

# Deep Learning Prediction Model of Mortality Including Brain-type Natriuretic Peptide in Patients with Acute Decompensated Heart Failure

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Predicting mortality in patients with acute decompensated heart failure remains difficult for non-specialists. In addition, the influence of various heart failure complications on mortality has not been sufficiently confirmed. The purpose of this research is to assess the possibility of predicting the mortality risk in patients with acute decompensated heart failure after discharge using deep learning based on a registry of Japanese hospitalized patients with high rates of comorbid atrial fibrillation, chronic kidney disease, and anemia. We randomly divided data from fifteen clinical characteristics in 1,012 hospitalized patients into training and validation datasets. Next, we introduced the datasets into a prediction model using an automated-deep learning algorithm (Prediction One). Our deep learning-based model demonstrated a high ability to predict mortality risk ( $c$ -statistics = 0.75, sensitivity = 0.607, and  $1 - \text{specificity} = 0.192$ ). Prediction accuracy can be improved by appropriately incorporating input variables such as the brain-type natriuretic peptide level, red blood cell count, left ventricular ejection fraction, number of administered medications, length of hospitalization, and Nohria–Stevenson classification stage. We demonstrated that our deep learning model based on multiple clinical characteristics is useful for predicting the mortality risk in hospitalized patients with heart failure. In particular, we showed that our model including brain-type natriuretic peptide is effective for predicting the acute decompensated heart failure mortality risk.

## 1. Introduction

Heart failure (HF) mortality prediction is important to patients, their healthcare providers, healthcare systems, and payers.<sup>(1)</sup> Predicting the type, stages, and progression of HF helps in tailoring medication and selecting interventions effectively and evaluating disease management. However, accurately assessing outcomes in patients with HF has proven difficult. The first

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attempts at providing accurate predictions of the mortality risk in patients with HF (HF mortality risk) were based on statistical approaches. The American Heart Association's (AHA) Get With the Guidelines (GWTG) is a program designed to assist hospitals in designing systems of care.<sup>(2)</sup> The HF module of GWTG-HF was launched in 2005, and the risk score scale for in-hospital mortality was validated using its data.<sup>(3)</sup>

Machine learning and artificial intelligence are being studied as useful clinical tools by the scientific community. Machine learning strategies have great potential in HF fields.<sup>(4,5)</sup> Machine learning algorithms such as linear discriminant analysis, random forest, gradient boosting classifier, decision tree classifier, support vector machine, and K-nearest neighbor have been tried to predict HF mortality risks.<sup>(6)</sup> Shin *et al.* showed that machine learning algorithms have better discrimination than the conventional statistical models in most studies on predicting the risks of readmission and mortality in patients with HF.<sup>(7)</sup> Focusing on machine learning and using eight variables, Adler *et al.* achieved 0.81 for c-statistics in their mortality risk prediction.<sup>(8)</sup> Deep learning is also being considered for predicting the HF mortality risk.<sup>(9)</sup> However, Tanna *et al.* mentioned that the potential utility of novel machine learning tools has yet to be determined through a systematic literature review of statistical and machine learning approaches.<sup>(10)</sup> It is important to consider the influence of age, HF duration, race/ethnicity, region, complications of atrial fibrillation, chronic kidney disease (CKD), and other complications in predicting the HF mortality risk.<sup>(11)</sup>

Natriuretic peptide, brain-type natriuretic peptide (BNP), and N-terminal prohormone of brain natriuretic peptide (NT-proBNP) levels are increased in patients with HF, and these levels may be important for prediction.<sup>(12)</sup> BNP and NT-proBNP are most often used to diagnose HF globally.<sup>(13)</sup> Moderate to high-quality evidence suggests that a 100 pg/mL increase in BNP is associated with a 14% increase in the HF mortality risk.<sup>(14)</sup>

We previously established the Clue of Risk Stratification in Elderly Patients with Heart Failure (CURE-HF) registry from data obtained in a prospective, multicenter, and cohort study conducted in Nagano Prefecture, Japan.<sup>(15–17)</sup> This registry comprises data from Japanese hospitalized patients with acute decompensated heart failure (ADHF), who on average are older and have higher rates of comorbidities including atrial fibrillation, CKD, and anemia than the patients in registries from Europe and the United States. The purpose of this research is to assess the potential for predicting ADHF mortality risk after discharge using a deep learning technique trained with data from the CURE-HF registry of Japanese hospitalized patients with specific clinical characteristics. Additionally, the effects of adding BNP, a typical HF biomarker, is focused as an input variable on the basis of input variables used in the GWTG-HF program.

