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ORIGINAL ARTICLE

Prognostic significance of the blood urea nitrogen to creatinine ratio in in-hospital cardiac arrest after targeted temperature management

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Abstract

Background: Targeted temperature management (TTM) has been reported to improve outcomes in in-hospital cardiac arrest (IHCA) patients but little has been investigated into the relationship between prognoses and the blood urea nitrogen to creatinine ratio (BCR).

Methods: A retrospective analysis of data from IHCA survivors treated with TTM between 2011 and 2018 was conducted based on the Research Patient Database Registry of the Partners HealthCare system in Boston. Serum laboratory data were measured during IHCA and within 24 hours after TTM completion. Intra-arrest and post-TTM BCRs were calculated, respectively. The primary outcome was neurologic status at discharge. The secondary outcome was in-hospital mortality.

Results: The study included 84 patients; 63 (75%) were discharged with a poor neurologic status and 40 (47.6%) died. Regarding poor neurological outcome at discharge, multivariate analysis revealed that post-TTM BCR was a significant predictor (adjusted OR, 1.081; 95% CI, 1.002–1.165; $p = 0.043$) and intra-arrest BCR was a marginal predictor (adjusted OR, 1.067; 95% CI, 1.000–1.138; $p = 0.050$). Post-TTM BCR had an acceptably predictive ability to discriminate neurological status at discharge, with an area under the receiver-operating characteristic curve of 0.644 (95% CI, 0.516–0.773) and a post-TTM BCR cutoff value of 16.7 had a sensitivity of 61.9% and a specificity of 70.0%.

Conclusion: Post-TTM BCR was a significant predictor of the neurologic outcome at discharge among IHCA patients receiving TTM. IHCA patients with elevated intra-arrest BCR also had a borderline poor neurological prognosis at discharge.

Keywords: Blood urea nitrogen; Cardiac arrest; Creatinine; Neurologic outcome; Survival; Targeted temperature management

1. INTRODUCTION

In-hospital cardiac arrest (IHCA) poses a public health threat and carries an unsatisfactory prognosis, though most existing literature focuses on out-of-hospital cardiac arrest. Approximately 292 000 adult IHCAs occur in the United States annually with survival and good functional status to discharge rates at most 36.4% and 23%, respectively.[1-5] Targeted temperature management (TTM) has been reported to improve the outcome in these patients.[6,7] Although most research on cardiac arrest (CA) emphasizes situational differences such as witnessed arrest, bystander cardiopulmonary resuscitation, or shockable cardiac rhythm, little has been investigated into the relationship between prognoses and biomarkers.[8-12]

Renal function has been suggested to predict patient outcomes in a few circumstances, including CA and acute coronary syndrome, as chronic kidney disease is notorious for increased cardiovascular risks.[13,14] The blood urea nitrogen (BUN) to creatinine (Cr) ratio (BCR) is a promising indicator reflecting more than patient fluid or nutritional status. It is also positively associated with mortality in heart failure, kidney disease, COVID-19, and stroke.[15-21] Moreover, others have shown that patients with lower BCR are more likely to have preserved neurologic function following an ischemic stroke.[19,22,23]

Because BCR has been shown to predict the outcome in the above events, it is of interest whether its prognostic ability still holds true in IHCA patients who receive TTM. There has also been less evidence previously for biomarkers to exhibit their predictive effects on CAs. Therefore, this study aims to examine the hypothesis that high BCR in IHCA patients treated with TTM is associated with an increased risk of death and poor neurological progress.

