International Journal of General Medicine

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ORIGINAL RESEARCH

The "Dilution Effect" of Augmented Renal Clearance on the Prognostic Utility of NT-proBNP in Patients with Severe Traumatic Brain Injury

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Background: Augmented renal clearance (ARC) constitutes a prevalent phenomenon in patients with severe traumatic brain injury (sTBI). Although N-terminal pro-B-type natriuretic peptide (NT-proBNP) serves as a valuable prognostic biomarker, its renal clearance may be accelerated in the presence of ARC, theoretically compromising its predictive accuracy. The present study aimed to quantify this "dilution effect" and construct an ARC-adjusted nomogram to optimize mortality prediction.

Methods: This retrospective cohort study enrolled 352 patients with sTBI admitted to the Geriatrics ICU between June 2020 and June 2024. ARC defined as creatinine clearance >130 mL/min/1.73 m^2. Patients were stratified into ARC and Non-ARC cohorts. To mitigate baseline demographic confounders, propensity score matching (PSM) was employed. The primary endpoint was 28-day mortality. The impact of ARC on serum NT-proBNP concentrations and its subsequent prognostic value was evaluated using receiver operating characteristic (ROC) curves, logistic regression, and decision curve analysis (DCA). NT-proBNP values were log-transformed and included the continuous NRI value to quantify the incremental predictive power of the new model.

Results: Within the original cohort, 141 patients (40.1%) exhibited ARC. In the matched cohort (n=186), patients with ARC demonstrated significantly lower serum NT-proBNP levels compared to the Non-ARC group (P=0.0089), suggesting a distinct biomarker dilution effect. Multivariate analysis identified ARC status as an independent protective factor for mortality, whereas elevated NT-proBNP persisted as a risk factor. Consequently, the predictive accuracy of NT-proBNP was markedly attenuated in the ARC group (AUC=0.637) relative to the Non-ARC group (AUC=0.833). A novel nomogram integrating ARC status, Age, log-NT-proBNP, APACHE II, and Hypertension was developed. This ARC-adjusted model exhibited improved risk stratification capabilities (continuous NRI=0.590) and yielded a higher net clinical benefit than the baseline model.

Conclusion: ARC is associated with significantly depressed serum NT-proBNP levels in sTBI patients, suggesting a "dilution effect" driven by enhanced renal elimination. Clinicians should interpret NT-proBNP levels with caution in this population, as reliance on standard cutoff values may lead to an underestimation of mortality risk.

Keywords: severe traumatic brain injury, augmented renal clearance, NT-proBNP, dilution effect, nomogram, prognosis

Introduction

Severe traumatic brain injury (sTBI) remains a primary cause of mortality and long-term disability worldwide.[1,2] Accurate early-phase prognostication is imperative for guiding clinical decision-making and optimizing resource allocation. While neurological indices such as the Glasgow Coma Scale (GCS) are fundamental, the "brain-heart axis" has garnered increasing attention; specifically, the massive sympathetic surge following brain injury can precipitate neurogenic stunned myocardium and cardiac dysfunction. In this context, N-terminal pro-B-type natriuretic peptide (NT-proBNP), a sensitive marker of hemodynamic stress and myocardial strain, has emerged as a critical prognostic tool. Elevated NT-proBNP levels have been consistently correlate increased mortality and adverse functional outcomes in the TBI population.[3–5]

https://doi.org/10.2147/IJGM.S593500
Received: 3 January 2026
Accepted: 31 March 2026
Published: 13 April 2026

Nevertheless, the diagnostic efficacy of circulating biomarkers is intrinsically dependent on the balance between their production and elimination. NT-proBNP is primarily cleared via renal excretion, making its serum concentration susceptible to variations in renal function.[6] Augmented Renal Clearance (ARC)—defined as creatinine clearance >130 mL/min/1.73 m^2—is a prevalent yet often overlooked phenomenon in the intensive care unit (ICU).[7,8] It is particularly common among younger sTBI patients who often exhibit a hyperdynamic response to trauma.[9,10]

Despite its prevalence, the impact of ARC on renal-dependent biomarkers remains underappreciated. Theoretically, glomerular hyperfiltration in ARC could accelerate NT-proBNP elimination, leading to a "dilution effect" where serum levels are falsely low relative to actual cardiac stress. Consequently, standard prognostic cutoffs established in general populations may be misleading for sTBI patients with ARC, potentially causing clinicians to underestimate mortality risks.

To date, the interplay between ARC, serum NT-proBNP, and their combined prognostic value in sTBI remains fully elucidated. Therefore, this study investigates the influence of ARC on NT-proBNP levels and its prognostic validity in sTBI patients. Utilizing propensity score-matched (PSM) analysis to minimize baseline confounders, we sought to: (1) quantify the difference in NT-proBNP levels between ARC and non-ARC patients; (2) evaluate how ARC confounds and attenuates the predictive power of NT-proBNP for 28-day mortality; and (3) develop a novel, ARC-adjusted nomogram to recalibrate risk stratification. By addressing this diagnostic "blind spot," our findings provide a refined framework for interpreting cardiac biomarkers in hypermetabolic states, ultimately enabling more precise risk assessment and personalized management for critically ill sTBI patients.

Materials and Methods

Study Design and Population

This retrospective cohort study was conducted at the First Affiliated Hospital with Nanjing Medical University between June 2020 and June 2024. The inclusion criteria were: (1) Age >18 years; (2) Diagnosis of severe TBI (GCS score≤8 on admission). Patients were excluded if they had: (1) a history of chronic heart failure (New York Heart Association class II–IV or Left Ventricular Ejection Fraction < 50%); (2) chronic kidney disease;[11] (3) Acute Kidney Injury;[12] (4) Incomplete clinical or laboratory data. The study protocol was approved by the Ethics Committee of the First Affiliated Hospital with Nanjing Medical University (2024-SR-077), with the requirement for informed consent waived due to the retrospective nature of the analysis.

Definition of Augmented Renal Clearance

ARC was defined as a measured creatinine clearance (CrCl) > 130 mL/min/1.73 m^2. CrCl was calculated from 24-hour urine collection using the standard formula: CrCl (mL/min) = [Urine Creatinine (μmol/L) × 24-hour Urine Volume (mL)]/[Serum Creatinine (μmol/L) × 1440 min].[13] The calculated CrCl was normalized to a standard body surface area (BSA) of 1.73 m^2.