## 2. Materials and Methods

### 2.1 Patients

The CURE-HF registry enrolled 1,036 consecutive patients hospitalized with a primary diagnosis of ADHF and discharged after treatment at 13 institutions between July 2014 and August 2019.<sup>(15–17)</sup> This registry is a comprehensive database that aggregates patient medical

records collected through clinical practice in hospitals. The diagnosis of ADHF was based on the criteria used in the Framingham study.<sup>(18)</sup> The exclusion criteria were patients aged < 20 years and those with acute coronary syndromes. After admission, medical therapy was initiated at the attending physician's discretion at each local site. Baseline clinical data, including demographic characteristics, past medical history, laboratory data, and echocardiography findings were obtained during a compensated state of ADHF. All-cause deaths were tracked for two years. Follow-up data were obtained either from hospital charts and direct contact with the patients or referring physicians. To ensure an accurate assessment of clinical events, additional information was obtained from visits or telephone conversations with living patients or their family members, as well as from medical records obtained from other hospitals, as necessary, between June and August 2021. These data were fully anonymized before analysis by the investigators, who were blinded to the participants. The study was approved by each participating institutional review board or ethics committee. All study participants signed written informed consent forms prior to enrollment. This study was conducted in accordance with the Declaration of Helsinki tenets and registered in the University Hospital Medical Information Network (UMIN 000024470).

## 2.2 Variables

The variables used in the GWTG-HF program were selected as the base variables to establish the prediction model for ADHF mortality risk after discharge: age (years), heart rate (beats/min), systolic blood pressure (mmHg), blood urea nitrogen level (BUN, mg/dL), sodium (mEq/L), and presence of chronic obstructive pulmonary disease (COPD). Furthermore, the following variables were incorporated: body mass index (BMI, kg/m<sup>2</sup>), BNP level (pg/mL), red blood cell count (RBC, ×10<sup>4</sup>/μL), estimated glomerular filtration rate (eGFR, mL/min/1.73 m<sup>2</sup>), diastolic blood pressure (mmHg), left ventricular ejection fraction (LVEF, %), number of administered medications (NM), length of hospitalization (LOH, days), and Nohria–Stevenson classification stage (NS). The Nohria–Stevenson classification stage was assigned by following the guidelines of the European Society of Cardiology.<sup>(19)</sup> Therefore, fifteen clinical characteristics were incorporated into the prediction model.

## 2.3 Data analysis

Among the patients in the CURE-HF registry, 1012 hospitalized patients had values for the six input variables used in GWTG-HF program. The 1012 patients were assigned random numbers and their records were divided into two groups: 90% (911) for training dataset and 10% (101) for validation dataset in deep learning (Fig. 1).

The prediction model for ADHF mortality risk after discharge was developed using an automated deep learning algorithm (Prediction One, Sony Network Communications, Tokyo, Japan; <https://predictionone.sony.biz/>).<sup>(20,21)</sup> Prediction One software employs an ensemble learning technique to make predictions using two algorithms: a neural network and a gradient boosting tree (Fig. 1). The neural network automatically selects the number of layers for the model within the range from 2 to infinity, with the software making the selection. The output