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2. METHODS

2.1. Study design and setting

We conducted a retrospective cohort study examining the factors associated with survival and neurological outcomes following CA based on the Research Patient Database Registry (RPDR) of the Partners HealthCare System in Boston. Inclusion criteria were IHCA undergoing a resuscitation attempt and receiving subsequent TTM between January 2011 and December 2018, 18 years of age or older, and the acquisition of a blood sample during CPR following CA and within 24 hours after TTM completion. Patients were excluded if they died during TTM, had missing data, did not complete TTM or reach the target temperature, or had a do-not-resuscitate order. All resuscitative measures, including, but not limited to, chest compressions, airway management, vasopressor administration, defibrillation, and other advanced resuscitative measures, were routinely performed and documented in accordance with the advanced cardiac life support guidelines. The RPDR Database is a multi-centered registry which is composed of over 6.5 million patients who had services at Brigham and Women's Hospital, Massachusetts General Hospital, Faulkner Hospital, Spaulding Rehabilitation Hospital, Newton Wellesley Hospital, North Shore Medical Center or McLean hospital, and over 2 billion records from patient encounters, laboratories and results, and other medical care. This study was approved by the Partners HealthCare Institutional Review Board (Protocol number: 2019P000111).

The definition of TTM includes patients who receive cooling of body temperature regardless of the cooling technique or the cooling interval to the target temperature. The decision to apply TTM with therapeutic hypothermia eventually relies on the judgment of the treating clinicians and TTM protocols may not be identically standardized among all hospitals in the Partners HealthCare System but are accepted by national academic societies. Cooling was initiated to reach the target temperature as rapidly as possible. Any method of cooling, such as ice packs, cooling blankets, or the Arctic Sun System, can be used to initiate cooling to the target temperature between 33°C and 36°C. For eligible patients, the desired target temperature is maintained for 24 hours. Rewarming to 37°C at a rate of 0.25°C per hour should begin 24 hours after reaching the target temperature. Controlled rewarming typically takes 8 to 16 hours. Advanced critical care, such as ventilation, oxygenation, glucose control, and hemodynamic optimization, were executed according to the guidelines.

2.2. Data collection and outcomes

Routine patient demographic characteristics, past medical history, physiologic measures, data of blood analyses, CA event variables, and patient outcomes were retrospectively extracted and collected from the registry database and hospital notes according to the standardized Utstein-style definitions by trained researchers using a data collection form.[24] Intra-arrest and post-TTM BCR were also calculated according to laboratory data during IHCA and within 24 hours after TTM, respectively. The resuscitation duration was defined as the time from the onset of CA to the termination of resuscitation efforts. Return of spontaneous circulation (ROSC) was defined by a palpable pulse. The sequential organ failure assessment (SOFA) score within 24 hours after IHCA was used to evaluate the severity of multiple organ dysfunction. Acute kidney injury (AKI) was defined as oligo-anuria (daily urine output <0.5 ml/kg/h) and/or an increase in serum creatinine (≥0.3 mg/dl from admission value within 48 hours or a 1.5 time from baseline level).[25]

Neurological status at discharge was assessed using the Glasgow–Pittsburgh Cerebral Performance Categories (CPC) scale and recorded as CPC 1 (good performance), CPC 2 (moderate disability), CPC 3 (severe disability), CPC 4 (vegetative state), or CPC 5 (brain death or death).[26] The neurological status was further dichotomized by the CPC to good (1-2) or poor (3-5). The primary outcome was neurologic status at discharge. The secondary outcome was in-hospital mortality.

2.3. Statistical analysis

Categorical variables were presented as n (%) and compared with the chi-square test or Fisher's exact test, as appropriate. Continuous variables were presented as mean ± standard deviation (SD) or median (interquartile range, IQR). Multivariable logistic regression was utilized to determine the independent predictors of in-hospital mortality and poor neurological status at discharge. All biologically plausible variables or a p value of <0.20 in the univariable analysis were considered for inclusion in the multivariable logistic regression model. The receiving-operating characteristic (ROC) curve analysis and the area under curve (AUC) were delineated to assess the predictive power of BCR on outcomes in IHCA survivors receiving TTM. Odds ratios (OR) with 95% confidence intervals (CIs) were presented. All analyses were processed using the IBM SPSS Statistics software (version 20.0; IBM Corp., Armonk, NY, USA). All tests were 2-tailed, and a p value <0.05 was considered statistically significant.