Urine collection was initiated immediately following placement of an indwelling urinary catheter (typically within 1 hour of ICU admission). The exact 24-hour collection period was strictly timed and recorded. Total urine volume was measured using calibrated drainage containers. Upon completion of the collection, the entire urine volume was thoroughly mixed before a 20 mL aliquot was extracted for laboratory creatinine analysis. These procedures were executed by specialized ICU nursing staff to minimize sampling errors.[14,15]

Propensity Score Matching

To minimize selection bias and isolate the effect of renal clearance on NT-proBNP levels, we performed Propensity Score Matching (PSM). A 1:1 nearest-neighbor matching algorithm with a caliper width of 0.1 was applied. The matching covariates included Age, Gender, APACHE II score, GCS and Albumin. Balance between groups was assessed using Standardized Mean Differences (SMD).

Statistical Analysis

Data management and analyses were performed using R software (version 4.2.3; The R Foundation for Statistical Computing). Continuous variables were expressed as median (interquartile range [IQR]) and compared between groups

using the Mann–Whitney *U*-test. Categorical variables were summarized as frequencies (percentages) and compared using the Chi-square test. Serum NT-proBNP levels were log-transformed for regression analysis and visualization to normalize the distribution.

Univariate and multivariate logistic regression analyses were performed to identify independent predictors of 28-day mortality. Variables with $P < 0.05$ in univariate analysis were entered into the multivariate model using the Enter method. To prevent multicollinearity, the GCS score was intentionally excluded from the multivariable analysis as it is a fundamental component of the APACHE II score. Multicollinearity among independent variables was assessed using variance inflation factor (VIF), with VIF > 5 indicating significant multicollinearity. The prognostic performance of NT-proBNP was evaluated using Receiver Operating Characteristic (ROC) curves, and the Area Under the Curve (AUC) was compared between ARC and Non-ARC groups using the DeLong test. Optimal cutoffs were determined using the Youden index. Model improvement was quantified using Net Reclassification Improvement (NRI) and Integrated Discrimination Improvement (IDI).

A prognostic nomogram was established based on the independent predictors identified in the multivariate analysis. The comprehensive performance of the model was evaluated by assessing discrimination via the concordance index (C-index/AUC) and calibration through plots using 1,000 bootstrap resamples to compare predicted versus observed probabilities. Furthermore, the clinical utility of the nomogram was determined using Decision Curve Analysis (DCA) to estimate the net benefit across a range of threshold probabilities.

Analyses for mechanism validation (comparison of NT-proBNP levels and ROC curves between ARC and non-ARC groups) were performed in the propensity score-matched cohort (n=186). Multivariate logistic regression, model comparison, nomogram development, calibration, decision curve analysis, and subgroup analyses were performed in the original cohort (n=352).

Results

Baseline Characteristics and Propensity Score Matching

A total of 352 patients with severe TBI were included in the original cohort, as detailed in the study flowchart (Figure 1). The cohort comprised 141 (40.1%) patients in the ARC group and 211 (59.9%) in the Non-ARC group. Patients with ARC were significantly younger (median 57 vs 69 years, $P < 0.001$) and had lower APACHE II scores (17 vs 20, $P < 0.001$) compared to the Non-ARC group Notably, despite similar intracranial hemorrhage volumes, ARC patients presented with significantly lower median serum NT-proBNP levels (897.00 vs 1201.00pg/mL, $P = 0.001$) After 1:1 propensity score matching, 93 pairs (n=186) were generated. The matching process successfully balanced most baseline demographics, including Age, Gender, Hypertension, and APACHE II scores (Standardized Mean Differences < 0.1) (Table 1), with minor imbalances in GCS score adjusted through multivariate regression.

The "Dilution Effect" of ARC on Serum NT-proBNP Levels

In the matched cohort, serum NT-proBNP levels remained significantly lower in the ARC group compared to the non-ARC group (896.10 vs 1296.00 pg/mL, P=0.009). This difference persisted after log transformation (P=0.0089 by Wilcoxon test), as illustrated in Figure 2, suggesting a potential association between ARC and reduced NT-proBNP levels consistent with a "dilution effect."

Risk Factors for 28-Day Mortality

In the univariate analysis, ARC status was associated with significantly reduced odds of 28-day mortality (OR= 0.264, P<0.001), while elevated NT-proBNP was associated with increased risk (OR=1.035 per 100 pg/mL, P<0.001). Other significant risk factors included hypertension (OR=2.169), higher APACHE II scores (OR=1.104), and lower GCS scores (OR=0.792). In the multivariate logistic regression model, both ARC and NT-proBNP remained independent predictors. ARC was independently protective (OR=0.446, P=0.007), whereas NT-proBNP remained an independent risk factor for mortality (OR=1.031, P<0.001). Hypertension (P=0.025) and APACHE II score (P=0.005) also retained significance (Table 2). Collinearity diagnostics using variance inflation factor (VIF) confirmed no significant multicollinearity among

