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ORIGINAL ARTICLE

Clinical application of artificial intelligence algorithm for prediction of one-year mortality in heart failure patients

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Abstract

Risk prediction for heart failure (HF) using machine learning methods (MLM) has not yet been established at practical application levels in clinical settings. This study aimed to create a new risk prediction model for HF with a minimum number of predictor variables using MLM. We used two datasets of hospitalized HF patients: retrospective data for creating the model and prospectively registered data for model validation. Critical clinical events (CCEs) were defined as death or LV assist device implantation within 1 year from the discharge date. We randomly divided the retrospective data into training and testing datasets and created a risk prediction model based on the training dataset (MLM-risk model). The prediction model was validated using both the testing dataset and the prospectively registered data. Finally, we compared predictive power with published conventional risk models. In the patients with HF ($n = 987$), CCEs occurred in 142 patients. In the testing dataset, the substantial predictive power of the MLM-risk model was obtained (AUC = 0.87). We generated the model using 15 variables. Our MLM-risk model showed superior predictive power in the prospective study compared to conventional risk models such as the Seattle Heart Failure Model (c-statistics: 0.86 vs. 0.68, $p < 0.05$). Notably, the model with an input variable number ($n = 5$) has comparable predictive power for CCE with the model (variable number = 15). This study developed and validated a model with minimized variables to predict mortality more accurately in patients with HF, using a MLM, than the existing risk scores.

Keywords Heart failure · Machine learning · Risk prediction · Prognosis

Abbreviations

HF	Heart failure
BNP	B-type natriuretic peptide
SHFM	Seattle heart failure model
GWGT-HF	Get with the guidelines-heart failure
MAGGIC	Meta-analysis global group in chronic heart failure
LVEF	Left ventricular ejection fraction
LVAD	Left ventricular assist device
CCE	Critical clinical events

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Introduction

Heart failure (HF) is a complex syndrome characterized by heterogenous pathophysiology [1]. The systemic state of a patient is often affected by various circumstances, not only by cardiac factors but also by extra-cardiac factors such as fluid volume retention, renal function, and neurohormonal activation, resulting in dynamic changes in patient state [2–4]. Because of the complex interaction of multiple factors affecting the HF state, several methods for risk stratification

using multiple factor have already been proposed in clinical settings, such as the Seattle Heart Failure Model (SHFM) [5, 6], the Get With The Guidelines-Heart Failure (GWTG-HF) risk model [7], and the Meta-analysis Global Group in Chronic Heart Failure (MAGGIC) score [8]. Some of these models require a large number of variables, such as 24 variables in SHFM, to increase the accuracy of prediction. However, most of these models use only simple linear models without considering nonlinear interactions between multiple factors. There is a possibility that methods based on non-linear interactions improve the predictive power compared with those based on linear interaction. Indeed, several studies have demonstrated the superiority of the models based on non-linear interaction using machine learning methods compared with models based on linear interaction [9–13]. Although they have a higher accuracy rate, these nonlinear risk prediction models have not been widely available in clinical settings. These machine learning models based on non-linear interactions also require a large number of predictor variables. When considering clinical application, reducing the variables seems to be beneficial in order to reduce the burden on the clinical site.

With this background, this study aimed to verify the hypothesis that non-linear models based on machine learning methods improve the predictive power for clinical outcomes compared with conventional risk stratification tools based on a linear model. If so, we also aimed to identify the determinants of the operation of our model to facilitate clinical application. First, we aimed to create a non-linear prediction model for 1-year mortality with higher predictive power using retrospective data. If such a model is established, it can be applied to replanning patient care including advance care planning. Second, we validated our model using prospective data. Third, we optimized our model with the minimum independent variable size without sacrificing the model accuracy rate to facilitate the clinical application of our model.

Methods

Study design

This was a cross-sectional study of patients with HF admitted to the National Cerebral and Cardiovascular Center (NCVC) of Japan. The validation study was performed using the data of National Hospital Organization Kyoto Medical Center (KMC).

