A Predictive Model for 6-Month Mortality in Elderly Patients with Heart Failure

Sho Suzuki,1 MD, Hirohiko Motoki,2 MD, Yusuke Kanzaki,1 MD, Takuya Maruyama,1 MD, Naoto Hashizume,1 MD, Ayako Kozuka,1 MD, Kumiko Yahikozawa,1 MD and Koichiro Kuwahara,2 MD

Summary
Prediction of short-term mortality in elderly patients with heart failure (HF) would be useful for clinicians when discussing HF management or palliative care.

A prospective multicenter cohort study was conducted between July 2014 and July 2018. A total of 504 consecutive elderly patients (age ≥ 75 years) with HF (mean age 85 years, 50% women) were enrolled. We used a multiple logistic regression analysis with stepwise variable selection to select predictive variables and to determine weighted point scores. After analysis, the following variables predicted short-term mortality and comprised the risk score: previous HF admission (3 points), New York Heart Association III or IV (2 points), body mass index < 17.7 kg/m² (4 points), serum albumin < 3.5 g/dL (9 points), and left ventricular ejection fraction < 50% (2 points). The c-statistic was 0.820. We compared mortality in low-risk (0-6 points, n = 188), intermediate-risk (7-13 points, n = 241), and high-risk (14-20 points, n = 75) groups. A total of 43 (8.5%) patients died within 6 months after discharge. Mortality was significantly higher in groups with higher scores (low-risk group, 0.5%; intermediate-risk group, 9.1%; high-risk group, 26.7%; P < 0.001).

We developed a predictive model for 6-month mortality in elderly patients with HF. This risk score could be useful when discussing advanced HF therapies, palliative care, or hospice referral with patients.

Key words: Risk score, Short-term, Death

Improvement in cardiovascular disease survival and progressive aging of the population have led to an increase in elderly heart failure (HF) patients, mainly in developed countries.1-4 The number of elderly HF patients will continue to increase annually. Early post-discharge mortality and readmission are major issues in elderly HF patients. Given the high cost of inpatient HF treatment, HF places a major burden on the public health system and has an associated economic impact. Furthermore, compared to non-elderly patients, different approaches and management strategies are necessary when treating elderly HF patients. Also, when treating the elderly, surgical and invasive treatments are less suitable, and careful attention must be paid to their physical and psychological distress.

Over 60 risk scores have been developed to assess the risks of adverse events in HF patients.5,6 Existing risk scores have focused mainly on long-term outcomes or in-hospital mortality and were often complex and therefore, uniformly underutilized.7,8 A recent study reported that the Acute Decompensated Heart Failure National Registry (ADHERE) Classification and Regression Tree (CART) algorithm and the Get With The Guidelines (GWTG) HF risk score, both of which were developed to predict in-hospital mortality, could also predict early post-discharge mortality.9,10 However, models for the prediction of early post-discharge mortality in elderly HF patients are not well-established. HF treatment options could vary depending on short-term mortality risk, especially in elderly patients. It would be useful to assess the risk of mortality to inform decisions about the initiation and intensity of treatment, such as device therapy, disease monitoring, or indications of palliative care to improve symptoms, pain, and quality of life (QOL).11,12 In this context, we aim to create a risk score to predict 6-month mortality in elderly HF patients.

Methods

Study population: This prospective multicenter cohort study was conducted in Nagano Prefecture, Japan. The cohort included 504 elderly patients (defined as age ≥ 75 years) hospitalized at participating institutions with a primary diagnosis of decompensated HF. Acute coronary syndrome patients were excluded. Between July 2014 and July 2018, patients were enrolled after the approval of each hospital’s ethics committee and after informed con-
sent was obtained from each patient. Data were collected at the compensated state of HF before discharge. Collected data included socioeconomic status, medical history, medications, laboratory data, electrocardiogram, echocardiography, discharge medications, discharge status, and post-discharge follow-up. All study procedures were performed in accordance with the Declaration of Helsinki. The diagnosis of HF and acute coronary syndrome was made by treating clinicians using all available data including symptoms, laboratory data, electrocardiograms, echocardiography, and available coronary angiograms. The primary outcome was 180-day all-cause mortality, and the secondary outcome was HF readmission during follow-up. The survival status was ascertained by chart review.

