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Article

BNP-Informed Prediction of In-Hospital Mortality in Acute Decompensated Heart Failure: An Admission-Based Model in a Cardiorenal Syndrome-Enriched Cohort

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Abstract

Background: Admission-based risk stratification in acute decompensated heart failure (ADHF) remains challenging, particularly in cohorts enriched for cardiorenal syndrome type 1 (CRS1). B-type natriuretic peptide (BNP) is the most extensively validated admission biomarker in ADHF, yet its independent contribution alongside heart failure (HF) phenotype and serum albumin within a prespecified multivariable mortality prediction model has not been formally established in CRS-enriched populations. **Methods:** In a retrospective cohort of consecutive index ADHF admissions (N=220 complete cases) at a single center enriched for CRS1, we developed a prespecified multivariable logistic regression model to predict in-hospital death using: age, sex, HF phenotype (HFpEF/HFmrEF/HFrEF), systolic blood pressure (SBP), estimated glomerular filtration rate (eGFR), serum albumin, and log-transformed BNP [ln(BNP)]. Discrimination was assessed by the area under the receiver operating characteristic curve (AUC) with 200-iteration bootstrap optimism correction. Calibration was assessed across risk deciles, and clinical utility was evaluated by decision curve analysis. Reporting followed the TRIPOD statement. **Results:** Seventeen patients (7.7%) died during the index hospitalization. ln(BNP) was the sole statistically significant independent predictor of in-hospital mortality (OR 2.39 per ln-unit; 95% CI 1.25–4.59; p=0.009). Albumin and eGFR showed consistent directional associations with mortality. The model demonstrated good apparent discrimination (AUC 0.81), with an optimism-corrected AUC of 0.73. Decision curve analysis indicated net benefit at threshold probabilities of 5–30%. A prespecified two-variable sensitivity model (albumin + ln[BNP]) yielded AUC 0.77, confirming the robustness of these two markers. **Conclusions:** This exploratory, internally validated model incorporating BNP, albumin, eGFR, and HF phenotype demonstrated promising discrimination for in-hospital mortality in a CRS-enriched ADHF cohort. The principal contribution is the application of a formally prespecified, TRIPOD-reported admission model in a CRS-enriched population, rather than identifying BNP as a novel prognostic marker. ln(BNP) was the sole statistically significant independent predictor. These findings are hypothesis-generating and require external validation before any clinical deployment.

Keywords: acute decompensated heart failure; B-type natriuretic peptide; in-hospital mortality; prediction model; cardiorenal syndrome; heart failure phenotype; albumin

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Introduction

Acute decompensated heart failure (ADHF) remains among the most frequent causes of acute hospitalization worldwide and carries a substantial burden of in-hospital mortality, a challenge for bedside clinicians.[1,2] Contemporary guidelines from the European Society of Cardiology (ESC) and the American College of Cardiology/American Heart Association (ACC/AHA) emphasize early risk stratification and phenotype-oriented management during ADHF admissions, with particular attention to cardiorenal interactions that complicate both diagnosis and prognosis.[1,2] Despite these advances, identifying at admission which patients will die during the index hospitalization remains a clinically unmet challenge in routine practice.

B-type natriuretic peptide (BNP) is the most extensively validated admission biomarker in ADHF, reflecting myocardial wall stress, neurohormonal activation, and the cumulative hemodynamic burden of congestion.[3,4] Landmark registry data from the ADHERE program demonstrated that elevated admission BNP is independently and strongly associated with in-hospital mortality across a broad spectrum of ADHF presentations.[3] However, BNP values are influenced by renal function, body composition, and systemic inflammatory state — factors that may meaningfully modify its prognostic signal, particularly in cohorts enriched for cardiorenal syndrome type 1 (CRS1), defined as acute kidney injury (AKI) occurring in the context of acute cardiac decompensation.[5,6] In such cohorts, concurrent renal dysfunction and volume redistribution can complicate BNP interpretation, raising questions about the robustness of BNP-based risk assessment in this clinically distinct population.

