Usefulness of Incorporating Hypochloremia into the Get With The Guidelines−Heart Failure Risk Model in Patients With Acute Heart Failure

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Although hypochloremia is strongly associated with adverse prognosis in acute heart failure (AHF), it is unknown whether incorporating hypochloremia into the preexisting risk model improves the model performance. We calculated the Get With The Guidelines −Heart Failure (GWTG-HF) risk score in 1,428 patients with AHF (derivation cohort) and developed 2 risk scores incorporating brain natriuretic peptide (BNP) into the GWTG-HF risk score (GWTG-BNP risk score) and incorporating both BNP and hypochloremia (GWTG-BNP-Cl risk score). Hypochloremia was defined as <98 mmol/L. The external validation and comparison of model performance were performed in an independent group of 1,256 patients with AHF (validation cohort). All models were tested for in-hospital mortality. Hypochloremia was observed in 9.4% and 12.2% of the derivation and validation cohorts, respectively. Hypochloremia was an independent predictor of in-hospital mortality in the derivation cohort (odds ratio 2.02; p = 0.028). In the validation cohort, the GWTG-HF, GWTG-BNP, and GWTG-BNP-Cl risk scores demonstrated good discrimination (area under the curve: 0.742, 0.749, and 0.763, respectively). However, the GWTG-BNP-Cl risk score was more reliable than the GWTG-HF and GWTG-BNP risk scores in risk reclassification (net reclassification improvement: 0.491 and 0.408, respectively; p <0.01 for both). Moreover, this score demonstrated a good calibration of the GWTG-BNP-Cl model (Hosmer-Lemeshow test: p = 0.479). In conclusion, incorporating hypochloremia into the preexisting risk model improves the model performance. **© 2021 Elsevier Inc. All rights reserved.** **(Am J Cardiol 2022;162:122−128)**

As the number of patients with heart failure is increasing because of the aging society,[1,2] acute decompensation of heart failure is one of the main reasons for the increase in hospital resource use and healthcare costs.[3] Appropriate acute heart failure (AHF) risk stratification models are important, as they may improve patient triage and reduce healthcare costs. The Get With The Guidelines−Heart Failure (GWTG-HF) risk model is one of the most sophisticated and well-validated risk models for predicting in-hospital mortality.[4] Moreover, adding the brain natriuretic peptide (BNP) to the GWTG-HF model has been shown to improve the model performance.[5] Although recent studies reported that hypochloremia is strongly associated with mortality in patients with AHF,[6,7] it is unclear if hypochloremia increases the prognostic predictability and if incorporating this factor into the preexisting risk model can improve its performance. Therefore, we aimed to create a novel risk model and examine its performance.

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The REALITY-AHF study was supported by the Cardiovascular Research Fund, Japan. This study was partly supported by grant 18K15862 from JSPS KAKENHI Grant-in-Aid for Early-Career Scientists, Japan.

See page 126 for disclosure information.

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https://doi.org/10.1016/j.amjcard.2021.09.020

Methods

We used 2 data sets of patients with AHF to examine whether incorporating hypochloremia, defined as a serum chloride level<98 mmol/L,[8−10] can improve the model performance. First, we developed a new risk model that incorporates hypochloremia using a derivation cohort (Registry Focused on Very Early Presentation and Treatment in Emergency Department of Acute Heart Failure [REALITY-AHF] cohort). We then evaluated the model performance in an independent external validation cohort (Nara Registry and Analyses for Heart Failure [NARA-HF] cohort). The primary end point of this study was in-hospital mortality. We excluded patients with missing data on chloride and BNP levels at admission and those with missing GWTG-HF risk scores due to missing data on any of the components required to calculate it.