Study population

Retrospective study

We retrospectively identified all hospitalized patients requiring HF treatment between January 2013 and May 2016 in the NCVC via the diagnosis at discharge of diagnosis procedure combination system. According to the Framingham criteria [14], HF was diagnosed by at least two attending physicians. As for the patients, whether or not the HF episode met the Framingham criteria was reviewed by the investigators via medical records. We excluded patients who did not meet the criteria as judged by the investigator or attending physician for each patient as previously described [15]. We identified 1204 HF hospitalizations. Because we assumed that this model would be applied to patients with advanced HF and multiple HF hospitalization history and could be used for the index for replanning patient care in the end-stage of HF to determine an initiation timing of advanced care planning, this study used the last hospitalization data in patients with multiple HF hospitalization histories. Patients who died during the corresponding hospitalization period for HF were excluded from the analysis. Finally, data from 987 patients were included in this study.

Prospective study

We started a single-center, observational, ongoing, and prospective cohort that included all patients requiring hospitalization since January 2019 with a diagnosis of HF by at least two cardiologists. Whether the HF episode met the Framingham criteria was reviewed by the investigators, including well-trained nurses and clinical research coordinators, and was finally approved by the cardiologist in the investigation team. One-hundred-and-ninety-seven HF patients between January and March 2019 were enrolled in this analysis.

Validation study

We also performed the validation study using the data of KMC. The data of the patients with hospitalized due to HF were collected in 2017, retrospectively. For the validation study, we convert the NT-proBNP values to BNP values using the formula published in the previous study [16].

Laboratory tests

All biochemical analyses were performed as routine clinical examinations. BNP were measured by the human brain natriuretic peptide kit (TOSOH corporation, Tokyo, Japan) as previously described [17].

Echocardiography

Using the medical records, we retrospectively reviewed the echocardiographic data of the enrolled patients during hospitalization. Left ventricular (LV) dimensions were measured according to the American Society of Echocardiography guidelines [18]. LV ejection fraction (EF) was measured

using the modified Simpson method or semiquantitative two-dimensional visual estimation method, as previously described [19].

Clinical outcomes

After the discharge date, we investigated all causes of death and implantation of an LV assist device (LVAD) through medical chart review or a letter. Critical clinical events (CCEs) in this study were defined as all-cause death or LVAD implantation. Thus, non-survivors were defined as patients with the above critical events: all-cause death or LVAD implantation.

Machine learning algorithm

We used a machine learning framework of a tree-based algorithm called a gradient boosting machine to create our non-linear model for the binary classification of survival or non-survival categories. Instead of using a multilayer neural network model, we chose a tree-based algorithm as a non-linear model to achieve both higher prediction accuracy and better model interpretability. Model interpretability helps us to create an important feature list that is essential for creating an optimized model with minimum independent variables, which increases the usability of the model in clinical practice. We implemented all the methods with the open-source Python (version 3.6) programming language and Scikit-learn library with Lenovo X390 with Windows 10 OS, 1.60 GHz 4 core, and 16GM memory.

LightGBM

In this study, we used LightGBM [20, 21], which is a gradient boosting algorithm framework, to create a nonlinear model. Most of the existing gradient boosting frameworks are algorithms that often provide better predictions, but the model creation process requires a longer computational time. LightGBM, a recent improvement of the gradient boosting framework, inherited the original high predictivity of gradient boosting but resolved the computational time bottleneck by adopting a leaf-wise tree growth strategy. Moreover, LightGBM helps to solve the missing value problem and imbalanced data problem inside the framework by providing related hyper-parameters in the frameworks.

Overview of procedures

We followed a normal procedure to create our model. First, we randomly split our dataset into two parts, where 70% was used as the training data and the remaining 30% was used as the testing dataset, as shown in the flow chart (Fig. 1, upper panel). Second, we fine-tuned our model hyper-parameters by using 10% of our training data as the validation dataset. Third, we validated our model using a test dataset and validation with a prospective dataset. Forth, we also validated the model using other facilitate data of patients with HF.