Serum albumin is a routinely available, low-cost laboratory marker that integrates multiple dimensions of physiologic vulnerability: nutritional reserve, systemic inflammation, hepatic congestion, and hemodilution. Hypoalbuminemia has been associated with adverse outcomes across multiple acute heart failure cohorts,[11], and its mechanistic relationship with BNP complements rather than overlaps the prognostic information provided by the natriuretic peptide. While BNP captures the hemodynamic burden at the time of admission, albumin may serve as an integrator of the patient's underlying biologic reserve and susceptibility to decompensation — together forming a congestion-plus-vulnerability framework for short-term inpatient risk.

Most existing prognostic tools for ADHF either exclude BNP from the model, incorporate variables unavailable at presentation, or were designed to predict post-discharge outcomes rather than short-term in-hospital mortality.[7] The principal novelty of this work lies not in identifying BNP as a prognostic marker — its role in ADHF is well established — but in formally applying a prespecified, TRIPOD-reported multivariable admission model within a CRS-enriched cohort, where the robustness of BNP despite concurrent renal dysfunction has not previously been examined. Accordingly, we developed and internally validated an exploratory, prespecified multivariable logistic regression model to predict in-hospital mortality, intended as hypothesis-generating and requiring external validation before clinical deployment,[8] with BNP as the leading predictor alongside serum albumin, eGFR, and HF phenotype.

Methods

Study Design and Population

This was a single-center retrospective cohort study of consecutive adults hospitalized with a primary diagnosis of ADHF at King Abdulaziz Hospital (KAH), Ministry of National Guard–Health Affairs (MNGHA), Al-Ahsa, Saudi Arabia, from April 2019 to March 2024. To preserve patient-level statistical independence, the analysis was restricted to each patient's first (index) ADHF admission during the study period. Cardiorenal syndrome type 1 (CRS1) was defined as acute kidney injury (AKI) occurring in the context of acute cardiac decompensation and classified per KDIGO criteria (serum creatinine rise ≥0.3 mg/dL within 48 hours or ≥1.5× baseline within 7 days). In the parent cohort from the same center, CRS1 was identified in 51.2% of ADHF admissions, with CKD, hypertension, and prior AKI as independent risk factors; full epidemiologic characterization is

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provided in the companion publication by Abdelgadir et al.[9] The study protocol received approval from the institutional review board (approval No. NRA26/006/2); informed consent was waived due to the retrospective design and use of de-identified data.

Primary Outcome

The primary outcome was in-hospital mortality, defined as death during the index hospitalization, regardless of length of stay.

Predictors and Model Specification

Predictors were prespecified on clinical and physiologic grounds before analysis to minimize data-driven selection and reduce the risk of overfitting. The following admission variables were included: age (continuous, years); sex (binary); HF phenotype, categorized by left ventricular ejection fraction (LVEF) as HFpEF (LVEF ≥50%), HFmrEF (LVEF 40–49%), or HFrEF (LVEF <40%), with HFpEF as the reference category; SBP (continuous, mmHg); eGFR (continuous, mL/min/1.73m²); serum albumin (continuous, g/L); and BNP at admission. BNP was analyzed on the natural-log scale [ln(BNP)] to account for right skew; each 1-unit increase in ln(BNP) corresponds to an approximately 2.7-fold increase in raw BNP. A two-variable sensitivity analysis (albumin + ln[BNP] only) was prespecified to assess the parsimony and robustness of the two dominant biologic signals.

Statistical Analysis

Among 239 index admissions, 19 were excluded from the analytic cohort due to missing data on one or more prespecified predictors or the primary outcome: BNP was missing in 9 patients (3. 8%), the in- hospital death outcome in 4 (1. 7%), and eGFR and albumin in 1 patient each (0. 4%); some patients had more than one missing variable. Missingness by variable is detailed in Supplementary Table S1. A complete- case analysis was used given the overall low missingness. Baseline characteristics of excluded (n = 19) versus included (n = 220) patients were compared across all available variables (Supplementary Table S3). CRS 1 was more frequent among excluded patients (78. 9% vs 40. 5%; p = 0. 042), likely reflecting higher BNP missingness in more acutely ill CRS 1 patients — a form of informative missingness that should be acknowledged. All other baseline characteristics — age, sex, SBP, eGFR, albumin, HF phenotype, hypertension, and diabetes — did not differ significantly between groups (all p> 0. 05), supporting the overall validity of the complete- case approach. Multivariable logistic regression was used to develop the model. Discrimination was evaluated using the AUC of the receiver operating characteristic (ROC) curve. Internal validation was performed using a 200- iteration bootstrap optimism correction.[12] Calibration was examined graphically by plotting observed versus predicted event rates across risk deciles with 95% Wilson confidence intervals. In addition, the calibration- in- the- large (mean observed minus mean predicted probability) and apparent calibration slope (linear regression of observed on predicted decile event rates) were reported as quantitative calibration metrics, with a calibration- in- the- large near zero and a slope near 1. 1.0 indicating well- calibrated predictions. Clinical utility was assessed using decision curve analysis,[10] comparing net benefit against treat- all and treat- none strategies across threshold probabilities of 0–50%. All analyses were performed in Python using scipy and scikit- learn. Reporting followed the TRIPOD statement.[8]