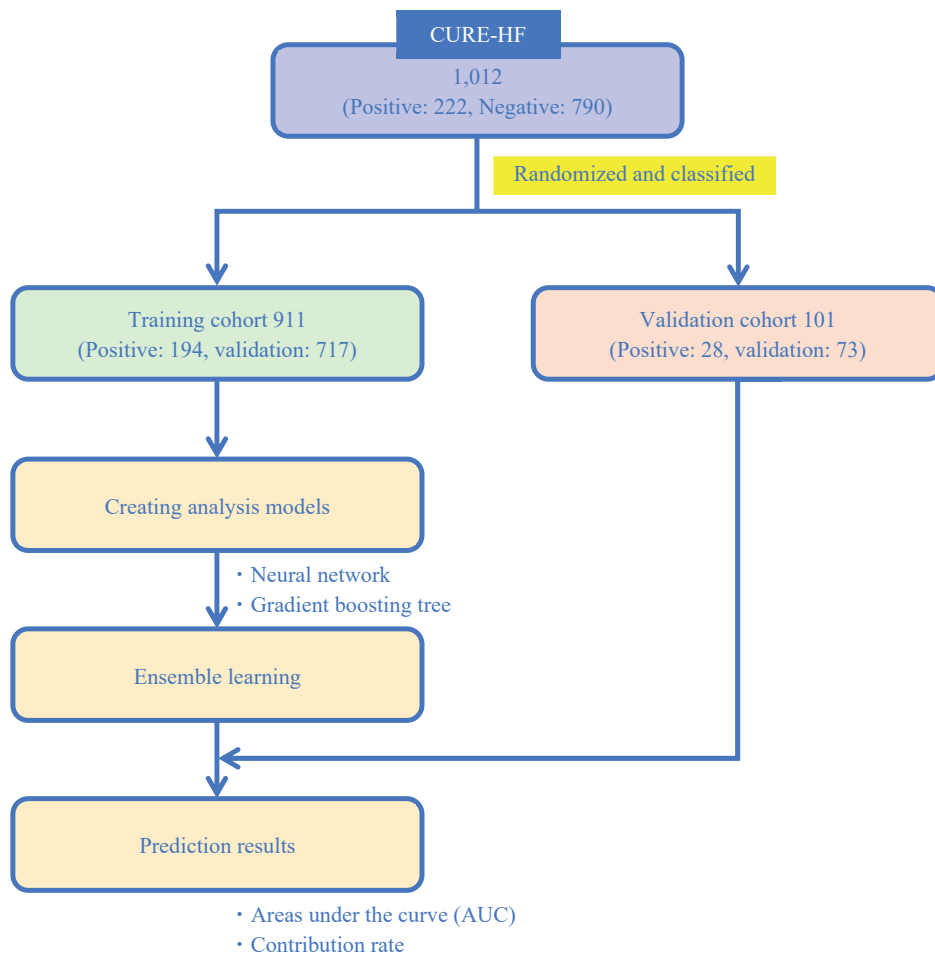


Fig. 1. (Color online) Patient selection and block diagram of deep learning. The number of patients included in this study comprised 1,012 hospitalized patients, whose records were divided into two groups: 90% (911) for training dataset and 10% (101) for validation dataset in deep learning.

weightings (hyperparameters) of the neural networks and the gradient boosting trees are automatically optimized. Predictions are calculated using ensemble learning, incorporating the weights and the threshold levels for the outputs of the two models.<sup>(22)</sup> The rationale behind the use of Prediction One is that the software automatically performs preprocessing such as missing value completion and variable normalization and it does not require hyperparameter tuning.

The tuning of the model was performed to increase the sensitivity by optimizing it to better identify patients with ADHF at mortality risk. Prediction models of ADHF mortality risk after discharge were established by deep learning using the training dataset while increasing the number of input variables using the contribution rate as an indicator.<sup>(23)</sup> The model performance was assessed by a discrimination test using receiver operating characteristic (ROC) analysis.<sup>(24)</sup> ROC curves were generated to investigate the discriminatory power of clinical characteristics. The areas under the curves (AUCs) were calculated to provide an overall summary of the detection accuracies of the clinical characteristics. Here, the *AUC* is empirically classified into

three levels: poor when  $0.50 \leq AUC \leq 0.69$ , good when  $0.70 \leq AUC \leq 0.89$ , and excellent when  $0.90 \leq AUC \leq 1$ . *Sensitivity*, *specificity*, and *c-statistics* were used for model evaluation in the test dataset. The weight of each variable was investigated automatically to measure how it contributed to the model's diagnostic accuracy. To compare the usefulness of the prediction models, we investigated the *c-statistics* (*AUC*) of the AI-based models.