Ethics

This study was composed of the two data sets (retrospective and prospective), which were approved by our institutional ethics committee: the research ethics committee of NCVC (M26-127, M30-142 and M30-548). The studies were designed to be carried out without obtaining individual informed consent according to the "opt-out" principle, as previously described [15]. Instead, we publicized a summary of the study protocol with the contact information for our office on the institution's website, which provided patients with the ability to refuse enrollment in the study. Both protocols were also registered in the Japanese University Hospital Medical Information Network Clinical Trials Registration (the retrospective study: UMIN 000034409; the prospective study: UMIN 000035428). In addition, regarding validation study using the data of KMC, the study protocol was approved by KMC ethics committee (19–074). All methods were carried out in accordance with relevant guidelines and regulations.

Statistical analyses

Results are expressed as the median and interquartile range (IQR). Fisher's exact test or the χ^2 test was used to compare categorical variables, as appropriate. The area under the

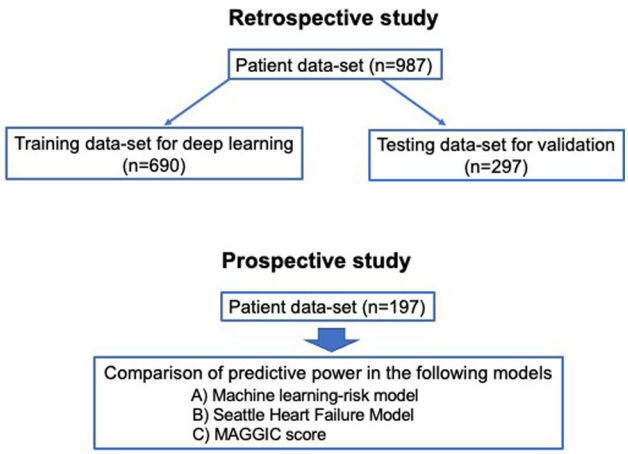

Fig. 1 Study flow chart. Upper panel: we randomly split our dataset into two parts, where 70% was used as training data and the remaining 30% was used as the testing dataset. Lower panel: we analyzed the predictive power of our method using prospective data ($n=197$) to validate the machine learning risk model and compare its predictive power with that of the conventional tool (Seattle Heart Failure Model and MAGGIC score)

receiver operating characteristics (ROC) curve (AUC) and C-statistics were also calculated. The AUCs were compared using an algorithm developed by Delong et al [14]. We used R with the pROC package to perform the Delong test in this study. Statistical analyses regarding the comparison of AUC curves were performed using R 3.5.0, and the qROC software packages [22]. SHFM risk score [5] and MAGGIC risk score [8] were calculated by published formula and the patients with a lack of data were excluded from the analysis.

Results

Baseline patient characteristics

The enrolled patients in the retrospective study are summarized in Table 1 and characterized as follows; New York Heart Association class III and IV on admission (42.4% and 43.4%, respectively), male (60.8%), LVEF on admission (median: 35.0%, IQR [22.5, 52.5%]), LV end-diastolic diameter on admission (median: 54.0 mm, IQR [47.0, 61.0 mm]), and plasma BNP levels on admission (median: 600.2 pg/ml, IQR [296.3, 1041.1 pg/ml]). The median length of hospitalization was 19 days (IQR: 13, 27 days).

Mortality following hospital discharge in patients with HF

Of the 987 enrolled patients, CCE (all-cause death or LVAD implantation) occurred in 142 patients within 1 year from the discharge date.

Minimum variable selection

Our cross-sectional data consist of 987 samples and each sample has 172 predictor variables. We categorized the predictor variables into seven groups: general variables (13), pre-admission variables (15), hospital variables (32), current post-admission variables (46), 1-year post-discharge variables (11), 2-year post-admission variables (11), and others (44). As our model predicts outcome events within one year, after we deleted 1- and 2-year post-admission variables, 150 variables remained. In the next step, we deleted variables with more than 30% missing values. In the following step, we performed correlation analysis and kept a single variable from a highly correlated pair ($r \geq 0.75$). Finally, we used 39 variables to create our non-linear model using a machine learning method. To improve the applicability of our model in clinical practice, we chose the variable selection process in our final step of model creation and optimized the model with a better prediction accuracy with fewer predictor variables. Using the LightGBM framework, we ranked 39 variables with respect to the importance of the trained model. Then, we rebuilt our model with a subset of these 39 variables, as shown in Supplemental Fig. 1. The results of the training dataset are shown in Supplemental Fig. 2. Initially, we started with the five most important variables to train LightGBM with the same hyper-parameter settings as our original 39 variables model. One by one, we increase the variables and rebuild the model iteratively. If the newly added variable did not increase the c-static value, we excluded the variables from the targeted variable list. We terminated this iterative process, while the testing c-statistic was the maximum. Finally, we identified the first set of 15 variables, which showed better predictive performance, as