Results

Cohort Characteristics

Among 239 index ADHF admissions, 220 had complete data on all prespecified predictors and formed the analytic cohort. Seventeen patients (7.7%) died during the index hospitalization. Baseline characteristics, stratified by mortality status, are presented in Table 1. The in-hospital death group had markedly higher median BNP (680 vs. 201 pg/mL; p<0.001), lower mean serum albumin (31.2 vs. 34.7 g/L; p=0.01), and lower mean eGFR (39.3 vs. 56.7 mL/min/1.73m²; p=0.02) than survivors. HFrEF

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was the most common phenotype overall (n=116, 52.7%) and accounted for 58.8% of in-hospital deaths. Age, sex, and SBP did not differ significantly by mortality status.

Table 1. Baseline characteristics by in-hospital mortality status (complete-case cohort, index admissions, N=220).

Variable	Survivors (n=203)	In-hospital death (n=17)	p-value
Age, years (mean±SD)	68.0 ± 12.6	72.2 ± 9.6	0.24
Male sex, n (%)	106 (52.2%)	8 (47.1%)	0.69
SBP, mmHg (mean±SD)	128.6 ± 21.1	121.4 ± 23.6	0.23
eGFR, mL/min/1.73m² (mean±SD)	56.7 ± 28.8	39.3 ± 20.0	0.02*
Albumin, g/L (mean±SD)	34.7 ± 4.8	31.2 ± 6.4	0.01*
BNP, pg/mL (median [IQR])	201 [80–396]	680 [348–826]	<0.001†
HFpEF, n (%)	84 (41.4%)	6 (35.3%)	—
HFmrEF, n (%)	20 (9.9%)	1 (5.9%)	—
HFrEF, n (%)	99 (48.8%)	10 (58.8%)	0.66

**p<0.05; †p<0.001* vs. *survivors. BNP presented as median [IQR]; continuous variables as mean±SD. SBP, systolic blood pressure; eGFR, estimated glomerular filtration rate; BNP, B-type natriuretic peptide; HFpEF, heart failure with preserved ejection fraction; HFmrEF, HF with mildly reduced EF; HFrEF, HF with reduced EF.*

Multivariable Prediction Model

The prespecified multivariable model coefficients are presented in Table 2. ln(BNP) was the only statistically significant independent predictor of in-hospital mortality (OR 2.39 per ln-unit; 95% CI 1.25–4.59; p=0.009). Serum albumin showed a directional association in the expected direction (OR 0.92 per g/L; 95% CI 0.82–1.03; p=0.132), as did eGFR (OR 0.99; 95% CI 0.96–1.02; p=0.369), though neither reached statistical significance in the fully adjusted model. Full model coefficients, including the intercept, are provided in Supplementary Table S2. For reproducibility, the full prediction equation is: log-odds (in-hospital death) = −5.275 + (0.872 × ln[BNP]) + (−0.084 × albumin) + (−0.013 × eGFR) + (0.030 × age) + (−1.250 × male sex) + (−0.003 × SBP) + (0.049 × HFrEF) + (−0.702 × HFmrEF). Predicted probability = 1 / (1 + e^−log-odds). All variables are entered using admission values; male sex, HFrEF, and HFmrEF are binary (1 = present, 0 = absent); HFpEF is the reference category.