The REALITY-AHF was a prospective multicenter study (20 Japanese hospitals, including 9 university and 11 community hospitals), designed to evaluate the association between time to treatment and clinical outcome in patients with AHF presenting at the emergency department (ED). The study design has been reported elsewhere in detail.[11] The AHF diagnosis was made based on the Framingham criteria.[12] The exclusion criteria were treatment with an intravenous drug performed before ED arrival, previous heart transplantation, undergoing either chronic peritoneal dialysis or hemodialysis, acute myocarditis, and acute coronary syndrome requiring emergency/urgent revascularization. Patients with missing BNP or N-terminal-proBNP data were also excluded, as well as those with a BNP level <100 pg/ml or N-terminal-proBNP level <300 pg/ml at baseline. Patients were recruited from August 2014 to December 2015. At the ED phase, baseline physical findings and blood samples were evaluated for all patients as baseline data. The study information, including objectives, inclusion and exclusion criteria, and the names of participating hospitals, was published in the publicly available University Hospital Information Network (unique identifier: UMIN000014105) before the first patient was enrolled. The REALITY-AHF complied with the Declaration of Helsinki, and an institutional review board approval was obtained in each participating center.

NARA-HF retrospectively enrolled consecutive patients with AHF admitted to Nara Medical University Hospital from January 2007 to March 2011 and prospectively enrolled patients from April 2011 to December 2018.[13−15] Diagnosis of HF was also made based on the Framingham study criteria. Patients with acute myocardial infarction, acute myocarditis, or AHF with acute pulmonary embolism were excluded. NARA-HF did not exclude patients with hemodialysis and BNP <100 pg/dL at the time of admission, based on its inclusion/exclusion criteria; however, we excluded them from the present analyses for consistency with the REALITY-AHF cohort. The present study was approved by the Nara Medical University Institutional Ethics Committee and performed according to the 1975 Declaration of Helsinki guidelines for clinical research protocols. Informed consent was obtained from all patients.

Continuous variables are expressed as means and SDs or as medians with interquartile ranges. The categorical variables are expressed as numbers and percentages. Associations between the variables and in-hospital mortality were evaluated using univariate and multivariate logistic regression models and generalized linear regression models. Unadjusted and adjusted odds ratios were estimated with their 95% confidence intervals; we also estimated the predicted in-hospital mortality.

For the derivation, we confirmed if hypochloremia was an independent predictor of in-hospital mortality independently of the GWTG-HF risk score and log-transformed BNP at admission (log BNP), as adding log BNP to GWTG-HF has already been shown to improve the model prediction performance.[5,16] In further analysis, log BNP levels were dichotomized to high/low levels according to the most appropriate cutoff derived from the Classification and Regression Trees analysis.[17] Next, we performed the multivariate logistic regression analysis again to determine if hypochloremia remains independently associated with the in-hospital mortality after adjusting for the GWTG-HF risk score and high/low BNP level at admission. Based on the results of this multivariate logistic regression, we assigned an integer weight proportional to the regression beta coefficient for the GWTG-HF risk score, high/low BNP, and hypochloremia to create a new risk model. We defined the GWTG-BNP and GWTG-BNP-Cl risk scores, which comprise the GWTG-HF risk score and high/low BNP, and the GWTG-HF risk score, high/low BNP, and presence/absence of hypochloremia, respectively.

For the validation, we examined whether hypochloremia was an independent predictor of in-hospital mortality even after adjusting for the GWTG-HF risk score and log-transformed BNP in the NARA-HF cohort. Next, we calculated the GWTG-HF, GWTG-BNP, and GWTG-BNP-Cl risk scores to compare these 3 models. The discrimination and calibration performance of the GWTG-HF, GWTG-BNP, and GWTG-BNP-Cl risk scores was assessed using the Hosmer-Lemeshow test and the area under the receiver operating characteristic curve, respectively. The net reclassification improvement was calculated between the risk scores to compare the performance of the 3 models.[18]

Results

Among the 1,682 patients registered to REALITY-AHF and the 1,391 patients registered to NARA-HF, 1,428 patients from REALITY-AHF were finally included and analyzed (201 patients were excluded because of the absence of BNP, 44 patients for no chloride levels, and 9 patients for no GWTG-HF risk score) and 1,256 patients from NARA-HF (79 patients were excluded for undergoing hemodialysis, 37 patients for BNP level <100 pg/dL, and 19 patients for missing data on BNP levels). The characteristics of the patients with and without hypochloremia are shown in Table 1. The prevalence of patients with hypochloremia was 9.4% in the REALITY-AHF cohort and 12.2% in the NARA-HF cohort. Overall, the patient characteristics associated with hypochloremia were similar between the 2 cohorts and included lower blood pressure, lower prevalence of hypertension, lower rates of mineralocorticoid receptor-antagonist intake, lower sodium level,