Table 1 Baseline patient characteristics

	Overall patients
Patients number	987
Age (y.o.)	78 (69, 84)
Gender (male %)	60.8
BMI (kg/m^2)	22.5 (19.9, 25.2)
NYHA class	
Class III, *N*, (%)	418 (42.4)
Class IV *N*, (%)	428 (43.4)
Etiology	
Ischemic, *N*, (%)	297 (30.1)
Non ischemic, *N*, (%)	234 (23.7)
Valvular, *N*, (%)	215 (21.8)
Hypertensive, *N*, (%)	196 (19.9)
Others, *N*, (%)	45 (4.6)
History	
Hypertension, *N*, (%)	659 (69.8)
Diabetes mellitus, *N*, (%)	363 (37.2)
Vital signs and others on admission	
Systolic blood pressure (mmHg)	119 (105, 138)
Diastolic blood pressure (mmHg)	68 (58, 82)
Heart rate (bpm)	77 (66, 93)
Echocardiography	
LVEDD (mm)	54.0 (47.0, 61.0)
LVESD (mm)	42.5 (33.0, 53.0)
LVEF (%)	35.0 (22.5, 52.5)
Laboratory data	
BNP (pg/ml)	600.2 (296.3, 1041.1)
BUN (mg/dl)	23 (17, 33)
Creatinine (mg/dl)	1.08 (0.85, 1.56)
Hb (g/dl)	12.0 (10.6, 13.4)
Hct (%)	36.7 (32.3, 40.7)
CRP (mg/dl)	1.35 (0.13, 1.27)

Values are the median (IQR) and patients number, N (%)

BMI body mass index, *NYHA* New York Heart Association, *DM* diabetes mellitus, *LVEDD* Left ventricular end-diastolic diameter, *LVESD* Left ventricular end-systolic diameter, *LVEF* left ventricular ejection fraction, *BUN* blood urea nitrogen, Hb hemoglobin, *Hct* hematocrit, *CRP* C reactive protein

shown in Table 2. We also created two other models with the best 10 variables and the best five variables.

Table 2 Variables used for operating AI algorithm

No	Variables	IMP
1	Troponin levels	1093
2	Systolic blood pressure on admission	955
3	BMI at discharge	938
4	Hematcrit at discharge	877
5	BNP levels at discharge	855
6	CRP at discharge	831
7	LDLC on admission	771
8	Systolic blood pressure at discharge	770
9	WBC at discharge	753
10	Diastolic blood pressure at discharge	747
11	Creatinine levels at discharge	736
12	TG on admission	732
13	TRPG on admission	670
14	BUN on admission	651
15	LVEF on admission	621

IMP feature importance calculated by LightGBM, *BMI* body mass index, *BNP* B-type natriuretic peptide, *CRP* C reactive protein, *LDLC* low density lipoprotein cholesterol, WBC white blood cell, *TG* triglyceride, *TRPG* tricuspid peak gradient, *BUN* blood urea nitrogen, *LVEF* left ventricular ejection fraction

Predictive power of risk models for clinical outcomes

The results of predictive power in the validation study are shown in Fig. 2, which used the 15 variables (Table 2, No. 1–15). Next, we analyzed the association between variable numbers and predictive power. The predictive power for the clinical outcomes in the retrospective cohort is shown in Fig. 2 A, B, and C, which are based on 15 (No. 1–15 in Table 1), ten (No. 1–10 in Table 1), and five variables (No. 1–5 in Table 1). The differences in predictability between A (No. 1–15) and B (No. 1–10) and between A (No. 1–15) and C (No. 1–5) was not statistically significant ($p = 0.762$ and 0.690, respectively).