## 2.4 Statistical analysis

Statistical analyses were performed with the Statistical Package for the Social Sciences (SPSS) version 20.0 (SPSS Inc, Chicago, IL). Unless otherwise stated, all data were expressed as mean  $\pm$  SD. A value of  $p < 0.05$  was taken to represent statistical significance.

## 3. Results

### 3.1 Baseline characteristics of patients

Table 1 shows the fifteen baseline characteristics of the hospitalized patients. The study population included the following demographic information: 44.8% of the study population consisted of females, 54.4% were aged 80 years or older, and 21.0% had a classification of New York Heart Association (NYHA)<sup>(25)</sup> equal to or greater than three when discharged. Common comorbidities included dyslipidemia, diabetes mellitus, hyperuricemia, atrial fibrillation, coronary artery disease, cerebrovascular disease, and malignant tumors. The complication records included 51.6% of comorbid atrial fibrillation, 39.2% of CKD, and 17.8% of anemia. Blood test results at the time of discharge indicated that 76.4% of the study population had CKD (eGFR  $< 60$  mL/min/1.73 m<sup>2</sup>) and 58.3% had anemia (males with Hb  $< 13$  g/dL; females with Hb  $< 12$  g/dL). The features of patients in this CURE-HF registry include high rates of comorbid atrial fibrillation, CKD, and anemia. Patients in the comorbid atrial fibrillation group were more likely to have worse NYHA class of  $\geq 3$  and to have CKD (eGFRs) at the time of discharge ( $p < 0.05$ , Mann–Whitney test). There was not a strong enough statistical difference to support the idea that the severity of HF symptoms (NYHA classes  $\geq 3$ ) among patients was related to their anemia (Hb) levels at discharge. However, the  $p$ -value of 0.054 suggests a potential difference that may require a larger sample size to become evident.

### 3.2 Predicting models of ADHF mortality risk after discharge

Table 2 summarizes the calculated results of each prediction model using the validation dataset classified into the four diagnostic criteria of true positive (TP), true negative (TN), false positive (FP), and false negative (FN). For comparison, a conventional statistical analysis was conducted with GWTG-HF program data and the results are also shown in Table 2. The established prediction models of deep learning are shown as Models 1 to 6. The contribution rates of four input variables, namely age, systolic blood pressure, heart rate, and COPD, were comparatively high. No significant difference in the sum of TP and TN diagnostic criteria was

Table 1

Baseline characteristics of Japanese hospitalized patients in CURE-HF registry used as the factors in the prediction model of mortality.\*<sup>1</sup>

	Overall ( <i>n</i> = 1012)	Dead ( <i>n</i> = 222)	Alive ( <i>n</i> = 790)	<i>p</i> -value
Age (years)	81.0 (71.0–87.0)	85.0 (79.0–89.0)	79.0 (69.0–86.0)	< 0.01* <sup>2</sup>
Heart rate (beats/min)	70.0 (60.0–80.0)	69.5 (60.0–81.0)	70.0 (60.0–80.0)	0.64* <sup>2</sup>
Systolic blood pressure (mmHg)	112.0 (100.0–125.0)	108.0 (98.0–120.8)	114.0 (102.0–126.0)	< 0.01* <sup>2</sup>
BUN (mg/dL)	24.5 (18.4–32.9)	28.1 (21.3–39.0)	23.2 (18.0–31.0)	< 0.01* <sup>2</sup>
Sodium (mEq/L)	139.0 (137.0–141.0)	139.0 (136.0–141.0)	139.0 (137.0–141.0)	< 0.01* <sup>2</sup>
COPD	53/1012	20/222	33/790	< 0.01* <sup>2</sup>
BMI (kg/m <sup>2</sup> )	21.0 (18.9–23.8)	20.2 (17.9–23.1)	21.3 (19.1–24.0)	< 0.01* <sup>2</sup>
BNP (pg/mL)	291.6 (138.0–531.0)	433.8 (183.0–663.9)	266.0 (130.3–474.1)	< 0.01* <sup>2</sup>
Red blood cell (×10 <sup>4</sup> /μL)	401.0 (347.0–458.0)	374.0 (336.0–422.0)	407.0 (353.0–464.0)	< 0.01* <sup>2</sup>
eGFR (mL/min/1.73m <sup>2</sup> )	46.0 (33.0–59.0)	39.0 (29.1–53.2)	47.3 (34.7–60.0)	< 0.01* <sup>2</sup>
Diastolic blood pressure (mmHg)	65.0 (57.0–74.0)	61.0 (55.0–69.0)	66.0 (58.0–74.0)	< 0.01* <sup>2</sup>
LVEF (%)	49.0 (35.0–61.9)	49.1 (33.0–61.4)	49.0 (35.5–62.0)	0.45* <sup>2</sup>
Number of administered medications ( <i>n</i> )	1: 695 (69%) 2: 163 (16%) 3 > : 152 (15%) missing: 2	1: 105 (47%) 2: 44 (20%) 3 > : 72 (32%) missing: 1	1: 590 (75%) 2: 119 (15%) 3 > : 80 (10%) missing: 1	—
Length of hospitalization (days)	19.0 (13.0–29.0)	20.0 (14.0–33.8)	19.0 (13.0–29.0)	
Nohria–Stevenson classification ( <i>n</i> )	1: 32 (3%) 2: 767 (76%) 3: 55 (5%) 4: 158 (16%)	1: 4 (2%) 2: 160 (72%) 3: 17 (8%) 4: 41 (18%)	1: 28 (4%) 2: 607 (77%) 3: 38 (5%) 4: 117 (15%)	—