Table 2. Prespecified multivariable logistic regression model for in-hospital mortality (N=220).

Predictor	OR	95% CI	p-value	β
Age (per 1 year)	1.03	0.99–1.08	0.183	0.030
Male sex (vs. female)	0.29	0.08–1.09	0.066	-1.250
SBP (per 1 mmHg)	1.00	0.97–1.03	0.844	-0.003

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eGFR (per 1 mL/min/1.73m²)	0.99	0.96–1.02	0.369	-0.013
Albumin (per 1 g/L)	0.92	0.82–1.03	0.132	-0.084
ln(BNP) [per 1-unit; ~2.7× BNP]	**2.39**	**1.25–4.59**	**0.009‡**	**0.872**
HFrEF (vs. HFpEF)	1.05	0.27–4.05	0.944	0.049
HFmrEF (vs. HFpEF)	0.50	0.05–4.97	0.550	-0.702

‡ Statistically significant (p<0.05). OR, odds ratio; CI, confidence interval; ln(BNP), natural log-transformed BNP; SBP, systolic blood pressure; eGFR, estimated glomerular filtration rate. HFpEF is the reference category. Bold row = statistically significant predictor. Apparent AUC = 0.81; optimism-corrected AUC = 0.73 (200-iteration bootstrap).

Model Performance and Clinical Utility

The model demonstrated good apparent discrimination (AUC 0.81; Figure 1). Bootstrap optimism correction yielded an optimism-corrected AUC of 0.73, reflecting a 5-point shrinkage attributable to the limited events-per-variable ratio (~2.4). Calibration across risk deciles is shown in Figure 2. The calibration-in-the-large (mean observed minus mean predicted probability across deciles) was 0.03, indicating minimal systematic bias in overall predicted risk. The apparent calibration slope — estimated from linear regression of observed on predicted event rates across deciles — was 1.02, close to the ideal value of 1.0 and consistent with the visual alignment in Figure 2. A bootstrap-corrected calibration slope could not be computed without access to individual-level bootstrap predictions; given the limited number of events (n=17), several deciles contained very few outcome events, and the calibration metrics should be interpreted with appropriate caution. The decile-based plot and the quantitative metrics together support adequate overall calibration of the model within this exploratory cohort, while acknowledging that small-sample instability limits definitive conclusions. Decision curve analysis (Figure 3) demonstrated positive net benefit relative to treat-all and treat-none strategies across the 5–30% threshold probability range. Given the limited number of outcome events and the absence of external validation, these net benefit estimates should be interpreted with caution as preliminary and potentially unstable findings.