Next, we analyzed the predictive power of our method using prospective data (n = 197, Fig. 1, lower panel) as the validation study (Fig. 3A). We then compared the predictive power of the SHFM and MAGGIC risk model as a conventional predictive tool. Figure 3B and C show the AUC curves in the SHFM and MAGGIC risk model, respectively. The predictive power of the ML-risk model was superior to that of the SHFM ($p = 0.043$) and was not inferior to that of the MAGGIC risk model ($p = 0.205$). In addition, as shown in Supplemental Fig. 3, the predictability was decreased in the patients with HF with preserved

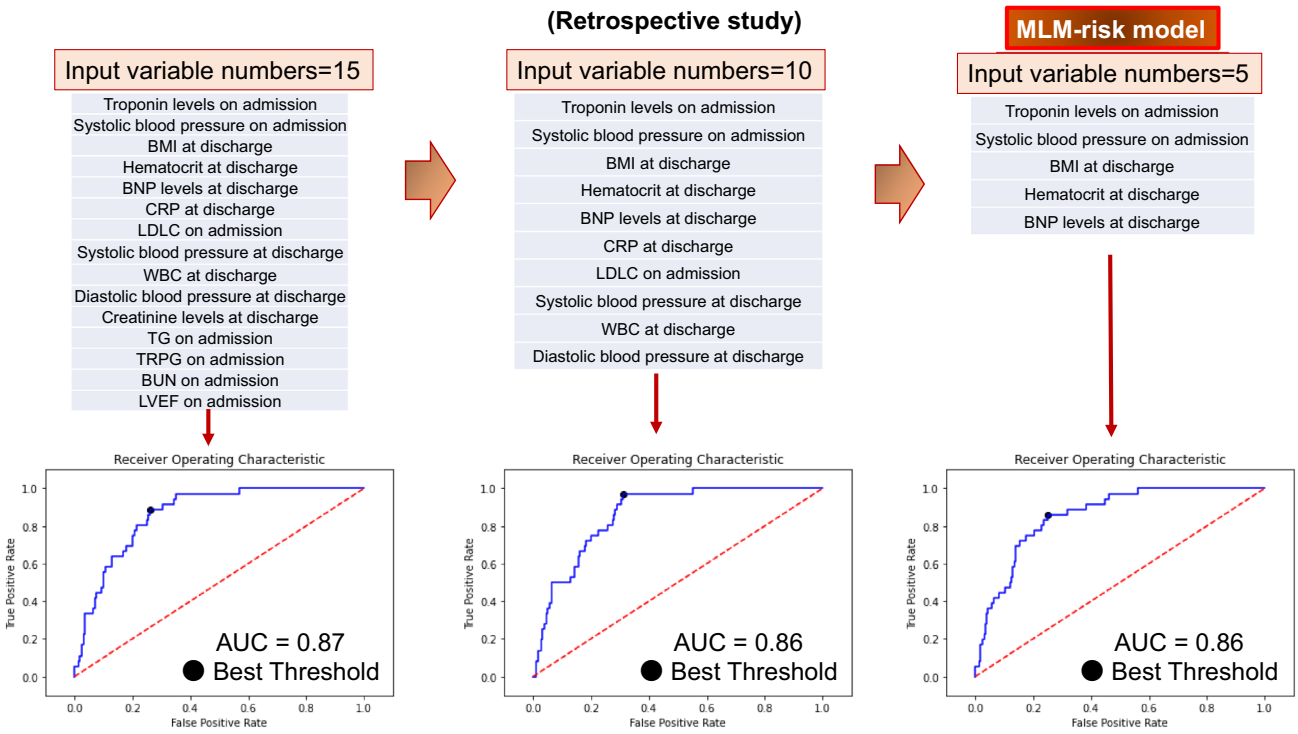

Fig. 2 The predictability of minimum number of variables risk model (MLM-risk model). Predictive power for the clinical outcomes in the retrospective cohort. **A**, **B**, and **C**, which are based on 15 (No. 1–15 in Table 1), ten (No. 1–10 in Table 1), and five variables (No. 1–5 in Table 1). The differences in predictability between A (No. 1–15) and B (No. 1–10) and between A (No. 1–15) and C (No. 1–5) was not statistically significant ($p = 0.762$ and 0.690, respectively)

EF (HFpEF). In contrast, the predictability was preserved in those with HFrEF.