3. RESULTS

There were 84 eligible patients (Fig. 1). The mean age was 67 ± 13 years, 63.1% (n = 53) were male, 67.8% (n = 57) were white, and 48.8% (n = 41) were smokers (Table 1). Of them, hypertension, diabetes mellitus, and renal insufficiency were the most common preexisting medical comorbidities. The mean Charlson Comorbidity Index score was 6.4 ± 3.0. Regarding resuscitation parameters and outcomes, the intra-arrest shockable rhythm for patients identified with IHCA was 23.8% (n = 20) and mean resuscitation duration was 16.8 ± 16.3 minutes. Less than one-third of patients had a possible cardiac cause (n = 25) and received the percutaneous coronary intervention (n = 26). Only six patients (7.1%) had extracorporeal membrane oxygenation and the mean SOFA score was 9.5 ± 2.4. We observed an in-hospital mortality rate of 47.6% (n = 40) and a poor neurological status rate of 75% (n = 63) at discharge.

Laboratory findings of the subjects during IHCA and after TTM were reported in Table 2. The mean BCR during IHCA and 24 hours after TTM were 20.1 ± 10.2 and 19.2 ± 10.1, respectively. After TTM, 44.8% (n = 30) had a thrombocytopenia of platelet count $<150 \times 10^3$/ul, 59.7% (n = 40) had prothrombin time prolongation and 40.3% (n = 27) had activated partial thromboplastin time prolongation.

Using multiple regression analysis to identify the predictors of outcomes of our study population (Table 3), post-TTM BCR was one of the independent factors to predict the poor neurological outcome at discharge (adjusted OR [aOR], 1.081; 95% CI, 1.002–1.165; p = 0.043). Additionally, intra-arrest BCR also had marginal significance in predicting neurological outcome at discharge in this cohort (aOR, 1.067; 95% CI, 1.000–1.138; p = 0.050). The ROC curve shows that post-TTM BCR as a biomarker had an acceptably predictive ability to discriminate poor neurological outcome at discharge, with an AUC of 0.644 (95% CI, 0.516–0.773). As a predictor of poor neurological outcome, a post-TTM BCR cutoff value of 16.7 had a sensitivity of 61.9% and specificity of 70.0%. The positive likelihood ratio and negative likelihood ratio were 2.06 and 0.54, respectively.

4. DISCUSSION

The principal finding in our study is that elevated BCRs are associated with adverse neurological prognosis at discharge in IHCA