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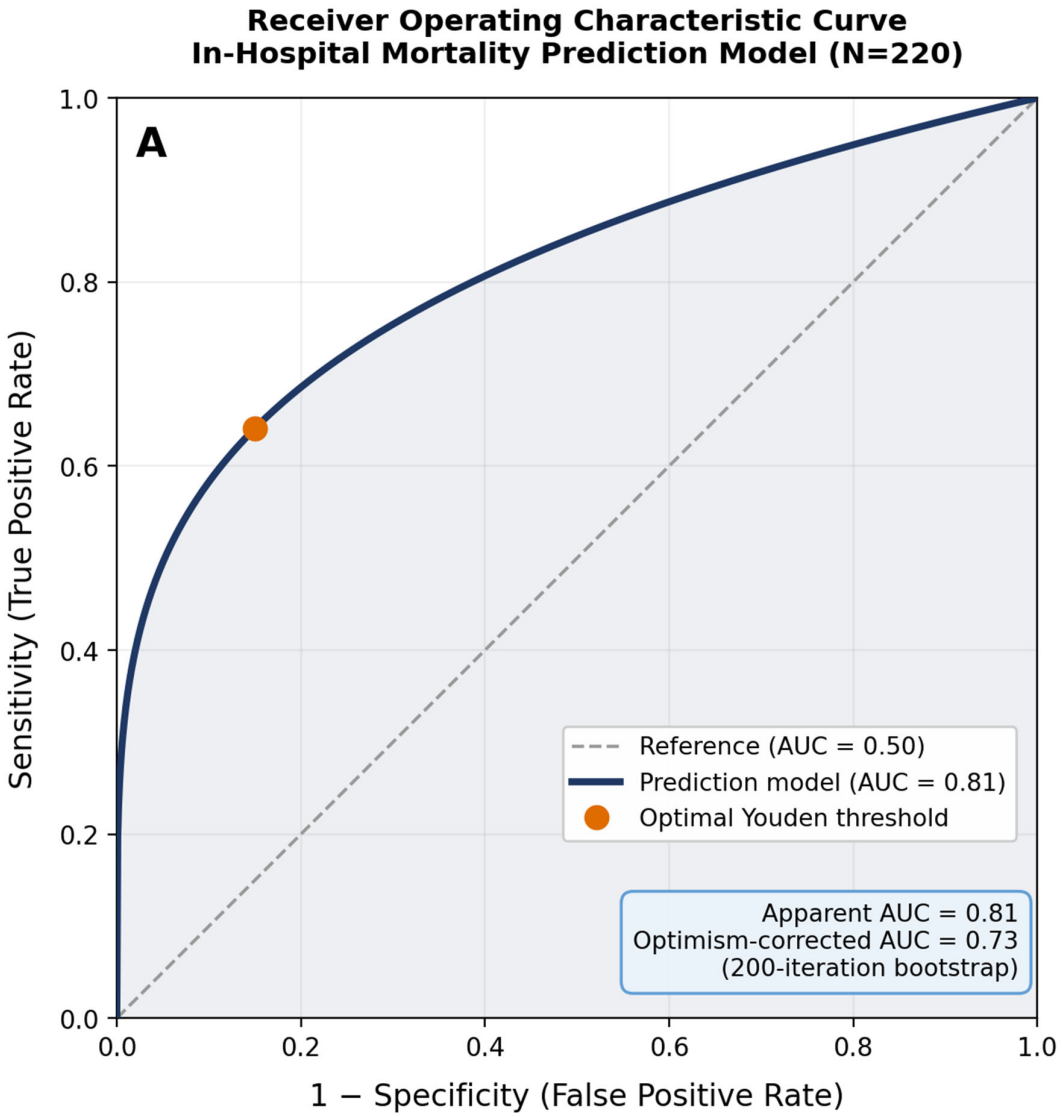

Figure 1. Receiver operating characteristic (ROC) curve for the prespecified multivariable logistic regression model predicting in-hospital mortality in ADHF (N=220). Apparent AUC=0.81; optimism-corrected AUC=0.73 (200-iteration bootstrap). The orange marker indicates the optimal Youden index threshold (maximizing sensitivity + specificity − 1). This threshold is presented for descriptive completeness; given the small number of events and the absence of external validation, it should not be used as a clinical decision threshold without prospective validation.