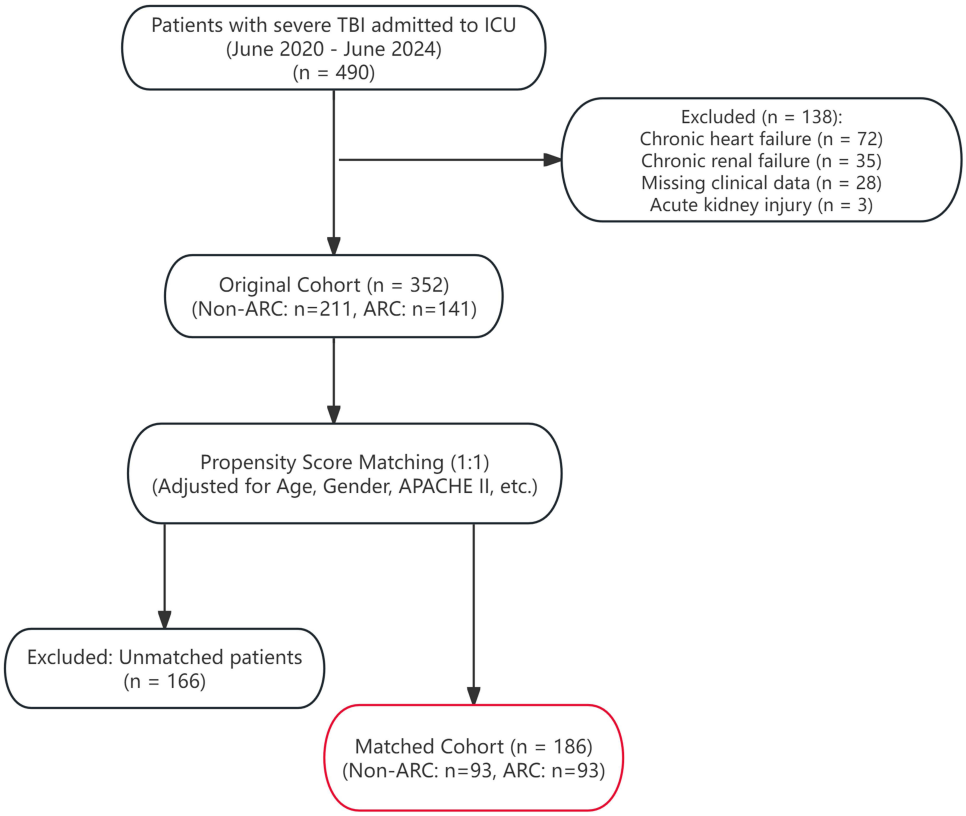

Figure 1 Flowchart of study participant selection. The study initially screened 490 patients with severe traumatic brain injury (TBI) admitted to the ICU between June 2020 and June 2024. After excluding 138 patients based on exclusion criteria (chronic heart/renal failure, missing data, or acute kidney injury), the original cohort consisted of 352 patients, including 211 in the Non-ARC group and 141 in the ARC group. Propensity score matching (PSM) was performed at a 1:1 ratio to balance baseline characteristics, resulting in a final matched cohort of 186 patients (93 in each group) for mechanism validation. The red box highlights the matched cohort (n=186) ultimately used for mechanism validation.
Abbreviation: PSM, propensity score matching.

the independent variables in the multivariate model (all VIF < 2). ARC status VIF = 1.37; NT-proBNP VIF = 1.15; APACHE II VIF = 1.13; Hypertension VIF=1.03.

Impact of ARC on the Predictive Performance of NT-proBNP

We evaluated the prognostic accuracy of NT-proBNP for 28-day mortality using ROC analysis. As shown in Figure 3, NT-proBNP demonstrated excellent discriminative ability in non-ARC patients (AUC=0.833, 95% CI:0.763–0.904). However, its predictive performance was significantly attenuated in ARC patients (AUC=0.637, 95% CI: 0.513–0.761) (P<0.001 by DeLong test). Furthermore, the optimal cutoff value derived from the Youden index in the non-ARC group (986 pg/mL) strongly stratified mortality risk (OR=23.29, P<0.001), whereas the corresponding cutoff in the ARC subgroup (847.26 pg/mL) failed to achieve statistical significance (OR=2.00, P=0.144) (Table 3).

Subgroup Analysis and Interaction Effects

Subgroup analysis was performed in the original cohort (n=352) to explore potential effect modification by clinical characteristics (Figure 4). The interaction tests revealed that the dilution effect of ARC on NT-proBNP prognostic utility was more pronounced in patients aged <65 years (P for interaction=0.024), male sex (P for interaction=0.01), those without hypertension (P for interaction=0.002), and those with APACHE II scores <20 (P for interaction=0.014). In contrast, no significant interaction was observed for other clinical parameters.

Table 1 Baseline Demographic and Clinical Characteristics of Patients with Severe Traumatic Brain Injury in the Original Cohort (n=352) and Matched Cohort (n=186)

Variable	Original Cohort (n=352)			Matched Cohort (n=186)			
	Non-ARC (n=211)	ARC (n=141)	P	Non-ARC (n=93)	ARC (n=93)	P	SMD
Age (years)	69 (59, 76.50)	57 (50, 64)	<0.001	60 (51, 68)	59 (54, 66)	0.729	0.039
Male, n (%)	65 (30.8)	38 (27.0)	0.51	21 (22.6)	23 (24.7)	0.863	0.051
BMI (kg/m^2)	23.46 (20.98, 26.03)	24.41 (21.97, 26.23)	0.061	23.40 (21.12, 26.13)	23.99 (21.51, 26.12)	0.689	0.025
Diabetes	85 (40.3)	49 (34.8)	0.35	33 (35.5)	34 (36.6)	1	0.022
Arterial Hypertension, n (%)	98 (46.4)	53 (37.6)	0.125	40 (43.0)	37 (39.8)	0.766	0.066
NT-proBNP (pg/mL)	1201.00 (317.50, 6645.00)	897.00 (311.00, 1453.00)	0.001	1296.00 (334.00, 6550.00)	896.10 (311.00, 1337.00)	0.009	0.658
APACHE II	20 (16.5, 23)	17 (14, 21)	<0.001	18 (15, 21)	18 (14, 22)	0.696	0.113
Glasgow coma scale	3.00 (3.00, 4.00)	4.00 (3.00, 4.00)	<0.001	3.00 (3.00, 4.00)	4.00 (3.00, 4.00)	<0.001	0.259
Intracerebral Hemorrhage volume, mL	18.90 (12.65, 24.90)	18.10 (12.80, 24.50)	0.374	18.90 (12.00, 25.00)	18.60 (13.40, 24.60)	0.736	0.036
Urine creatinine, mmol/24h	6044.00 (4145.00, 9203.50)	12,050.00 (9599.00, 16,100.00)	<0.001	6047.00 (4558.00, 8830.00)	11,851.00 (9364.00, 16,100.00)	<0.001	1.232
Serum creatinine, μmol/L	73.40 (60.00, 98.05)	53.20 (43.70, 68.20)	<0.001	72.20 (60.10, 96.50)	52.80 (42.80, 71.20)	<0.001	0.939
Serum albumin, g/L	30.00 (26.00, 35.00)	33.00 (30.00, 36.00)	<0.001	34.00 (29.00, 38.00)	32.00 (30.00, 35.00)	0.124	0.168
Lymphocyte ($10^9/L$)	2.35 (1.32, 3.75)	2.79 (1.35, 3.87)	0.285	2.27 (1.61, 3.14)	2.60 (1.20, 3.68)	0.67	0.062
Neutrophil ($10^9/L$)	4.37 (2.86, 6.10)	4.15 (2.43, 6.24)	0.19	4.26 (2.77, 6.36)	4.38 (2.69, 6.31)	0.835	0.034
Platelet ($10^9/L$)	244.00 (124.50, 365.50)	219.00 (140.00, 328.00)	0.514	211.00 (105.00, 348.00)	250.00 (146.00, 333.00)	0.246	0.155
Total fluid input, mL	2451.00 (1998.00, 3023.00)	2560.00 (2102.00, 3047.00)	0.374	2460.00 (2038.00, 2841.00)	2560.00 (2084.00, 3080.00)	0.297	0.153
28-day mortality, n (%)	109 (51.7)	31 (22.0)	<0.001	46 (49.5)	23 (24.7)	0.001	0.53