Table 1
Patient characteristics of those with and without hypochloremia in the REALITY-AHF and Nara-HF cohorts

Variable	REALITY-AHF			Nara-HF		
	non-hypochloremia (n = 1,294)	hypochloremia (n = 134)	p value	non-hypochloremia (n = 1,103)	hypochloremia (n = 153)	p value
Age (years)	80 [71, 86]	78 [67, 86]	0.133	77 [67, 83]	77 [68, 85]	0.346
Men (%)	735 (56.8%)	68 (50.7%)	0.210	638 (57.8%)	76 (49.7%)	0.068
Systolic blood pressure (mm Hg)	151 ± 36	133 ± 36	<0.001	147 ± 36	130 ± 36	<0.001
Diastolic blood pressure (mm Hg)	85 ± 25	76 ± 24	<0.001	85 ± 25	76 ± 23	<0.001
Heart rate (bpm)	98 ± 29	93 ± 27	0.099	98 ± 28	91 ± 24	0.004
Left ventricular ejection fraction (%)	46 [33, 69]	48 [36, 63]	0.165	44 [33, 60]	46 [38, 63]	0.141
NYHA Class III/IV at admission (%)	1,098 (84.9%)	115 (86.5%)	0.712	1,009 (91.5%)	144 (94.1%)	0.338
Heart failure (%)	661 (51.1%)	71 (53.0%)	0.742	216 (19.7%)	40 (26.1%)	0.079
Hypertension (%)	881 (68.1%)	74 (55.2%)	0.004	844 (76.5%)	103 (67.3%)	0.018
Diabetes mellitus (%)	470 (36.4%)	49 (36.6%)	>0.999	432 (39.2%)	72 (47.1%)	0.075
Chronic Obstructive Pulmonary Disease (%)	118 (9.1%)	19 (14.2%)	0.082	88 (8.0%)	18 (11.8%)	0.155
Coronary artery disease (%)	390 (30.2%)	36 (26.9%)	0.487	286 (25.9%)	31 (20.3%)	0.158
Medication at admission (%)						
Loop diuretics	661 (51.5%)	87 (64.9%)	0.004	507 (46.0%)	81 (52.9%)	0.120
Thiazide diuretics	61 (4.8%)	14 (10.4%)	0.013	66 (6.0%)	24 (15.4%)	<0.001
ACE-I	215 (16.6%)	25 (18.7%)	0.637	258 (23.4%)	38 (24.8%)	0.769
ARB	414 (32.1%)	27 (20.1%)	0.006	411 (37.3%)	39 (25.5%)	0.006
Beta blockers	570 (44.3%)	53 (39.6%)	0.333	346 (31.4%)	55 (35.9%)	0.296
Aldosterone blockers	289 (22.3%)	38 (28.4%)	0.141	173 (15.7%)	44 (28.8%)	<0.001
Laboratory data at admission						
Albumin (g/dL)	3.50 ± 0.56	3.37 ± 0.50	0.031	3.65 ± 0.49	3.57 ± 0.44	0.061
Hemoglobin (g/dL)	11.78 ± 2.30	11.64 ± 2.09	0.519	11.60 ± 2.42	11.28 ± 2.20	0.122
Creatinine (mg/dL)	1.12 [0.85, 1.62]	0.98 [0.69, 1.53]	0.006	1.11 [0.82, 1.70]	1.17 [0.91, 1.95]	0.064
BUN (mg/dL)	25 [18, 35]	24 [17, 37]	0.810	23 [17, 35]	28 [21, 47]	<0.001
Sodium (mmol/L)	140 [137, 142]	131 [128, 135]	<0.001	140 [138, 142]	131 [127, 135]	<0.001
Chloride (mmol/L)	105 [102, 108]	95 [92, 96]	<0.001	105 [102, 107]	94 [91, 96]	<0.001
Potassium (mmol/L)	4.2 ± 0.7	4.3 ± 0.9	0.387	4.2 ± 0.7	4.3 ± 0.9	0.033
CRP (mg/dL)	0.59 [0.20, 1.93]	1.45 [0.42, 4.50]	<0.001	0.50 [0.20, 1.70]	1.80 [0.30, 5.40]	<0.001
BNP (pg/ml)	753 [451, 1348]	668 [353, 1332]	0.306	897 [513, 1607]	1,097 [593, 1773]	0.048

ACEi = angiotensin-converting enzyme inhibitors; ARB = angiotensin receptor blockers; BNP = brain natriuretic peptide; BUN = blood urea nitrogen; CRP = C-reactive protein.