We also performed the additional analysis for validation of this model using KMC. As shown in the Supplemental Fig. 4, AUC of this model ranged 0.67–0.69. The enrolled patients in KMC are summarized in Supplemental Table 1 and characterized as follows; New York Heart Association class III and IV on admission (36.9% and 34.6%, respectively), male (61.2%), LVEF on admission (median: 43.5%, IQR [33.0, 54.0%]), and LV end-diastolic diameter on admission (median: 51.0 mm, IQR [45.0, 56.0 mm]). Differences were found in several patient characteristics as age, the rate of NYHA3-4, HF etiology, the rate of hypertension, blood pressure on admission, heart rate on admission, LV size and LVEF (Supplemental Table 1).

Discussion

This study demonstrated the strong predictive power of the nonlinear model compared with the conventional linear model. Our non-linear machine learning risk model predicts 1-year mortality in patients with HF and was validated using a prospective cohort. Moreover, we identified the minimum variables that are necessary to operate the model for predicting clinical outcomes, as shown in Table 2. Although the variables identified in this study are widely known as predictors of clinical outcomes in cardiovascular diseases [14], the machine learning used in this study was able to efficiently choose the variables based on non-linear models. This study also demonstrates that our model works with a small number of variables without sacrificing its predictive power. This strong prediction power with a minimum variable size ensures the practical application of our model in clinical settings. One unique point in the present study is that even if we decreased the number of variables in the machine learning models, the predictive power was not reduced (variable number = 15, AUC = 0.87; variable number = 10, AUC = 0.86; variable number = 5, AUC = 0.86), as shown in Fig. 2. Although the previous studies already demonstrated the efficacy of the machine learning models for prediction of heart failure outcomes [23–25], we focused on the development of predictive models for the association of variable numbers and predictive power for clinical outcomes.

Several studies have demonstrated the benefits of machine learning for predicting clinical outcomes in patients with HF [11–13, 26]. Kwon et al. developed deep-learning-based AI algorithms for predicting mortality in patients with acute HF using neural network models with a c-statistic of 0.782 [13]. Their models used demographic information and general routine clinical examinations as electrocardiography and echocardiography findings as inputs for the model in clinical use and demonstrated the superiority of machine learning algorithms compared with the other conventional models. However, these models require a large amount as 22–86 variables to operate the algorithms [13, 26]. In contrast, this study identified five to fifteen essential variables necessary to predict clinical outcomes in the operation of machine learning algorithms. Our study also demonstrates that our model is superior to the previous models, such as the SHFM or shows the comparable predictive power with the MAGGIC risk model. In addition, accurate predictability was shown in the machine learning algorithm focusing on the minimum number of variables (MLM-risk model) as shown in Fig. 3. Given the clinical application of the risk prediction model, MLM-risk model will be expected to reduce the burden on healthcare workers in clinical settings, such as in emergency room.

The reason for the differences in predictive power between the conventional tool and the MLM-risk model in this study is uncertain at present. One speculation is that since previous risk models did not involve biomarkers such