Notes: *P* values were calculated using the Mann–Whitney *U*-test for continuous variables and the Chi-square test for categorical variables. Data are presented as median (interquartile range) (IQR) for continuous variables and number (percentage) (n (%)) for categorical variables.

Abbreviations: ARC, Augmented Renal Clearance; BMI, Body Mass Index; NT-proBNP, N-terminal pro-B-type natriuretic peptide; APACHE II, Acute Physiology and Chronic Health Evaluation II; GCS, Glasgow Coma Scale.

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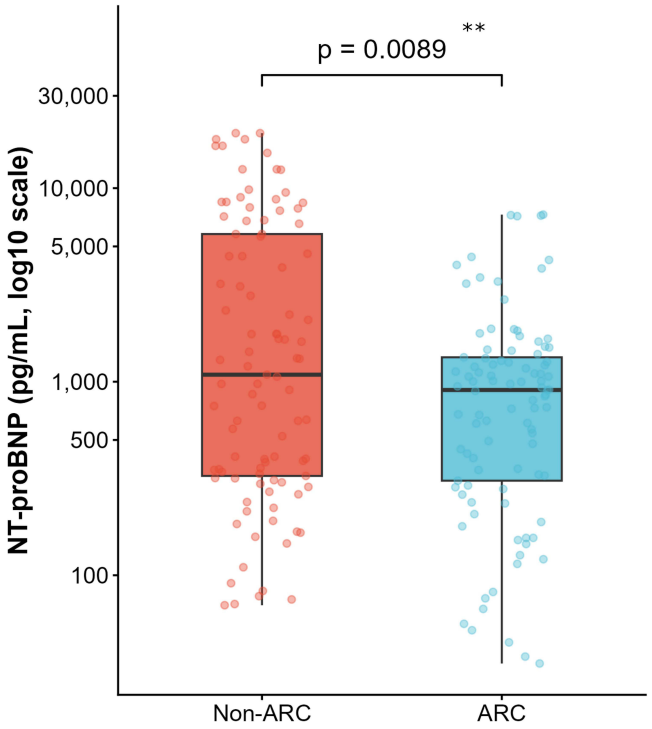

Figure 2 Comparison of serum NT-proBNP levels between Non-ARC and ARC groups in the matched cohort (n=186). The boxplot displays the distribution of log-transformed NT-proBNP levels.[6] Patients in the ARC group exhibited significantly lower NT-proBNP levels compared to the Non-ARC group (P = 0.0089). The horizontal line within the box represents the median, and the box edges represent the interquartile range. ** indicates p<0.001.

Model Development, Comparison, and Clinical Utility

To assess the added value of integrating ARC status into risk prediction, we compared four models using AUC, Net Reclassification Improvement (NRI), and Integrated Discrimination Improvement (IDI) (Table 4). Model 1 (age and

Table 2 Univariate and Multivariate Logistic Regression Analysis of Risk Factors for 28-Day Mortality in Patients with Severe Traumatic Brain Injury

Parameter	Univariate OR (95% CI)	Univariate P	Multivariate OR (95% CI)	Multivariate P
Age	1.019 (1.003, 1.036)	0.019	0.988 (0.968, 1.009)	0.253
Gender (Male)	1.408 (0.884, 2.241)	0.149		
BMI	0.990 (0.935, 1.048)	0.735		
ARC Status (Ref: Non-ARC)	0.264 (0.163, 0.427)	<0.001	0.446 (0.246, 0.801)	0.007
NT-proBNP (per 100 pg/mL)	1.035 (1.025, 1.044)	<0.001	1.031 (1.021, 1.041)	<0.001
Serum Creatinine	1.006 (1.000, 1.013)	0.057		
APACHE II Score	1.104 (1.054, 1.158)	<0.001	1.085 (1.026, 1.149)	0.005
GCS Score	0.792 (0.646, 0.972)	0.026		
Hemorrhage Volume	0.974 (0.944, 1.006)	0.114	0.978 (0.941, 1.016)	0.249
Hypertension	2.169 (1.403, 3.354)	<0.001	1.79 (1.075, 2.987)	0.025
Diabetes	1.266 (0.817, 1.961)	0.292		
Albumin (ALB)	0.968 (0.927, 1.012)	0.155		
CRP	1.000 (0.994, 1.007)	0.896		
Neutrophils	1.025 (0.920, 1.142)	0.661		
Lymphocyte	0.856 (0.734, 0.998)	0.047	0.94 (0.785, 1.125)	0.50

Notes: The multivariate model was adjusted for Age, ARC Status, BNP, APACHE II Score, Hypertension, and Lymphocyte count. P < 0.05 indicates statistical significance.

Abbreviations: OR, Odds Ratio; CI, Confidence Interval; ARC, Augmented Renal Clearance; NT-proBNP, N-terminal pro-B-type natriuretic peptide; APACHE II, Acute Physiology and Chronic Health Evaluation II; GCS, Glasgow Coma Scale.