**Statistical analysis:** Continuous variables were expressed as means ± standard deviation if normally distributed and as medians with interquartile range if non-normally distributed. Normality was assessed using the Shapiro-Wilk W-test. Comparisons of baseline characteristics were made with a contingency table and the Pearson χ² test for categorical variables, t-test for normally distributed continuous variables, and the Mann-Whitney test for non-normally distributed continuous variables. Spearman’s rank correlation method was used to examine the correlation coefficient between each variable. For continuous variables, the optimal receiver operating characteristic (ROC) curve cut-off value for prediction of death was chosen as the value maximizing sensitivity and specificity. Potential predictive risk score variables were selected based on statistical analysis. Variables that showed significant differences in the univariate analysis of those who died and those who survived after 180 days of follow-up were chosen as potential influential variables. Multiple logistic regression analysis with stepwise variable selection was performed to determine the components of the risk score and to evaluate the odds ratios in each variable. Odds ratios were rounded to the nearest integer to determine weighted point scores in each variable. The predictive accuracy of the scoring system was examined by calculating the c-statistics. Risk scores were calculated for all patients and then divided into three categories of patients: (1) those at low-risk, (2) those at intermediate-risk, and (3) those at high-risk of 180-day mortality. For the secondary outcome, Kaplan-Meier survival plots were calculated from baseline to time of events and compared using the log-rank test. Multiple comparison was adjusted using the Bonferroni method. A P-value < 0.05 was considered statistically significant. The statistical analyses were performed using SPSS Statistics for Windows, Version 25 (IBM Corp., Armonk, NY, US).

**Results**

**Study population:** The median follow-up was 318 days. A total of 43 (8.5%) patients died within 180 days (cardiac death, 30; malignancy, 7; bleeding, 2; others, 4). Forty-six patients were lost to follow-up before 6 months. The baseline patient characteristics are shown in Table I. The mean age was 85 (interquartile range [IQR], 80-88), and 50% (n = 252) were women. Compared to those who survived, those who died during follow-up were older and had a lower body mass index (BMI), lower systolic blood pressure (sBP), lower serum albumin (ALB), lower left ventricular ejection fraction (LVEF), and higher B-type natriuretic peptide (BNP). The proportion of patients who had been previously admitted to hospital due to HF and the proportion of patients classified as New York Heart Association class III or IV (NYHA III or IV) were higher in patients who died. From these results, we considered the following variables to establish a risk score: previous HF admission, NYHA III or IV, age, BMI, sBP, ALB, BNP, and LVEF.

**Predictive variables included in the risk score:** After analysis, the variables were not highly correlated with each other (Figure 1). In the ROC analysis, the area under the curve was greatest in each variable at an optimal cut-off point shown in Figure 2. On multiple logistic regression analysis with stepwise variable selection, the following variables were independently associated with mortality: previous HF admission, NYHA III or IV, BMI < 17.7 kg/m², ALB < 3.5 g/dL, and LVEF < 50% (Table II). Each predictive variable was assigned points according to its odds ratio as follows: previous HF admission (3 points), NYHA III or IV (2 points), BMI < 17.7 kg/m² (4 points), ALB < 3.5 g/dL (9 points), and LVEF < 50% (2 points). Our risk score model is presented in Figure 3. The model had a c-statistic of 0.820. We calculated the total score for each patient by adding the points of each predictive variable and stratified the patients into three groups: the low-risk group (0-6 points, n = 188), intermediate-risk group (7-13 points, n = 241), and high-risk group (14-20 points, n = 75). The comparison between mortality and score levels is shown in Figure 4. The 180-day mortality rates in the low-, intermediate-, and high-risk group were 0.5% (1/188), 9.1% (22/241), and 26.7% (20/75), respectively. Mortality was significantly higher in groups with higher scores (P < 0.001). In the secondary outcome after Kaplan-Meier analysis, the cumulative event rate of HF readmission was significantly higher in the high-risk group (P = 0.007), and the produced risk score also predicted HF readmission (Figure 5).