\*<sup>1</sup> Values are medians (interquartile ranges) or *n* (%).

\*<sup>2</sup> Mann–Whitney test was conducted.

observed in both the statistical model based on the GWTG-HF and the deep learning Model 1 with the same input variables. However, by exploring the input of different variables using deep learning, a combination of input variables was found on Model 4 that increased the number of true negatives and decreased the number of false positives.

We conducted a ROC analysis using the validation dataset to closely evaluate the performance of the prediction models of ADHF mortality risk. As a statistical approach, the *sensitivity*, *1 – specificity*, and *AUC* of the GWTG-HF model using the validation dataset were 0.750, 0.397, and 0.68, respectively. On the other hand, the optimal combination of input variables was found as Model 4 presented an optimal combination of input variables, that is, the *specificity* improved and *c-statistics* reached maximum at 0.75 (Table 3 and Fig. 2). Model 4 was added with the

Table 2  
Calculated results of four combinations of each method.

Method	Variables	TP	TN	FP	FN	Correct Number
GWTG-HF	Age, Heart rate, Systolic blood pressure, COPD	5	67	6	23	72
Deep learning						
Model 1	BUN, Sodium	1	72	3	27	73
Model 2	LVEF, BUN, Sodium	3	73	0	25	76
Model 3	LVEF, BUN, Sodium, NM	4	71	2	24	75
Model 4	Age, Heart rate, Systolic blood pressure, COPD	5	72	1	23	77
Model 5	BUN, Sodium, BNP, RBC, LVEF, NM, LOH, NS	2	72	1	26	74
Model 6	BNP, RBC, Diastolic blood pressure, LVEF, NM, LOH, NS	7	68	5	21	75

TP: true positive, TN: true negative, FP: false positive, FN: false negative, RBC: red blood cell, NM: number of administered medications, LOH: Length of hospitalization, NS: Nohria–Stevenson classification.

following six input variables to the GWTG-HF program: BNP level, RBC count, LVEF, number of administered medications, LOH, and Nohria–Stevenson classification. Additionally, we omitted the input variable of sodium level from the GWTG-HF program.

Figure 3 shows the comparison of contribution rates of the input functions of Models 1 and 4. Gradient boosting trees were used to determine the effect of input variables on the prediction accuracy, where the contribution rate indicates the degree of contribution to the prediction accuracy. For instance, if the contribution rate of a function is 0.1, the prediction accuracy improves by 0.1 upon incorporation of the function into the input variables. In generating Model 4, the following input variables were added to Model 1 in ascending order: number of administered medications, BNP level, LVEF, Nohria–Stevenson classification stage, and LOH.