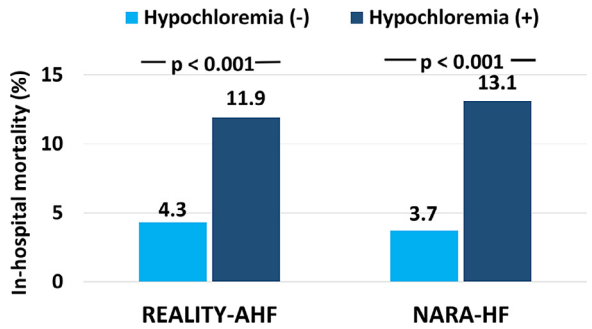

Figure 1. In-hospital mortality for patients with and without hypochloremia at admission in the REALITY-AHF and Nara-HF cohorts.

and higher C-reactive protein. In-hospital mortality was significantly higher in subjects with hypochloremia than in those without hypochloremia (Figure 1).

The results of the univariate and multivariate logistic regression analyses in the REALITY-AHF cohort are shown in Table 2, Supplementary Table 1, and Supplementary Figure 2. Hypochloremia was significantly associated with in-hospital mortality even after adjusting for the GWTG-HF risk score and log-transformed BNP as a continuous scale. Based on the Classification and Regression Trees analysis, log BNP >7.57 was chosen as the threshold, and we constructed 2 multivariate logistic models: the GWTG-BNP model, using the GWTG-HF risk score and high/low BNP, and the GWTG-BNP-Cl model, using the GWTG-HF risk score, high/low BNP level, and presence/absence of hypochloremia. Considering the coefficient for a 1-point increase in the GWTG-HF risk score, we assigned 7 points to high BNP and 8 points to hypochloremia in proportion to their coefficients. Therefore, the GWTG-BNP risk score can be calculated by adding 7 points to the GWTG-HF risk score if the log BNP level is higher than 7.57 (i.e., corresponding to BNP >1,940 pg/ml), and the GWTG-BNP-Cl risk score can be calculated by adding 7 points if the log BNP level is higher than 7.57, and 8 points if hypochloremia is present (Supplementary Figure 2).

Next, we checked if hypochloremia was significantly associated with in-hospital mortality in the NARA-HF cohort; we consistently found a significant and independent association between hypochloremia and high in-hospital mortality. After confirming this association (Supplementary Tables 1 and 2), we applied the original GWTG-HF risk score and the 2 newly developed risk scores (i.e., the GWTG-BNP and GWTG-BNP-Cl) to the NARA-HF cohort and examined the models' predictive performance. Although no significant difference was observed in

Table 2
Univariate and multivariable logistic regression analyses for in-hospital mortality in the derivation (REALITY-AHF) cohort

Variables	REALIT-AHF												
	Univariate				Multivariable			Multivariable (GWTG-BNP Model)			Multivariable (GWTG-BNP-Cl Model)		
	Odds Ratio	Coefficient	95% CI	p value	Odds Ratio	Coefficient	95% CI	p value	Odds Ratio	Coefficient	95% CI	p value	Odds Ratio	Coefficient	95% CI	p value
Hypochloremia (<98 mmol/L)	3.00	1.098	1.67−5.39	<0.001	2.02	0.701	1.08−3.77	0.028					1.97	0.677	1.05−3.69	0.034
GWTG-HF risk score					1.09	0.089	1.06−1.13	<0.001	1.10	0.093	1.07−1.13	<0.001	1.09	0.088	1.06−1.13	<0.001
Log BNP					1.20	0.180	0.90−1.60	0.221								
High BNP (log BNP>7.57)									1.89	0.636	1.07−3.32	0.027	1.91	0.647	1.08−3.37	0.026

BNP = Brain natriuretic peptide; CI = Confidence Interval.

the area under the curve, a significant net reclassification improvement was observed when the model was updated from the GWTG-HF to the GWTG-BNP risk score and from the GWTG-BNP to the GWTG-BNP-Cl risk score. This finding implies that adding hypochloremia to the GWTG-BNP risk score improves the prognostic predictability (Table 3).