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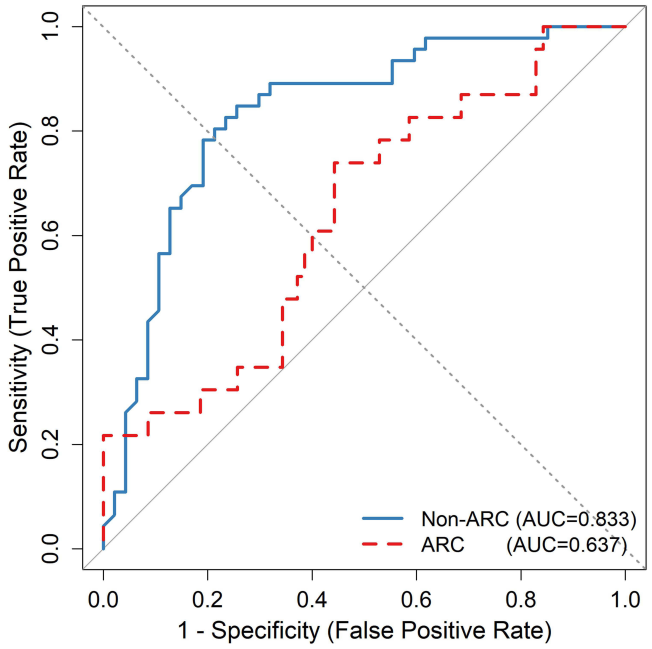

Figure 3 Receiver operating characteristic (ROC) curves for the prognostic value of NT-proBNP (n=186). ROC analysis was performed to evaluate the predictive ability of NT-proBNP for 28-day mortality in the matched cohort. The area under the curve (AUC) was significantly higher in the Non-ARC group (AUC = 0.833; solid blue line) compared to the ARC group (AUC = 0.637; dashed red line), suggesting a reduced prognostic utility of NT-proBNP in the presence of ARC.
Abbreviation: ROC, receiver operating characteristic.

gender) showed limited discriminative ability with an AUC of 0.585 (95% CI: 0.530–0.651). The addition of APACHE II score and hypertension in Model 2 significantly improved the AUC to 0.682 (95% CI: 0.624–0.740, P=0.016 vs Model 1). A substantial increase in model performance was observed in Model 3 with the inclusion of log10NT-ProBNP, reaching an AUC of 0.811 (95% CI: 0.771–0.857, P<0.001 vs Model 2).

Notably, although the further addition of ARC status in Model 4 yielded a modest increase in AUC to 0.856 (95% CI:0.790–0.881) and the DeLong test showed no statistically significant difference compared to Model 3 (P=0.317), the reclassification indices demonstrated significant incremental value. Specifically, the category-free NRI for Model 4 versus Model 3 was 0.590 (95% CI: 0.397–0.848), and the IDI was 0.066 (95% CI:0.027–0.126). These results indicate that incorporating ARC status significantly improves the accuracy of risk stratification beyond traditional clinical factors and BNP levels.

Based on the identified independent predictors, a prognostic nomogram was constructed to facilitate clinical application (Figure 5A). The model integrates the four confirmed independent predictors: ARC status, log10NT-proBNP, APACHE II score, and Hypertension. The calibration curve demonstrated excellent agreement between the nomogram-predicted probabilities and the actual observed mortality rates, with the bias-corrected line closely tracking the ideal reference line

Table 3 Optimal Cutoff Values of NT-proBNP for Predicting 28-Day Mortality Stratified by ARC Status

Group/Method	Cutoff (pg/mL)	OR (95% CI) for Mortality	P-value
Total Population	856.32	9.40 (5.34–16.55)	<0.001
Non-ARC Subgroup	986	23.29 (10.82–50.15)	<0.001
ARC Subgroup	847.26	2.00 (0.79–5.05)	0.144

Notes: The Odds Ratio (OR) represents the risk of mortality for patients with NT-proBNP levels above the cutoff compared to those below the cutoff. The optimal cutoff values were determined using the Youden index from the ROC curve analysis.
Abbreviations: ARC, Augmented Renal Clearance; NT-proBNP, N-terminal pro-B-type natriuretic peptide; OR, Odds Ratio; CI, Confidence Interval.

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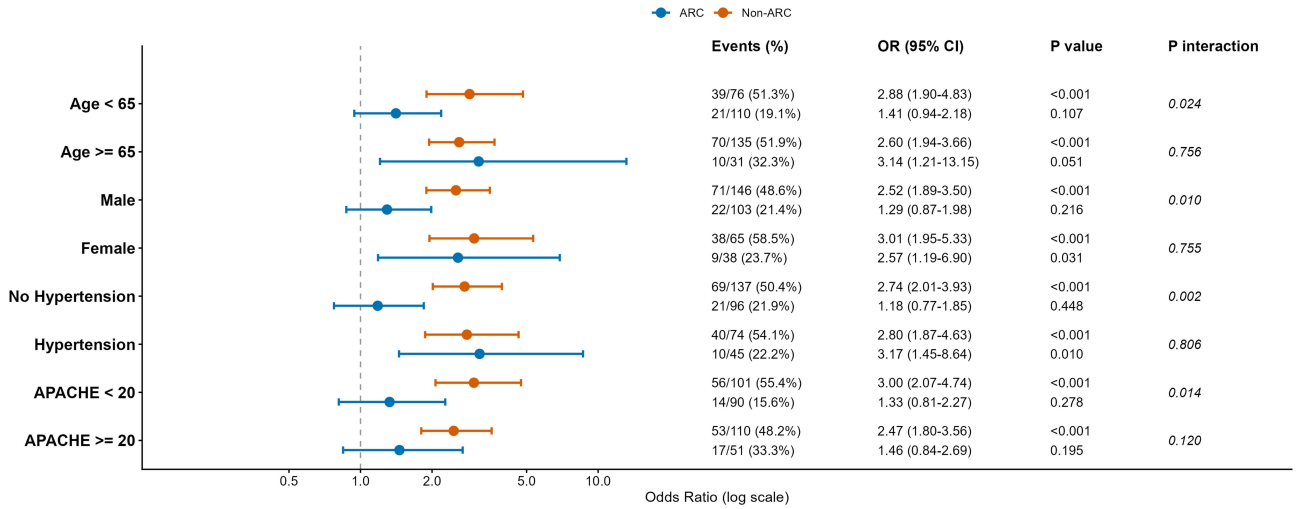

Figure 4 Forest plot of subgroup analysis for the association between NT-proBNP and mortality (n=352). The plot shows the odds ratios (OR) and 95% confidence intervals (CI) for the association between NT-proBNP and 28-day mortality across various subgroups, including Age, Sex, Hypertension status, and APACHE II score. The P-value for interaction indicates whether the effect size differs significantly across subgroups.
Abbreviations: OR, odds ratio; CI, confidence interval.