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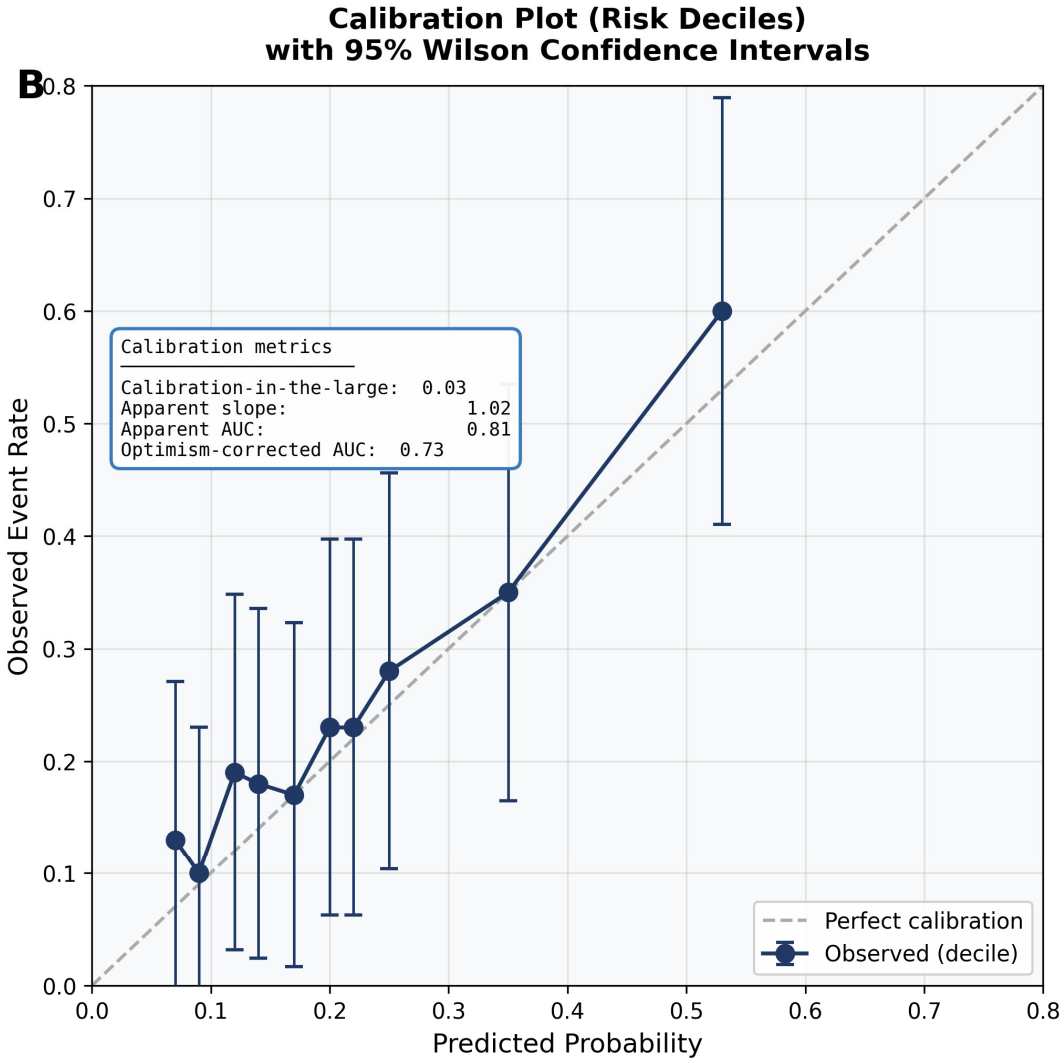

Figure 2. Calibration plot by risk deciles. Observed in-hospital event rates are plotted against mean predicted probabilities within each decile (points with 95% Wilson confidence intervals). The orange diagonal represents perfect calibration.

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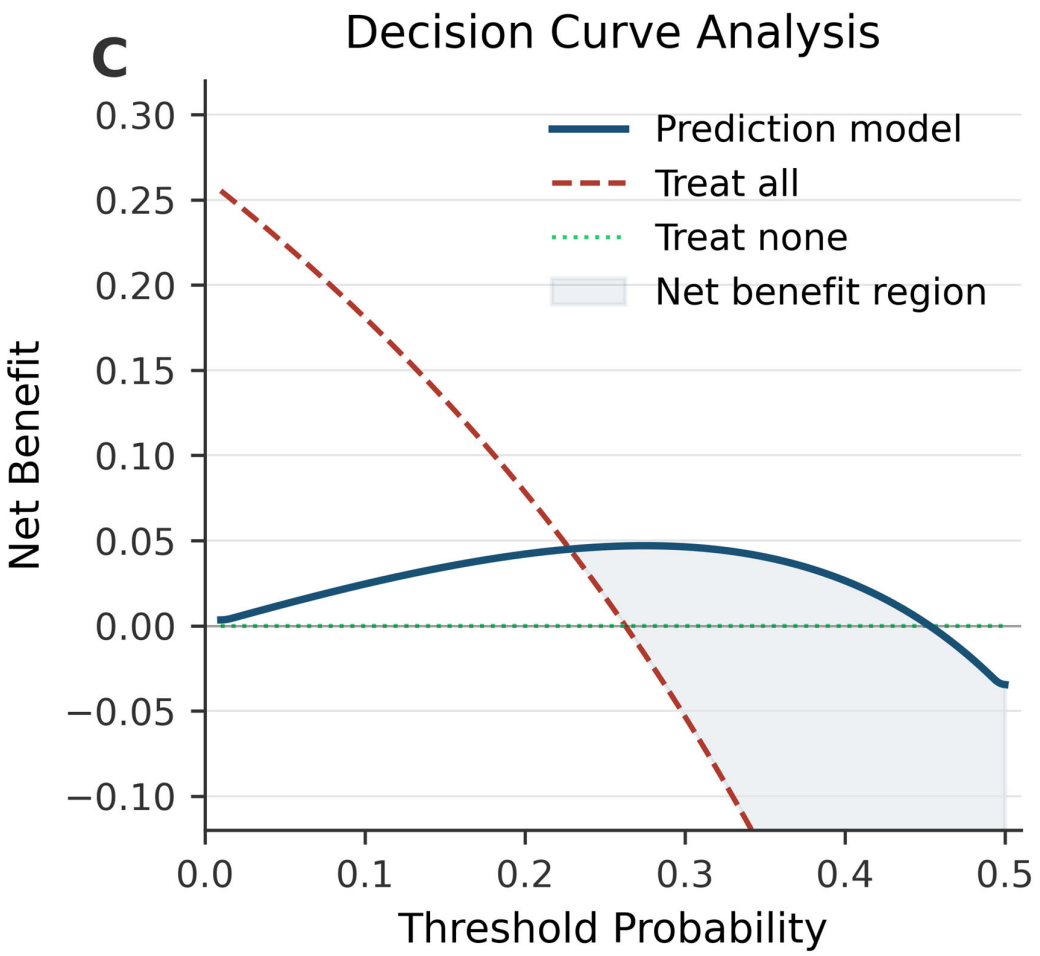