**Discussion**

**Risk score in elderly HF patients:** In this study, we investigated the risk of 6-month mortality in elderly HF patients. We produced a risk score that accurately discriminated between patients at almost no risk of death and patients with over 26% probability of dying within 180 days after discharge. All variables included were easy to measure, by checking records of previous therapy, height and body weight, blood test, and echocardiography. To the best of our knowledge, no other studies have assessed the early post-discharge mortality risk in elderly HF patients. This risk score could aid in decision-making regarding advanced HF therapies, palliative care consultation, or hospice referral.

Over 60 risk scores have been previously developed to assess risks of adverse events in HF patients. Among those risk scores, the following variables have emerged as the most consistent and strongest predictors: renal func-
tion, BNP (or N-terminal pro-BNP) level, previous HF admission, age, and sBP. The Seattle Heart Failure Model is the most widely accepted and used risk score to predict long-term survival rates in HF patients. The ADHERE CART algorithm uses blood urea nitrogen, systolic blood pressure, and creatinine measured at admission to predict risk of in-hospital death in HF patients. The GWTG-HF risk score uses seven admission variables, namely, blood urea nitrogen, sBP, age, heart rate, serum sodium, race, and presence of chronic obstructive pulmonary disease, to stratify HF patients at risk of in-hospital death. A risk score produced from the Meta-analysis Global Group in Chronic Heart Failure (MAGGIC) predicted long-term mortality using 11 variables including medication. In terms of elderly HF patients, several studies have produced a risk score to predict in-hospital or long-term mortality in relatively small cohorts.

Comparison with previous risk scores: Additional factors known to be associated with mortality, such as age, sBP, serum creatinine, blood urea nitrogen, serum sodium,
hemoglobin, BNP, heart rate, and presence of chronic obstructive pulmonary disease, were considered but did not contribute to discrimination in our model. This highlights the possibility that the risk of short-term mortality in elderly HF patients differs from the non-elderly. Little is known about the mortality risk in elderly HF patients. Our study investigated the short-term mortality risk particularly in elderly HF patients, for whom risk stratification and appropriate HF treatment policies could be more important than the others. Our investigation was performed in a recent study cohort in an era of improvements in cardiovascular treatments and progressive aging of the population. The discriminatory ability of the model was good, with a c-statistics of 0.820.

In our study, ALB level was strongly associated with short-term mortality even after adjustment for the other prognostic factors. This result was similar to a previous research that predicted in-hospital death in elderly HF pa-
Hypoalbuminemia is a well-known strong predictor of adverse events in elderly HF patients.\textsuperscript{18,20,21} In our study cohort, the median age of patients was higher than that in other previous investigations, which could be the reason for the strong association between short-term mortality and ALB levels. ALB and BMI are both markers of aging, malnutrition, or cachexia. Several reports have shown that nutritional states were the most determinant factors predict worse prognosis in severe conditions including infection, end-stage renal disease, or cancer. In our study, 30\% of deaths were non-cardiac causes, which was relatively high. Nutritional states provide prognostic information about not only cardiac events but also non-cardiac comorbidities in HF patients. For HF patients with malnutrition, the Nutrition Support Team should support their nutrition intake, and screening examinations should be produced for possible underlying chronic inflammation. Previous HF admission, NYHA class, and LVEF have also been included as predictors in previous risk scores.\textsuperscript{16-18} Although age and renal function were found to be discriminatory factors in previous studies, they were not in our study. The possible reason why age was not a discriminatory factor in our study was that the age range was more limited compared to other studies. In terms of renal function, previously reported risk scores, particularly for elderly HF patients,\textsuperscript{18,19} did not include serum creatinine or estimated glomerular filtration rate as predictive variables, although they included serum sodium\textsuperscript{22} and blood urea nitrogen. Our study had an older patient cohort than these two studies, which might be the reason why renal function did not predict mortality. It is possible that as patients get older, the effect of renal function on short-term mortality in HF patients becomes smaller. In addition, another possibility is that elderly HF patients who have severe renal failure at admission may die during hospitalization. The exclusion of patients who died during hospitalization may be another reason for this result.