(Figure 5B). Decision Curve Analysis (DCA) showed that the new nomogram (incorporating ARC status) provided a higher net benefit across a broad range of threshold probabilities compared to the baseline model (without ARC) or simple "treat-all" /"treat-none" strategies (Figure 5C). These findings suggest the potential clinical utility of the ARC-adjusted model for decision-making in sTBI management.

Discussion

To our knowledge, this is the first study to systematically quantify the "dilution effect" of ARC on serum NT-proBNP levels and its consequential impact on mortality prediction in severe TBI. Our findings reveal a critical "diagnostic blind spot": in nearly 40% of our cohort (the ARC group), the classic "brain-heart axis" signal appeared to be masked by renal hyperfiltration. While previous studies have established elevated NT-proBNP as a robust predictor of poor outcomes,[6,16] our data suggest that this dogma holds true only when renal function is "normal" or impaired. In the presence of ARC, the prognostic utility of NT-proBNP is significantly compromised (AUC dropped from 0.833 to 0.637), leading to a dangerous underestimation of mortality risk if standard reference ranges are applied.

The inverse relationship between renal function and natriuretic peptides is well-documented in renal failure, where reduced GFR leads to biomarker accumulation. Our study explores the opposite spectrum—renal hyperfiltration. We hypothesize a mechanism of "Pharmacokinetic Decoupling": in the hyperdynamic phase of severe TBI, the massive catecholamine surge and young age may drive a supraphysiological increase in GFR.[15,17] This phenomenon creates a divergence between biological

Table 4 Comparison of Model Performance (AUC, NRI, and IDI) for Predicting 28-Day Mortality

Model	AUC (95% CI)	P-value (DeLong)	NRI (95% CI)	IDI (95% CI)
Model 1: Demographics (Age + Gender)	0.585 (0.530–0.651)	Ref.	Ref.	Ref.
Model 2: (Model 1 + APACHE II + Hypertension)	0.682 (0.624–0.740)	0.016	0.408 (0.195–0.627)	0.056 (0.022–0.107)
Model 3: (Model 2 + log10BNP)	0.811 (0.771–0.857)	<0.001	0.607 (0.442–0.853)	0.150 (0.094–0.209)
Model 4: (Model 3 + ARC Status)	0.856 (0.790–0.881)	0.317	0.590 (0.397–0.848)	0.066 (0.027–0.126)

Notes: The DeLong test was used to compare the AUC between sequential models (Model 2 vs 1, Model 3 vs 2, and Model 4 vs 3). Reclassification indices: The category-free NRI (cNRI) and IDI were calculated using the immediately preceding model as the reference (eg, Model 4 was compared against Model 3) to evaluate the incremental predictive value of the newly added variable.
Abbreviations: AUC, Area Under the Receiver Operating Characteristic Curve; NRI, Net Reclassification Improvement; IDI, Integrated Discrimination Improvement; CI, Confidence Interval; ARC, Augmented Renal Clearance; 95% CI, Confidence Intervals.