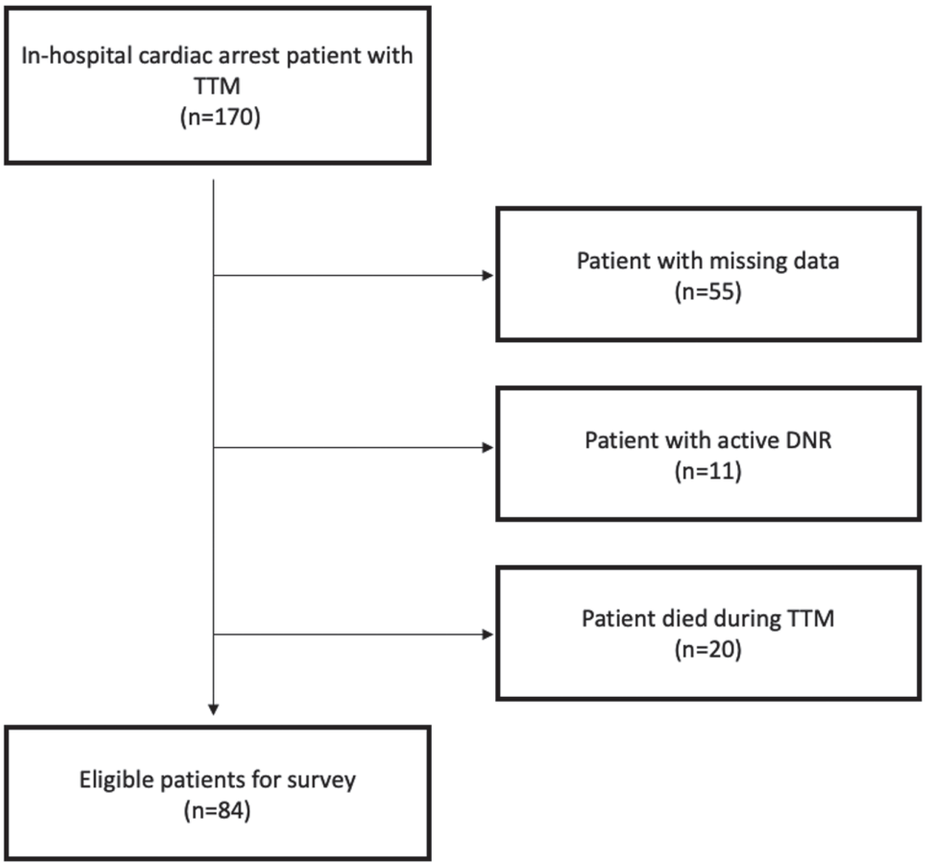

Fig. 1 Enrollment flow diagram of the study population from 2011 to 2018. DNR= do-not–resuscitate; TTM= targeted temperature management.

patients undergoing TTM. This is the first study to date that addresses the relationship between intra-arrest and post-TTM BCRs and IHCA patients, and a BCR greater than 16.7 mg/dL significantly predicts a high probability of poor neurological recovery at discharge.

Currently, compared with OHCA, few studies have addressed the prognostic factors in IHCA, and the reported outcomes widely vary.[1-5,27] A recent Korean cohort comprising 291 patients exhibited that 36.4% had survived to discharge, and 23.0% had a satisfactory neurologic status.[3] Nonetheless, our study demonstrated a survival to discharge rate of 52.4%; and 25.0% of all patients with IHCA had favorable neurologic outcomes. Our patients had better in-hospital survival; however, good neurological status at discharge was similar between these two studies. There may be several reasons for these results. First, TTM may significantly benefit IHCA patients.[6,7] All of our subjects received TTM, whereas only one out of 291 had in the other study. Although their patients undergoing extracorporeal membrane oxygenation were twice as many as ours, our subjects had a better prognosis regardless of the selection bias of opting for patients with better conditions in ECMO therapy.[28] Second, our relatively small sample size potentially interferes with the power of the results. Furthermore, in their study, good neurological status was substantial (17.0% among all patients with IHCA) at the 12-month follow-up. Given the lack of long-term status in our study, we cannot determine whether BCR possesses prediction capacity for long-term functional outcomes.

AKI has been found to be a prognostic predictor in both out-of-hospital and in-hospital CA.[29,30] Factors such as age, total inotrope dose, post-ROSC shock, and CPR interval, as well as blood pressure, heart rate, and lactate during the first 24 hours after CA, were reported to be relevant to AKI.[31,32] It usually develops within 3 days after ROSC, and improved survival and functional status at hospital discharge were noted in those recovering from it.[31] In a prospective multicenter cohort aimed at 6-month outcomes, it also influenced neurological performance and showed dose-dependent mortality, namely, higher risk of death in higher stages of AKI.[32]

The mechanism accounting for the relationship between BCR and CA remains to be elucidated. Initial hemodynamic deterioration may give rise to BCR elevation.[21] In fact, Fu et al.[33] used a rat model finding that prolonged CA resulted in worsening renal function, which could be improved following the restoration of spontaneous circulation. On top of poor baseline kidney function, patients who were older or who required higher doses of inotropes after ROSC were more likely to develop AKI, and that was indicative of an unfavorable outcome.[34] By contrast, high BUN values and BCR thereof may represent those with poor underlying health conditions.[35,36] A substantial increase in the long-term risk of death was observed in veterans with high initial BUN concentrations in a 9-year prospective cohort.[35]