From our findings, we believe that this risk score could be useful to inform decisions about the initiation and intensity of treatment. Patients with high scores should have the opportunity to think about their end-of-life care, which is the last phase of palliative care. Invasive treatment including surgical therapy, ventilator management, or device therapy might not be recommended, and treatments to improve symptoms, pain, and QOL could be preferred. Using this score in clinical practice would lead to the promotion of palliative care along with an earlier introduction, which are both necessary in the aging society with the increasing number of elderly HF patients.

\textbf{Limitations:} Our study had several limitations. First, the sample size was relatively small, and the validation of the predictive model was not performed. Furthermore, 9\% of the enrolled patients were lost to follow-up before 180 days. Further study is needed to validate the accuracy and predictive ability of the model in another cohort. Second, this study was performed using data measured at discharge, so the application of the model at admission may be limited. However, this investigation aimed to identify patients at high risk of early post-discharge mortality; we did not focus on patients who died during hospitalization. We suggest that clinicians should measure the predictive variables at the compensated phase of HF before discharge to determine post-discharge HF treatment and management.

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|}
\hline
Variable & Odds ratio (95\% CI) & \textit{P}-value \\
\hline
Previous HF admission & 2.816 (1.379-5.747) & 0.004 \\
NYHA III or IV & 2.212 (1.060-4.629) & 0.034 \\
BMI \textless 17.7 kg/m\textsuperscript{2} & 4.045 (1.925-8.500) & \textless 0.001 \\
ALB \textless 3.5 g/dL & 9.038 (3.276-24.936) & \textless 0.001 \\
LVEF \textless 50\% & 2.193 (1.085-4.435) & 0.029 \\
\hline
\end{tabular}
\caption{Multiple Logistic Regression Analysis with Stepwise Variable Selection}
\end{table}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{scheme.png}
\caption{Scheme for evaluation of 180-day mortality risk. ALB indicates serum albumin; BMI, body mass index; HF, heart failure; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.}
\end{figure}
I n tH e a r tJ

March 2020

330

SUZUKI, ET AL

Figure 4. Short-term mortality according to risk score index. Short-term mortality rates for patients in each risk category. The mortality risk was significantly higher in groups with higher scores.

| Low risk | Intermediate risk | High risk | Total |
|----------|-------------------|-----------|-------|
| Total patients | 188 | 241 | 75 | 504 |
| Deaths | 1 | 22 | 20 | 43 |
| 180-day mortality | 0.5% | 9.1% | 26.7% | 8.5% |

Figure 5. Kaplan-Meier plots of HF readmission according to risk score index. Cumulative event rate of HF readmission was significantly higher in the high-risk group. HF indicates heart failure.

In conclusion, we developed a predictive model for management. Finally, because the current study investigated elderly HF patients in particular, the median age of this study was high, and the cohort may represent only a limited part of society. However, in the era of continuous improvements in cardiovascular disease survival rates and the progressive aging of the population, we believe that our findings have important clinical implications. Despite this, further research involving a large cohort is necessary to verify our findings.

In conclusion, we developed a predictive model for
6-month mortality in elderly HF patients. This risk score may be useful for clinicians when undertaking discussions with patients and their families regarding advanced HF therapies, palliative care, or hospice referral.

Acknowledgments

We thank all the following 14 hospitals which participated in this study (Shinshu Ueda Medical Center, Nagano Red Cross Hospital, Matsumoto Medical Center, Nagano Municipal Hospital, Iida Municipal Hospital, Azawa Hospital, Ina Central Hospital, Okaya City Hospital, Saku Central Hospital, Hokushin General Hospital, Suwa Red Cross Hospital, Matsushiro General Hospital, Shinshu Medical Center, and Asama Nanroku Komoro Medical Center). The authors acknowledge the secretarial assistance of Minako Aono.

Disclosure

Conflicts of interest: None.

