozano-Jiménez S, García Sebastian C, Vela Martín P, García Magallón B, Martín Centellas A, de Castro D, et al. Prevalence and prognostic impact of subclinical venous congestion in patients hospitalized for acute heart failure. *European Heart Journal. Acute Cardiovascular Care*. 2026; 14: 749–753. <https://doi.org/10.1093/ehjacc/zuaf097>
- [44] Phan J, Barroca C, Fernandez J. A Suggested Model for the Vulnerable Phase of Heart Failure: Assessment of Risk Factors, Multidisciplinary Monitoring, Cardiac Rehabilitation, and Addressing the Social Determinants of Health. *Cureus*. 2023; 15: e35602. <https://doi.org/10.7759/cureus.35602>
- [45] Biegus J, Mebazaa A, Davison B, Cotter G, Edwards C, Čelutkienė J, et al. Effects of Rapid Uptitration of Neurohormonal Blockade on Effective, Sustainable Decongestion and Outcomes in STRONG-HF. *Journal of the American College of Cardiology*. 2024; 84: 323–336. <https://doi.org/10.1016/j.jacc.2024.04.055>