Our research showed a positive association between BCR and unfavorable neurological recovery. It is of debate whether post-ROSC AKI is associated with the outcome.[31,37] A possible explanation for our result is that patients with poor general health status or nutritional status were subject to brain damage.[35,36] Moreover, it is inferred that IHCA patients with higher BCRs were prone to inadequate perfusion or hemorrhagic insults from small vessel diseases following ischemia.[19] Ischemic stroke patients with high BCRs tended to have inferior overall

Table 1

Demographic data and resuscitation outcomes of study subjects

	All Patients (n = 84)
Demographic	
Age (years), mean (S.D.)	67 ± 13
Male, n (%)	53 (63.1%)
Cigarette smoking, n (%)	41 (48.8%)
BMI (kg/m²), mean (S.D.)	28.4 ± 5.5
Underlying disease, n (%)	
Hypertension	54 (64.3%)
Diabetes mellitus	46 (54.8%)
Renal insufficiency	37 (44.0%)
Coronary heart disease	36 (42.9%)
Heart failure	34 (40.5%)
Arrhythmia	29 (34.5%)
Chronic obstructive lung disease	26 (31.0%)
Malignancy	23 (27.4%)
Peptic ulcer disease	19 (22.6%)
Cerebrovascular disease	13 (15.5%)
Hepatic insufficiency	6 (7.1%)
Connective tissue disease	5 (6.0%)
Charlson score, mean (S.D.)	6.4 ± 3.0
Initial shockable rhythm, n (%)	20 (23.8%)
Resuscitation duration (mins), mean (S.D.)	16.8 ± 16.3
Dosage of adrenalin, mean (S.D.)	3.5 ± 3.7
Cardiac cause, n (%)	25 (29.8%)
ECMO use, n (%)	6 (7.1%)
Subsequent PCI, n (%)	26 (31.0%)
SOFA after TTM completion, mean (S.D.)	9.5 ± 2.4
AKI after TTM completion, n (%)	26 (31.0%)
Length of hospital stay, mean (S.D.)	19.3 ± 29.5
In-hospital mortality, n (%)	40 (47.6%)
Poor neurologic status, n (%)	63 (75.0%)

AKI = acute renal failure; BMI = body mass index; ECMO = extracorporeal membrane oxygenation; PCI = percutaneous coronary intervention; S.D. = standard deviation; SOFA = sequential organ failure assessment; TTM = Targeted temperature management.

Table 2

Laboratory findings of study subjects

All Patients (n = 84)	Intra-arrest	Post-TTM
White blood cell count, $\times 10^3$/ul	12.42 ± 5.96	12.85 ± 6.22
Hemoglobin, g/dL	10.5 ± 2.3	9.9 ± 2.2
Platelet count, $\times 10^3$/ul	206.3 ± 120.3	159.6 ± 107.6
BUN, mg/dL	36.1 ± 25.3	35.8 ± 22.8
Creatinine, mg/dL	2.29 ± 2.21	2.19 ± 1.56
BUN/Creatinine ratio	20.1 ± 10.2	19.2 ± 10.1
BUN/Creatinine > 20, n (%)	37 (44.0%)	31 (36.9%)
Lactate, mmol/L	5.5 ± 5.2	3.1 ± 4.0
Glucose, mg/dL	197 ± 104	178 ± 80
Thrombocytopenia <150 000	–	30 (44.8%)
Thrombocytopenia<50 000	–	2 (3.0%)
Prolonged PT > 14.4 sec	–	40 (59.7%)
Prolonged aPTT > 36.6 sec	–	27 (40.3%)
Hypernatremia, sodium >145mmol/L	–	8 (9.5%)
Hyponatremia, sodium <136 mmol/L	–	27 (32.1%)
Hyperkalemia, potassium >5.0 mmol/L	–	9 (10.7%)
Hypokalemia, potassium <3.4 mmol/L	–	4 (4.8%)

BUN = blood urea nitrogen; PT = prothrombin time; aPTT = activated partial thromboplastin time; TTM = targeted temperature management.