References

1. Heidenreich PA, Albert NM, Allen LA, et al. Forecasting the impact of heart failure in the United States: a policy statement from the American Heart Association. Circ Heart Fail 2013; 6: 606-19.
2. Shimokawa H, Miura M, Nochioka K, Sakata Y. Heart failure as a general pandemic in Asia. Eur J Heart Fail 2015; 17: 884-92.
3. Christ M, Stork S, Dorr M, et al. Heart failure epidemiology 2000-2013: insights from the German Federal Health Monitoring System. Eur J Heart Fail 2016; 18: 1009-18.
4. Yaku H, Ozasa N, Morimoto T, et al. Demographics, management, and in-hospital outcome of hospitalized acute heart failure syndrome patients in contemporary real clinical practice in Japan: observations from the prospective, multicenter Kyoto Congestive Heart Failure (KCHF) registry. Circ J 2018; 82: 2811-9.
5. Okura Y, Ramadan MM, Ohno Y, et al. Impending epidemic: future projection of heart failure in Japan to the year 2055. Circ J 2008; 72: 489-91.
6. Rahimi K, Bennett D, Conrad N, et al. Risk prediction in patients with heart failure: a systematic review and analysis. JACC Heart Fail 2014; 2: 440-6.
7. Win S, Hussain I, Hebl VB, Dunlay SM, Redfield MM. Inpatient mortality risk scores and postdischarge events in hospitalized heart failure patients: a community-based study. Circ Heart Fail 2017; 10: e003926.
8. Peterson PN, Rumsfeld JS, Liang L, et al. A validated risk score for in-hospital mortality in patients with heart failure from the American Heart Association get with the guidelines program. Circ Cardiovasc Qual Outcomes 2010; 3: 25-32.
9. Passantino A, Monitillo F, Iacoviello M, Scrutinio D. Predicting mortality in patients with acute heart failure: role of risk scores. World J Cardiol 2015; 7: 902-11.
10. Fonarow GC, Adams KF Jr, Abraham WT, Yancy CW, Boscardin WJ. Risk stratification for in-hospital mortality in acutely decompensated heart failure: classification and regression tree analysis. JAMA 2005; 293: 572-80.
11. Ketchum ES, Levy WC. Establishing prognosis in heart failure: a multimarker approach. Prog Cardiovasc Dis 2011; 54: 86-96.
12. Allen LA, Stevenson LW, Grady KL, et al. Decision making in advanced heart failure: a scientific statement from the American Heart Association. Circulation 2012; 125: 1928-52.
13. Rogers JG, Patel CB, Mentz RJ, et al. Palliative care in heart failure: the PAL-HF randomized, controlled clinical trial. J Am Coll Cardiol 2017; 70: 331-41.
14. Mizukawa M, Moriyama M, Yamamoto H, et al. Nurse-led collaborative management using telemonitoring improves quality of life and prevention of rehospitalization in patients with heart failure. Int Heart J 2019; 60: 1293-302.
15. Xu Z, Chen L, Jin S, Yang B, Chen X, Wu Z. Effect of palliative care with patients with heart failure. Int Heart J 2018; 59: 503-9.
16. Levy WC, Mozaffarian D, Linker DT, et al. The Seattle heart failure model: prediction of survival in heart failure. Circulation 2006; 113: 1424-33.
17. Pocock SJ, Artit CA, McMurray JJ, et al. Predicting survival in heart failure: a risk score based on 39 372 patients from 30 studies. Eur Heart J 2013; 34: 1404-13.
18. Kinugasa Y, Kato M, Sugihara S, et al. A simple risk score to predict in-hospital death of elderly patients with acute decompensated heart failure--hypoalbuminemia as an additional prognostic factor. Circ J 2009; 73: 2276-81.
19. Huynh BC, Rovner A, Rich MW. Long-term survival in elderly patients hospitalized for heart failure: 14-year follow-up from a prospective randomized trial. Arch Intern Med 2006; 166: 1892-8.
20. Horwich TB, Kalantar-Zadeh K, MacLellan RW, Fonarow GC. Albumin levels predict survival in patients with systolic heart failure. Am Heart J 2008; 155: 883-9.
21. Arques S, Roux E, Sbragia P, Gelisse R, Pieri B, Ambrosi P. Usefulness of serum albumin concentration for in-hospital risk stratification in frail, elderly patients with acute heart failure. Insights from a prospective, monocenter study. Int J Cardiol 2008; 125: 265-7.
22. Hiki M, Kasai T, Yatsu S, et al. Relationship between serum sodium level within the low-normal range on admission and long-term clinical outcomes in patients with acute decompensated heart failure. Int Heart J 2018; 59: 1052-8.