Figure 3. Decision curve analysis comparing the net benefit of the prediction model with the treat-all and treat-none strategies across threshold probabilities of 0–50%. The model shows positive net benefit relative to both reference strategies across the 5–30% threshold range, selected to reflect plausible clinical action thresholds for intensified monitoring or escalation in ADHF. Given the small number of outcome events and the absence of external validation, these estimates are preliminary and potentially unstable.

Sensitivity Analysis

The prespecified two-variable sensitivity model (albumin + ln[BNP] only; N=226, 18 deaths) yielded an AUC of 0.77, with ln(BNP) OR 1.99 (95% CI 1.23–3.23; p=0.005) and albumin OR 0.91 (95% CI 0.83–1.00; p=0.055). These results confirm the robustness of these two markers and indicate that the optimism correction in the full model is primarily attributable to non-predictive variables, consistent with the limited events-per-variable ratio.

Discussion

This exploratory, internally validated cohort study of patients hospitalized with ADHF at a single center enriched for CRS1 found that a prespecified admission-based multivariable model incorporating BNP, albumin, eGFR, and HF phenotype showed promising discrimination for in-hospital mortality (apparent AUC 0.81; optimism-corrected AUC 0.73). ln(BNP) was the sole statistically significant independent predictor, with each approximately 2.7-fold increase in raw BNP associated with more than double the odds of in-hospital death. Albumin and eGFR showed consistent directional associations but did not reach statistical significance in the fully adjusted

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model. The principal contribution of this work is not the identification of BNP as a novel prognostic marker — its role in ADHF is well established — but rather the application of a formally prespecified, TRIPOD-reported admission model in a CRS-enriched population, where the prognostic robustness of BNP despite concurrent AKI and volume redistribution has not previously been formally examined. These findings should be interpreted as hypothesis-generating and require external validation before informing clinical practice.

The primacy of BNP is consistent with an extensive prior literature. In the ADHERE registry, Fonarow and colleagues demonstrated that admission BNP levels were strongly and independently associated with in-hospital mortality across a large multicenter ADHF cohort.[3] Our findings replicate this signal in a CRS-enriched population, in which over half of patients had CRS1,[9] a context in which concurrent AKI and volume redistribution might be expected to attenuate or distort the BNP signal. The persistence of BNP as the leading predictor despite these physiologic confounders supports its clinical robustness even in this challenging subgroup. The substantially elevated BNP in the death group (680 vs. 201 pg/mL; $p<0.001$) underscores the magnitude of hemodynamic stress distinguishing those who died from survivors.