#### 4. Discussion

The study results supported our working hypothesis that the prediction accuracy of ADHF mortality risk improved depending on the levels of the HF biomarker, BNP. The combinational assessment using multiple clinical characteristics from more than 1,000 randomized records of hospitalized patients showed promise for predicting the ADHF mortality risk. Sartipy *et al.* reported a c-statistic for AUC of 0.74 for predicting the HF mortality risk after discharge from the hospital or after a clinical visit in a large cohort of patients using the Kaplan-Meier survival time analysis method.<sup>(26)</sup> In addition, a meta-analysis using the Seattle Heart Failure Model to predict death during the following year reported a c-statistic of 0.69.<sup>(27)</sup> Logistic regression was also used to estimate the HF mortality risk with a preserved ejection fraction after three years of follow-up, and the c-statistic of the model was 0.72.<sup>(28)</sup> The AUC c-statistic of 0.75 for predicting the ADHF mortality risk after discharge was higher than those of published statistical

Table 3  
Results of ROC analysis of prediction models for HF mortality risk after discharge.

Model	<i>Sensitivity</i>	$1 - \textit{Specificity}$	<i>AUC</i>
1	0.643	0.274	0.70
2	0.714	0.329	0.70
3	0.500	0.178	0.68
4	0.607	0.192	0.75
5	0.607	0.452	0.54
6	0.429	0.192	0.62

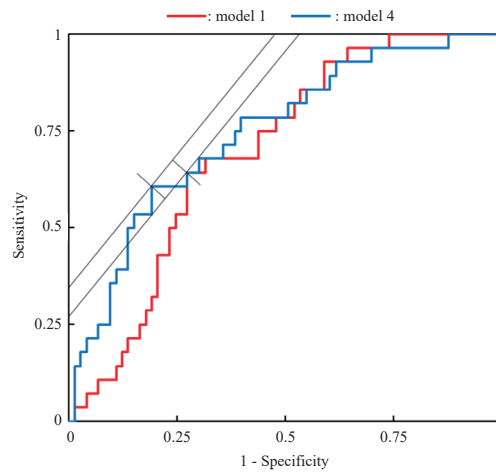


Fig. 2. (Color online) Ability of deep learning models to predict mortality using multifunctions.

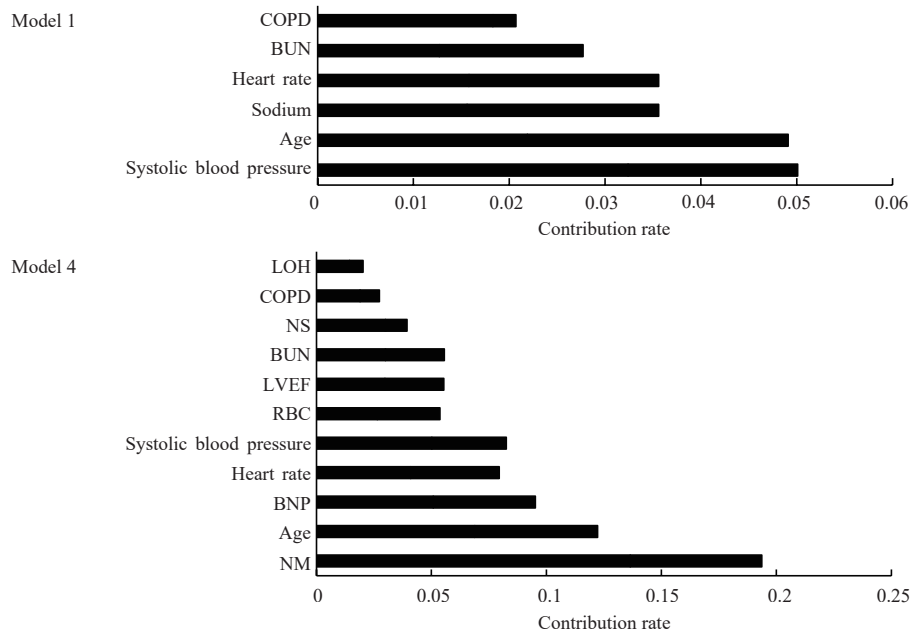


Fig. 3. Comparison of contribution rates of prediction model input functions.



approaches. The ROC analysis showed that Model 4 had “good” capability for discriminating between cardiac death or alive (Table 3 and Fig. 2). The prediction accuracy could be improved by appropriately adding input variables as the RBC count, LVEF, number of administered medications, LOH, and Nohria–Stevenson classification stage, which were not typical input variables for the prediction model of ADHF mortality risk. By using deep learning, we demonstrated that the handling of nonlinear relationships and the ability to integrate large and diverse datasets effectively can lead to the discovery of useful medical information buried within diagnostics, and can provide objectivity to medical information that physicians intuitively focus on.