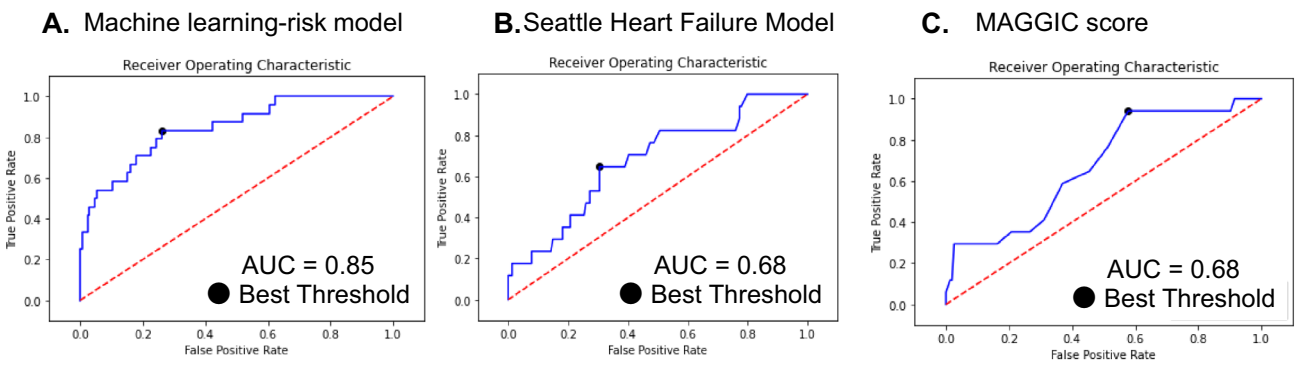

Fig. 3 Validation of machine learning risk model and comparison with conventional tools. In a validation study using prospective cohort data, the ROC curves are shown in **A**. ROC curves using the Seattle Heart Failure model and MAGGIC risk model are shown in **B** and **C** , respectively. The predictive power of the machine learning risk model was superior to that of the Seattle Heart Failure model ($p = 0.043$) and was not statistically different with that of the MAGGIC risk model ($p = 0.205$)

as BNP, we could not exclude the possibility that the differences in involved variables, such as BNP, contribute to their predictive power differences in the previous models and our current model. However, even when adding BNP values to the risk models in the previously validated studies [6, 27], their predictive power was also limited to below c-statics of 0.8. These findings and accumulating evidence raise the possibility that a non-linear model using the machine learning method might contribute to this difference. In addition, the previous models focused the variables on admission. In contrast, our model focused on the variables in both timings: on admission and before discharge. This might aid in planning therapies in post-discharge phases and contribute to the risk stratification after the discharge.

When this model was applied to the other facilitate data, the predictability was decreased. The reason for the differences in the two institutions is uncertain at present. One reason might be that a rate of patients with HFpEF tended to be higher in KMC. Indeed, LVEF was significantly higher in KMC than in NCVC (median LVEF: 43.5% vs. 35.0%, respectively). As described in the supplemental Fig. 3, the predictability of this model was decreased in patients with HFpEF, that might be associated with these findings. The other reason is that while the clinical outcomes in NCVC include the implantation of LVAD, it was not included in KMC protocol. Thus, differences in HF severity might be associated with these differences in predictability between the two institutes.

There were several limitations in this study. First, a limitation of this study was that the data was initially derived from a single center and hence may be subject to a particular demographic selection bias. It is ideal for developing the model using the data of multiple facilitates. Thus, further investigation will be necessary. Second, this study did not include the patients treated with sacubitril/valsartan and sodium-glucose cotransporter-2 (SGLT2) inhibitors, because this study completed the data collection before these medications were released in our country. Further investigation is necessary to determine whether this algorism can be applied to the patients treated with these medications. Third, since this is a retrospective study, some data at discharges such as troponin levels were unavailable. Lastly, the predictability of this model was decreased in patients with HFpEF. These findings also suggest that the causes of lethal events to death in HFpEF are different from those with HFrEF, in accordant with the previous literature [28, 29]. Since the number of enrolled patients with HFpEF is limited in this study, further study will be necessary to confirm this finding.

In conclusion, using a machine learning approach, this study developed a highly predictive algorithm with minimized input variable numbers for mortality in hospitalized patients with HF and validated its predictability using prospective registry data. Our non-linear model has strong predictive power, even when compared with the compared linear models.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00380-023-02237-w.

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Data availability The data that support the findings of this study are available from the corresponding author on reasonable request.

Declarations

Conflict of interest NK reports trust research/joint research funds from Philips Japan. YS reports trust research/joint research funds from NEC, Daiichi-Sankyo and Abbott. IC reports remuneration for lecture from Philips Japan. Other authors have nothing to disclose in connection with this article.

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