https://doi.org/10.2147/IJGM.S593500

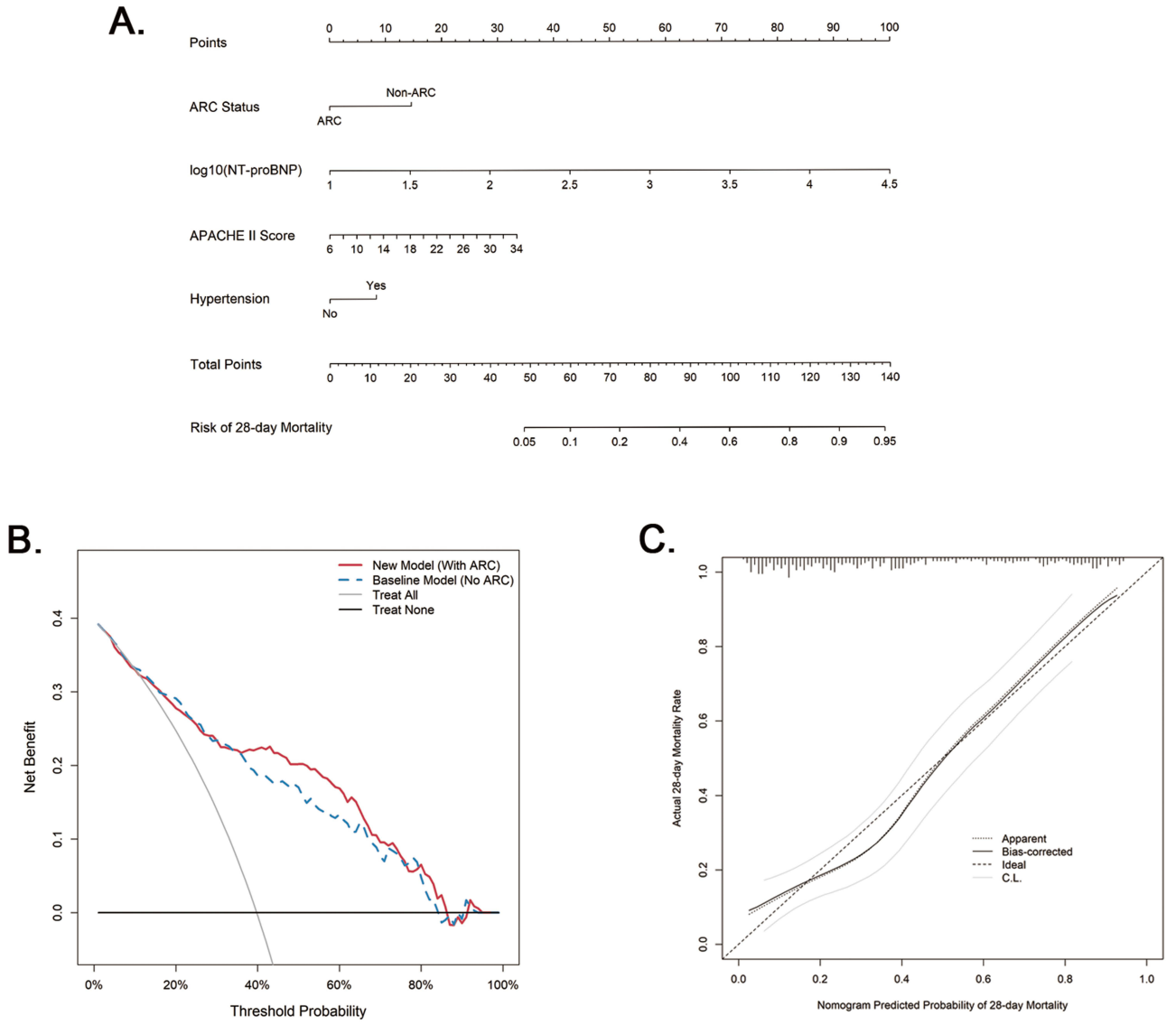

Figure 5 Construction, calibration, and clinical utility of the predictive nomogram for 28-day mortality (n=352). (**A**) The prognostic nomogram integrating ARC status, Age, log-transformed NT-proBNP, APACHE II score and Hypertension. To use the nomogram, locate the patient's value on each variable axis, draw a vertical line upwards to the "Points" axis to determine the score, sum the points for all variables to obtain the "Total Points," and draw a vertical line downwards to estimate the 28-day mortality probability. (**B**) Calibration curve of the nomogram. The x-axis represents the predicted mortality risk, and the y-axis represents the actual observed risk. The diagonal dashed line represents a perfect prediction by an ideal model. The solid line represents the bias-corrected performance of the nomogram (bootstrapping B=1000), indicating good agreement between predicted and observed outcomes. (**C**) Decision Curve Analysis (DCA) evaluating the clinical usefulness of the predictive models. The y-axis measures the net benefit. The blue solid line represents the "New Model" (incorporating ARC status), while the Orange dashed line represents the "Baseline Model" (without ARC status). The horizontal black line assumes no intervention (Treat None), and the gray line assumes intervention for all patients (Treat All). The New Model demonstrates an improved net benefit across the majority of threshold probabilities compared to the Baseline Model, suggesting potential incremental clinical utility.

production and serum concentration. As elucidated by Udy et al,[17] the TBI-induced surge in Atrial Natriuretic Peptide (ANP) acts as a physiological driver to increase glomerular filtration. If this mechanism holds, NT-proBNP—being metabolically inert and exclusively dependent on renal excretion—may become disproportionately cleared, potentially explaining the observed association between ARC and lower NT-proBNP levels. However, this proposed mechanism remains hypothetical and requires confirmation through prospective pharmacokinetic studies that directly measure renal clearance of NT-proBNP.

The most clinically relevant finding is the failure of conventional cutoffs. In our Non-ARC cohort, a cutoff of 986 pg/mL effectively stratified high-risk patients. However, in the ARC subgroup, even much lower levels failed to reach statistical significance for mortality prediction. This implies that for a young TBI patient with ARC, a "normal" NT-proBNP level should not be reassuring. This necessitates a paradigm shift in biomarker interpretation: renal function

should be viewed as a continuous variable that modulates biomarker "sensitivity." It is also important to note that although the optimal NT-proBNP cut-off value in the ARC group (847.26 pg/mL) was similar to that of the total population, the clinical interpretation differs fundamentally. The total population cut-off represents a weighted average of two distinct subgroups. In ARC patients, the same numerical value may reflect a higher underlying mortality risk due to biomarker dilution. Thus, the ARC-adjusted model serves as a recalibration tool to ensure that high-risk ARC patients are not overlooked by traditional cutoffs.

A key finding is the significant incremental value of ARC status beyond BNP for predicting mortality. While the AUC increase from Model 3 to Model 4 was modest (0.811 to 0.856, P=0.317), the reclassification metrics demonstrated superior utility: the category-free NRI was 0.590 (95% CI: 0.397–0.848) and the IDI was 0.066 (95% CI: 0.027–0.126). This divergence between AUC and reclassification indices is well-documented. As noted by Pencina et al,[18] when a baseline model is already strong (AUC > 0.8), the AUC metric becomes insensitive to new markers. In such cases, NRI and IDI offer a more clinically relevant assessment. Our significant NRI indicates that adding ARC status correctly shifted the risk prediction direction for approximately 59.0% of patients compared to using BNP alone. These results confirm that ARC status is a critical, independent prognostic indicator for mortality in ICU patients. Our nomogram (Figure 5A) operationalizes this concept by integrating ARC status as a correction factor. These findings suggest that the ARC-adjusted nomogram may provide incremental value, though further prospective multicenter validation is required to confirm its clinical utility.

Our study has several limitations. First, as a single-center retrospective study, selection bias cannot be entirely ruled out, although propensity score matching was used to mitigate this. Second, we relied on creatinine clearance (CrCl) estimated by the Cockcroft-Gault formula or urinary creatinine collection to define ARC; while practical, measured GFR using exogenous markers would be more precise. Third, we assessed baseline NT-proBNP levels; dynamic changes in BNP and renal function over time might provide additional prognostic information. Fourth, the observational nature of our study precludes definitive conclusions about causality; the observed association between ARC and reduced NT-proBNP levels suggests but does not prove a direct "dilution effect" mediated by renal hyperfiltration. Fifth, the subgroup analyses were exploratory and not adjusted for multiple testing, thus these findings should be interpreted with caution and require validation in future studies. Finally, our model requires external validation in multi-center cohorts to confirm its generalizability.