Choi *et al.* used quantitative features derived from echocardiographic images.<sup>(29)</sup> In addition to imaging data, electronic health record (EHR) data are also informative for HF risk prediction.<sup>(30)</sup> Moreover, wearable devices are being developed for the remote acquisition of real-time data from patients with HF to monitor potential risks.<sup>(31)</sup> In this research, the hospitalized patients were Japanese of higher average age with higher rates of comorbid atrial fibrillation, CKD, and anemia. Indeed, the deep learning model selected the following variables associated with these comorbidities as input variables: BNP level, which is associated with comorbid atrial fibrillation, and the red blood cell count, associated with anemia. Current HF mortality risk models do not typically include BNP measures (Seattle HF Model,<sup>(32)</sup> MAGGIC score,<sup>(33)</sup> 3C-HF,<sup>(34)</sup> and HF Meta-Score<sup>(35)</sup>). The addition of BNP to risk prediction models demonstrated increased discrimination by these multivariable models to predict adverse ADHF outcomes. There is a possibility that we have not incorporated an effective input variable. Therefore, this finding suggests that developing technology capable of measuring biomarkers frequently may be an effective approach to predict adverse ADHF outcomes.

Among the clinical characteristics of the CURE-HF registry used in this study, age, BUN, BNP levels, and LOH were positively correlated with the ADHF mortality risk. By contrast, heart rate, systolic blood pressure, red blood cell, and LVEF were negatively correlated with the cardiac death risk. Therefore, the prediction accuracy of our model was higher when the input variables with a positive correlation were included in Model 4. However, multicollinearity, a phenomenon that can occur when running multiple regression models, may influence the prediction accuracy when the number of input variables increases.<sup>(36,37)</sup> In the validation of common pitfalls in machine learning, such as data imbalance and overfitting, statistical methods such as cross-validation, regularization, and data augmentation are employed.<sup>(38–40)</sup> However, in machine learning using an extremely large number of input variables, verification using these methods is not straightforward. This problem occurs regardless of the analysis method, be it a statistical or machine learning method, and remains a problem for the future.

Quantitative evaluation of the association between estimation results and the input variables is difficult when using deep learning algorithms that rely only on neural networks. In this research, it became possible to visualize the effects of input variables, as shown in Fig. 3, because the Prediction One software employs ensemble learning to make predictions using two algorithms: a neural network and a gradient boosting tree. A method achieving both accuracy and causality identification, such as ensemble learning, might be necessary to effectively implement deep learning strategies in medical fields.

The limitations inherent to this study require further exploration. Our results should be validated in other populations, and the temporal changes in BNP levels according to HF progression and prognosis should be examined in future studies.

## **5. Conclusions**

By analyzing data from over 1000 Japanese hospitalized patients with ADHF and using deep learning, we demonstrated that our deep learning model based on multiple clinical characteristics, including HF markers, is useful for predicting the ADHF mortality risk after discharge. Furthermore, we showed that our model based on multiple clinical characteristics, including HF markers such as BNP, is effective for predicting the ADHF mortality risk. Therefore, developing wearable devices for the remote acquisition of real-time data from patients with ADHF is important to enable the monitoring of potential risks.

HF mortality risk prediction is critical for the accurate application of specific therapeutic approaches, which range from pharmacological to highly invasive mechanical ventricular assistance and cardiac transplantation strategies. Deep learning with ensemble learning using a neural network and a gradient boosting tree may offer valuable applications in the diagnosis, classification, and prediction of cardiovascular disease. Owing to the relatively small number of validation datasets, there is a limitation in deep learning research, and our results should be validated in other populations.

### **Ethics approval**

The present study was approved by the Institutional Review Board of Shinshu University School of Medicine (Approval No. 4237).

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### **Declaration of Competing Interest**

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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