Furthermore, the patients were classified into 4 risk groups representing the 4 risk quartiles (integer scores 0 to 36, 37 to 42, 43 to 48, and >48) to investigate whether the performance of the GWTG-BNP-Cl risk score was consistent in the REALITY-AHF and NARA-HF cohorts. We compared the observed and predicted in-hospital mortality rates by the GWTG-BNP-Cl risk score in the REALITY-AHF and NARA-HF cohorts (Figure 2). Although there were discernible differences between the predicted and observed in-hospital mortality rates, especially in patients with high scores, the calibration test demonstrated a good calibration of the GWTG-BNP-Cl model (Hosmer-Lemeshow test: p = 0.479).

Discussion

In this study, we derived a novel risk model for patients with AHF, which incorporated hypochloremia into the preexisting risk model based on GWTG-HF plus BNP levels. Furthermore, we validated this model in a different AHF cohort and found good discrimination and calibration. The model also showed significant net reclassification improvement compared with the GWTG-BNP model. As chloride levels are readily available biomarkers and routinely measured in our daily clinical practice, our novel risk model can improve risk stratification without additional cost and time.

As the number of patients with AHF has been growing dramatically recently, and has consequently increased the use of hospital resources, accounting for a high proportion of medical expenses, the use of risk stratification models based on current guidelines for Class IIa recommendation is warranted.[19] These models might allow proper triage and allocation of medical resources for patients with AHF, including patient disposition after admission. Risk models are helpful tools for physicians to estimate the patient prognosis and decide on the optimal treatment strategy, providing appropriate management uniformly. For this purpose, several risk models have been developed and proposed for patients with AHF. For instance, the GWTG-HF,[4] the Acute Decompensated Heart Failure National Registry,[20] and the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE) are models aimed at predicting in-hospital mortality.[21] Moreover, adding some biomarkers that recently became clinically available to these models is associated with improved model performance. Indeed, Shiraishi et al[5] reported that adding log BNP levels to GWTG-HF improved the performance of this risk score.

Because lower chloride levels have only recently emerged as a prominent prognostic factor in AHF, no risk model examined hypochloremia as a possible component. However, recent studies clearly showed that a low chloride level at admission is an outstanding prognostic

Table 3
Comparison of the areas under the curve (AUCs) of the GWTG-HF, GWTG-BNP, and GWTG-BNP-Cl scores for in-hospital mortality and NRI in the Nara-HF cohort

		Updated Model	
		GWTG-BNP Score (AUC: 0.749: 95%CI 0.686 to 0.811))	GWTG-BNP-Cl Score (AUC: 0.763, 95% CI 0.703 to 0.824)
Baseline model	GWTG score (AUC: 0.742, 95%CI 0.678 to 0.805)	$AUC_{comparison}$: p = 0.443 NRI: 0.237 [0.004 - 0.470], p = 0.046	$AUC_{comparison}$: p = 0.121 NRI: 0.491 [0.235 - 0.747], p <0.001
	GWTG-BNP score (AUC: 0.749: 95%CI 0.686 to 0.811)		$AUC_{comparison}$: p = 0.183 NRI: 0.408 [0.179 - 0.647], p = 0.008

BNP = Brain natriuretic peptide; CI = Confidence Interval; NRI = net reclassification improvement.

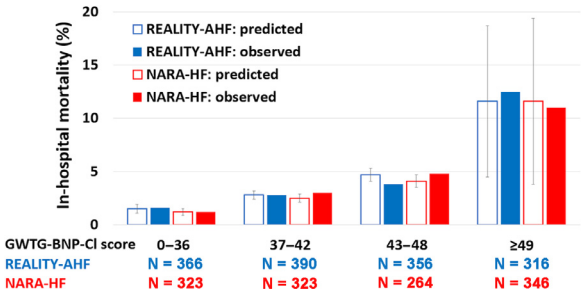

Figure 2. Observed and predicted in-hospital mortality in the REALITY-AHF and Nara-HF cohorts stratified by risk groups.

factor.[6,22–24] In this study, multivariate analysis showed that both high BNP levels and hypochloremia (<98 mmol/L) at admission were significantly and independently associated with in-hospital mortality. As a result, our novel risk model adding BNP and hypochloremia to the GWTG-HF risk score improved the performance of the preexisting model.