Conclusion

In conclusion, our findings suggest that ARC may exert a "dilution effect" on serum NT-proBNP levels in patients with severe TBI, which potentially limits the reliability of conventional prognostic cutoffs. The integration of ARC status into a prognostic nomogram appears to account for this pharmacokinetic influence, providing enhanced mortality risk stratification. Clinicians should consider that in hyperdynamic TBI patients, a relatively "low" NT-proBNP level does not necessarily equate to low clinical risk, as it may partly reflect accelerated renal elimination. However, prospective multi-center studies are warranted to validate the clinical utility of this ARC-adjusted nomogram before it can be recommended for routine application.

Use of AI Tools

During the preparation of this work, the authors used Gemini (Google's AI assistant) solely for language polishing and improving readability. The original research design, data analysis, statistical interpretation, and core scientific conclusions were conducted entirely by the authors. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Data Sharing Statement

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

Ethics Approval and Consent to Participate

All procedures and methods were performed in accordance with relevant guidelines and regulations. This study protocol was reviewed and approved by the Ethics Committee of the First Affiliated Hospital with Nanjing Medical University (2024-SR-077). All procedures were conducted in accordance with the Declaration of Helsinki. We confirm that all patient data were handled with strict confidentiality and in compliance with data protection regulations.

Acknowledgments

The authors thank the patients for participation in our study and the staffs of the Geriatric Intensive Care Unit at the First Affiliated Hospital with Nanjing Medical University for assistance.

Author Contributions

D.J. analyzed the data and performed statistical analysis. Q.Z. contributed to the writing. M.H., J.Z., and S.Z. reviewed the paper. Z.D. is the guarantor of this work, who had complete access to all the data in the study and takes ultimate responsibility for the study design and integrity of data analysis. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This work was supported by grants from Wu Jieping Medical Foundation Runze Fund for Critical Care Medicine (No. 320.6750.2024-2-2).

Disclosure

The authors have no conflicts of interest to declare in this work.

References

1. Hasanin A, Kamal A, Amin S, et al. Incidence and outcome of cardiac injury in patients with severe head trauma. *Scand J Trauma Resusc Emerg Med*. 2016;24:58. doi:10.1186/s13049-016-0246-z
2. Maas AIR, Menon DK, Manley GT, et al. Traumatic brain injury: progress and challenges in prevention, clinical care, and research. *Lancet Neurol*. 2022;21(11):1004–1060. doi:10.1016/S1474-4422(22)00309-X
3. Kirchhoff C, Leidel BA, Kirchhoff S, et al. Analysis of N-terminal pro-B-type natriuretic peptide and cardiac index in multiple injured patients: a prospective cohort study. *Crit Care*. 2008;12(5):R118. doi:10.1186/cc7013
4. Sviri GE, Soustiel JF, Zaaroor M. Alteration in brain natriuretic peptide (BNP) plasma concentration following severe traumatic brain injury. *Acta Neurochir*. 2005;148(5):529–33; discussion 533. doi:10.1007/s00701-005-0666-4
5. Chiollaz A-C, Pouillard V, Seiler M, et al. Evaluating NfL and NTproBNP as predictive biomarkers of intracranial injuries after mild traumatic brain injury in children presenting to emergency departments. *Front Neurol*. 2025;16:1518776. doi:10.3389/fneur.2025.1518776
6. Wettersten N, Horiuchi Y, van Veldhuisen DJ, et al. B-type natriuretic peptide trend predicts clinical significance of worsening renal function in acute heart failure. *Eur J Heart Fail*. 2019;21(12):1553–1560. doi:10.1002/ejhf.1627
7. Udy AA, Baptista JP, Lim NL, et al. Augmented renal clearance in the ICU: results of a multicenter observational study of renal function in critically ill patients with normal plasma creatinine concentrations*. *Crit Care Med*. 2014;42(3):520–527. doi:10.1097/CCM.0000000000000029
8. Bilbao-Meseguer I, Rodríguez-Gascón A, Barrasa H, Isla A, Solinís MÁ. Augmented renal clearance in critically ill patients: a systematic review. *Clin Pharmacokinet*. 2018;57(9):1107–1121. doi:10.1007/s40262-018-0636-7
9. Lipman J, Lewis RE. The long walk to a short half-life: the discovery of augmented renal clearance and its impact on antibiotic dosing. *J Antimicrob Chemother*. 2025;80(12):3367–3374. doi:10.1093/jac/dkaf378
10. Hefny F, Stuart A, Kung JY, Mahmoud SH. Prevalence and risk factors of augmented renal clearance: a systematic review and meta-analysis. *Pharmaceutics*. 2022;14(2). doi:10.3390/pharmaceutics14020445
11. **Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Update Work Group**. KDIGO 2017 clinical practice guideline update for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). *Kidney Int Suppl*. 2017;7:1–59. Erratum: *Kidney Int Suppl* 2017;**7**(3):e1.
12. Kellum JA, Lameire N. Diagnosis, evaluation, and management of acute kidney injury: a KDIGO summary (Part 1). *Crit Care*. 2013;17(1):204. doi:10.1186/cc11454
13. Luo Y, Wang Y, Ma Y, Wang P, Zhong J, Chu Y. Augmented renal clearance: what have we known and what will we do? *Front Pharmacol*. 2021;12:723731. doi:10.3389/fphar.2021.723731
14. Kawano Y, Morimoto S, Izutani Y, et al. Augmented renal clearance in Japanese intensive care unit patients: a prospective study. *J Intensive Care*. 2016;4:62. doi:10.1186/s40560-016-0187-7

15. Ochoa Gautier JB, Martindale RG, Rugeles SJ, et al. How much and what type of protein should a critically ill patient receive? *Nutr Clin Pract*. 2017;32(1_suppl). doi:10.1177/0884533617693609
16. Schou M, Dalsgaard MK, Clemmesen O, et al. Kidneys extract BNP and NT-proBNP in healthy young men. *J Appl Physiol*. 2005;99 (5):1676–1680. doi:10.1152/japplphysiol.00641.2005
17. Udy AA, Jarrett P, Lassig-Smith M, et al. Augmented renal clearance in traumatic brain injury: a single-center observational study of atrial natriuretic peptide, cardiac output, and creatinine clearance. *J Neurotrauma*. 2016;34(1):137–144. doi:10.1089/neu.2015.4328
18. Pencina MJ, D'Agostino RB, D'Agostino RB, Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. *Stat Med*. 2008;27(2):157–172. doi:10.1002/sim.2929