outcomes, and were more likely to suffer hemorrhagic transformation.[19,22,23] For another, since BCRs represent patient volume status, hydration may prevent adverse neurological recovery in stroke patients with BCRs greater than 15.[22,38] Furthermore, cerebral microbleeds and white matter lesions occur easily in those with chronic kidney disease, which could also account for poor neurological recovery in IHCA patients.[39-42]

Several studies indicate that BCR acts as a surrogate for survival, though our finding only exhibited borderline significance. Its association with acute decompensated heart failure has been widely investigated.[15-17,21] Severe inflammation often develops in critically-ill patients, and inflammatory cytokines not only reduce the host immune response but enhance protein catabolism, resulting in BCR elevation.[36] In a 5-year cohort, an initial BUN on admission to the intensive care unit was independently associated with in-hospital and long-term survival even following adjustment of kidney diseases.[43] Additionally, stroke patients with an increased BCR were associated with higher mortality.[19,22,23] Lastly, elevation in BCR and BUN levels was found to be a risk factor for an adverse COVID-19 prognosis alongside disease severity.[20,44,45]

This research has several strengths. First, to our knowledge, it is the first study to demonstrate the disadvantages of neurological recovery with increasing BCR in adult IHCA patients. In addition, since the registry involved a large and diverse population from multiple facilities, our findings are fairly generalizable. Moreover, because BUN and creatinine belong to routine blood tests, it is feasible to adopt post-TTM BCR, even intra-arrest BCR, as a predictor in clinical practice. Still, our team has embarked on a plan to validate the results prospectively.

Our study comprises a few limitations. Due to the nature of retrospective study designs, we had difficulty obtaining all the parameters required for analysis, including baseline nutritional status and left ventricle ejection fraction, and fluid administration during CPR and TTM, which may interfere with BCR. In addition, potential selection bias exists for those without BUN or creatinine records were omitted, and IHCA patients with better conditions were more likely to receive TTM. Moreover, it was not possible to acquire detailed information on the immediate cause of death from the claims data, such as septic shock or acute coronary syndrome. Some variables that might influence the outcomes, for instance, CPR quality or witnessed arrest, were not documented either. Nonstandardized TTM protocols could also contribute to residual confounding.

Table 3

Logistic regression analysis of predictors of poor neurological outcome at discharge in this cohort

	Crude OR (95% CI)	*p*	Adjusted OR [a] (95% CI)	*p*
Intra-arrest BCR	1.068 (0.999–1.142)	0.055	1.067 (1.000–1.138)	0.050
	Crude OR (95% CI)	*p*	Adjusted OR [b] (95% CI)	*p*
Post-TTM BCR	1.074 (1.000–1.153)	0.051	1.081 (1.002–1.165)	0.043*

BCR = blood urea nitrogen to creatinine ratio;CI = confidence interval; OR = odds ratio; TTM = targeted temperature management.

*$p < 0.05$.

[a]Variables included in the model: Age, initial rhythm, epinephrine dosage, percutaneous coronary intervention, cerebrovascular disease, intra-arrest BUN/Cr ratio.

[b]Variables included in the model: Age, initial rhythm, epinephrine dosage, percutaneous coronary intervention, cerebrovascular disease, post-TTM BUN/Cr ratio, post-TTM lactate, post-TTM glucose.

Hence, further analysis to delineate the causal interactions is challenging. Finally, favorable neurological outcomes were deemed as a CPC score of 1 or 2 at discharge. However, it has been reported that neurological deficits could be ameliorated within 6 months following the event.[46] The result therefore might be underestimated even though it corresponded to the observations of other studies.

In conclusion, post-TTM BCR was a significant predictor of neurologic outcome at discharge among IHCA patients receiving TTM. Also, IHCA patients with an elevated intra-arrest BCR had borderline poor neurological prognosis at discharge. To the best of our knowledge, this is the first report to address such an issue. Future research is needed to confirm these findings and explore the potential causal relationship.

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