This result is not surprising, and the model we developed in the present study has several strengths. Although Shiraishi et al[5] showed that adding log BNP to the GWTG-HF model improved the model performance, as validated by our study, they did not suggest a specific cutoff of the log BNP or BNP levels; therefore, it is challenging to implement the model into daily clinical practice. Our study defined a clear cutoff for both BNP and chloride levels, allowing the model to be practical and user-friendly even in the emergency care setting. Furthermore, although several risk prediction scores/models showed moderate discrimination and were validated in a validation cohort (i.e., different from the derivation cohort), not all derivation cohorts are independent of the derivation cohort, as some studies merely divided the main cohort into 2 subgroups and used them as derivation and validation cohorts. This method implies that these 2 cohorts have similar backgrounds and do not reflect the heterogeneity of patients with AHF; therefore, the external validity of the model was not tested appropriately. In addition, the model calibration was rarely clarified in the proposed models. For instance, model calibration was examined only in the OPTIMIZE and GWTG-HF models among the 3 risk models mentioned above; however, only the OPTIMIZE model was tested for calibration in an external independent cohort. We derived our model using the REALITY-AHF cohort and verified its performance in an independent cohort, NARA-HF, showing a good calibration. It should also be noted that our model exceeded the GWTG-HF and GWTG-BNP risk scores in model performance.

Several possible mechanisms have been proposed to explain the association between hypochloremia and prognosis, although they are still unclear. Hypochloremia induces the activation of the renin-angiotensin system. A reduced chloride delivery to the macula densa due to hypochloremia causes an increased release of renin from the juxtaglomerular apparatus through tubuloglomerular feedback in the kidney.[25] Moreover, hypochloremia is associated with diuretic resistance. This finding is supposedly due to hypochloremia leading to activation of Na-Cl and Na-K-2Cl cotransporters through with-no-lysine [K] kinases phosphorylation, resulting in the reabsorption of sodium.[26] Indeed, low chloride levels at admission were reported to be inversely associated with loop diuretic response in patients with AHF.[7] These unique roles of chloride in homeostasis may be responsible for the additional prognostic value.

Our study has some limitations. First, the REALITY-AHF cohort included only patients hospitalized through the ED; hence, it is unclear whether this prognosis risk model can be applied to nonhospitalized patients. Second, our model has been delivered and validated in Japanese cohorts, and its applicability to non-Japanese patients is unknown. However, the characteristics of AHF are similar between Japanese and non-Japanese patients, and we found very few differences between REALITY-AHF and other large-scale national registries for Japanese patients with AHF.[27,28] Nevertheless, this point should be acknowledged.

In conclusion, the risk score we developed, including hypochloremia and BNP, showed improved discrimination, calibration, and reclassification comparedwith the existing risk prediction models for in-hospital mortality in patients with AHF. Further studies are expected to validate this model in other cohorts and prove its usefulness in predicting clinical outcomes.

Clinical trial registration

http://www.umin.ac.jp/ctr/UMIN000014105

Disclosures

Dr. Yuya Matsue is affiliated to a department endowed by Philips Respironics, ResMed, Teijin Home Healthcare, and Fukuda Denshi and received an honorarium from

Otsuka Pharmaceutical Co and Novartis Japan. Dr. Takahiro Okumura received research grants from Ono Pharmaceutical Co., Ltd., Bayer Pharmaceutical Co., Ltd., Daiichi-Sankyo Pharma Inc., and Amgen Astellas BioPharma K.K. outside the submitted work, and received honorariums from Ono Pharmaceutical Co., Ltd., Novartis Pharma K.K., Otsuka Pharmaceutical Co., Ltd., and Medtronic Japan Co., Ltd. The other authors have no conlicts of interest to declare.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2021.09.020.

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