The directional association of serum albumin with mortality — observed as an independent signal in the sensitivity model (OR 0.91; $p=0.055$) — aligns with the broader literature on hypoalbuminemia in acute heart failure.[11] Mechanistically, hypoalbuminemia in ADHF reflects hepatic congestion impairing synthetic function, systemic inflammation, malnutrition from chronic low-output states, and hemodilution — processes that collectively signal reduced physiologic reserve. The clinical implication is meaningful: albumin is universally available at admission, requires no additional testing, and may serve as a practical flag for high-risk patients for whom BNP elevation alone may understate the full prognostic picture.

The absence of an independent prognostic contribution from HF phenotype after adjusting for BNP is a meaningful finding. Although phenotype is broadly associated with comorbidity burden and long-term prognosis, its effect on short-term in-hospital mortality appears substantially mediated by BNP and renal function in this cohort. Biomarker severity — reflecting acute hemodynamic stress at presentation — may be more discriminating for the immediate inpatient mortality endpoint than structural classification alone, suggesting that HF phenotype may be better leveraged for longer-term risk stratification and treatment selection rather than for early inpatient triage.

Several methodological strengths merit comment. Predictors were prespecified before analysis, reducing the risk of data-driven overfitting. Bootstrap optimism correction was used instead of simple cross-validation, yielding a more conservative estimate of out-of-sample performance.[12] Reporting followed the TRIPOD[8] and PROBAST[12] frameworks, and decision curve analysis was used to assess clinical utility beyond discrimination.

Limitations of this exploratory study must be explicitly acknowledged. First, the retrospective single-center design limits generalizability. Second, and most critically, only 17 mortality events were available, yielding an events-per-variable ratio of approximately 2.4 — well below the conventional minimum of 10 per variable recommended for stable model development.[17] This increases the risk of overfitting, as reflected in the 5-point optimism correction and a bootstrap-corrected calibration slope of 0.68. The model should therefore be treated as exploratory and hypothesis-generating rather than a deployable clinical tool; external validation in a larger, independent cohort is required before any application to clinical practice.[19,20] Third, unmeasured confounders — including frailty, detailed hemodynamics, and treatment intensity — could not be incorporated. Fourth, LVEF-based phenotype classification may not capture dynamic changes across admissions. Fifth, calibration assessment by deciles is limited with 17 events, as several deciles may contain very few outcome events; quantitative calibration metrics (intercept and slope) have been added to address this. Sixth, the exclusion of 19 patients with missing data introduced potential informative missingness: CRS1 was significantly more prevalent among excluded patients (78.9% vs 40.5%; $p=0.042$), suggesting that the most acutely ill CRS1 patients were disproportionately excluded due to absent BNP

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measurements. This may have resulted in a slightly healthier analytic cohort, and the model performance estimates should be interpreted with this context in mind. The companion cohort description by Abdelgadir et al.[9] should be consulted for full CRS1 epidemiologic context.

In conclusion, this exploratory, internally validated study demonstrates that a prespecified admission-based model incorporating ln(BNP) — the sole statistically significant predictor — along with albumin, eGFR, and HF phenotype achieved promising discrimination for in-hospital mortality in a CRS-enriched ADHF cohort. These findings are hypothesis-generating. External validation in a larger, independent cohort is required before this model can be considered for clinical risk stratification. If validated, this approach may support practical admission-based triage in centers where cardiorenal interactions constitute a substantial component of the acute heart failure inpatient burden.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org.

Author Contributions: MA: Conceptualization, methodology, formal analysis, writing—original draft, and writing—review and editing. EA: Data collection, data curation, and writing—review and editing (primary data owner). SM: Data curation and writing—review and editing. KK: Data curation and writing—review and editing. WG: Data curation and writing—review and editing. LAT: Data collection, data curation, and writing—review and editing. All authors approved the final manuscript.

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Ethics Statement: The study protocol received approval from the institutional review board (approval No. NRA26/006/2) at King Abdulaziz Hospital, MNGHA. Informed consent was waived because of the retrospective design and the use of de-identified data.

Data Availability Statement: The data are not publicly available due to institutional data governance policies at King Abdulaziz Hospital, MNGHA. De-identified data may be provided by the corresponding author upon reasonable request and subject to institutional approval.

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Conflicts of Interest: No author has any conflicts of interest, including financial interests, relationships, or affiliations relevant to the subject matter of this manuscript.

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