









ORIGINAL RESEARCH

Prediction of Prehospital Change of the Cardiac Rhythm From Nonshockable to Shockable in Out-of-Hospital Patients With Cardiac Arrest: A Post Hoc Analysis of a Nationwide, Multicenter, Prospective Registry

Ryo Emoto , PhD; Mitsuaki Nishikimi , MD; Muhammad Shoib , BA; Kei Hayashida , MD, PhD; Kazuki Nishida , MD; Kazuya Kikutani , MD; Shinichiro Ohshimo , MD, PhD; Shigeyuki Matsui, PhD; Nobuaki Shime , MD, PhD; Taku Iwami, MD, PhD

BACKGROUND: Predicting a spontaneous rhythm change from nonshockable to shockable before hospital arrival in patients with out-of-hospital cardiac arrest can help emergency medical services develop better strategies for prehospital treatment. The aim of this study was to identify predictors of spontaneous rhythm change before hospital arrival in patients with out-of-hospital cardiac arrest and develop a predictive scoring system.

METHODS AND RESULTS: We retrospectively reviewed data of eligible patients with out-of-hospital cardiac arrest with an initial nonshockable rhythm registered in a nationwide registry between June 2014 and December 2017. We performed a multivariable analysis using a Cox proportional hazards model to identify predictors of a spontaneous rhythm change, and a ridge regression model for predicting it. The data of 25 804 patients were analyzed (derivation cohort, n=17 743; validation cohort, n=8061). The rhythm change event rate was 4.1% (724/17 743) in the derivation cohort, and 4.0% (326/8061) in the validation cohorts. Age, sex, presence of a witness, initial rhythm, chest compression by a bystander, shock with an automated external defibrillator by a bystander, and cause of the cardiac arrest were all found to be independently associated with spontaneous rhythm change before hospital arrival. Based on this finding, we developed and validated the Rhythm Change Before Hospital Arrival for Nonshockable score. The Harrell's concordance index values of the score were 0.71 and 0.67 in the internal and external validations, respectively.

CONCLUSIONS: Seven factors were identified as predictors of a spontaneous rhythm change from nonshockable to shockable before hospital arrival. We developed and validated a score to predict rhythm change before hospital arrival.

Key Words: defibrillation ■ nonshockable ■ out-of-hospital cardiac arrest ■ paramedics ■ rhythm change ■ shockable

Despite the notable progress in the field of resuscitation science, the survival rate of patients with out-of-hospital cardiac arrest (OHCA) with an initial nonshockable rhythm remains unacceptably

low,¹⁻³ and better management strategies in prehospital settings are required to further improve patient outcomes.^{4,5} The major challenges for emergency medical services (EMS) attending to such patients with a high

Correspondence to: Mitsuaki Nishikimi, MD, Hiroshima University, Kasumi 1-2-3, Minami-ku, Hiroshima, Japan. Email: m0528332626@yahoo.co.jp

Supplemental Material is available at <https://www.ahajournals.org/doi/suppl/10.1161/JAHA.121.025048>

For Sources of Funding and Disclosures, see page 8.

© 2022 The Authors. Published on behalf of the American Heart Association, Inc., by Wiley. This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial-NoDerivs](#) License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- Our study from a nationwide database of patients with out-of-hospital cardiac arrest identified 7 factors as predictors of a spontaneous rhythm change from nonshockable to shockable before hospital arrival.
- The Rhythm Change Before Hospital Arrival for Nonshockable score was developed to help predict a potential rhythm change from nonshockable to shockable before hospital arrival.

What Are the Clinical Implications?

- Shock with automated external defibrillator substantially increased the hazard ratio for spontaneous rhythm change, while asphyxiation and trauma as causes of cardiac arrest decreased the hazard ratio for spontaneous rhythm change.
- The Harrell's concordance index value of the Rhythm Change Before Hospital Arrival for Nonshockable score was nearly 0.70, which means that although the score has great predictive potential, other characteristics may need to be applied to further improve the score for optimal performance.

Nonstandard Abbreviations and Acronyms

CA	cardiac arrest
CHANS	Rhythm Change Before Hospital Arrival for Nonshockable
CV	cross validation
OHCA	out-of-hospital cardiac arrest

mortality risk in the ambulance are 2-fold: (1) Patients with cardiac arrest (CA) require immediate and intensive care as their outcomes are time sensitive; and (2) it is difficult for paramedics to solely focus on the patient alone because they must engage in multitasking while performing cardiopulmonary resuscitation (CPR), such as obtaining and recording medical information, securing vascular access to allow for timely pharmacological interventions, securing the airway by performing intubation when needed, and ensuring prompt transfer to the hospital. Attending to all of these complicated tasks simultaneously requires a high degree of coordination, which could result in some important tasks, such as recognition of a conversion to a shockable rhythm, failing to be prioritized.

Among the duties of EMS, immediate defibrillation upon cardiac rhythm change from nonshockable to shockable before hospital arrival—hereinafter, spontaneous rhythm change—is particularly important,

with the timing of this rhythm change being urgent.⁶ A previous study showed that subsequent spontaneous conversion of the initial rhythm from nonshockable to shockable during emergency medical resuscitation efforts was associated with a high likelihood of favorable neurological outcomes if defibrillation was performed within 20 minutes, which implies that prompt identification of a spontaneous rhythm change is critical.⁷ If EMS can predict such spontaneous rhythm change, they could be better prepared to prioritize immediate defibrillation when the opportunity arises as well as triage patients with CA who may have a better outcome based on a change in rhythm from nonshockable to shockable. However, few studies have been conducted to identify predictors of a spontaneous rhythm change in patients with OHCA, and there is no tool/methodology presently available to predict rhythm change before hospital arrival. We conducted this study to identify predictors and develop a predictive score that would allow EMS to predict spontaneous rhythm change in patients with OHCA and help them prepare for immediate defibrillation in the event of a spontaneous rhythm change.

METHODS

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

Study Design

This study was a retrospective, observational study conducted using the data from the JAAM-OHCA (OHCA Registry of the Japanese Association for Acute Medicine, which is a nationwide, prospective, multi-center registry of patients with OHCA who are transported to critical care medical centers or hospitals with an emergency care department across Japan (total of 125 institutions). The design and data collection methods for the registry are described in detail in previous reports.⁸ In brief, EMS personnel collect prehospital data based on the Utstein-style template,⁹ and physicians at the participant institutions collect in-hospital data, including the presumed etiology of the OHCA, along with the patients' treatments and outcomes. This registry includes the data of patients with OHCA entered in the registry between June 2014 and December 2017. This study was conducted with the approval of the institutional review boards of all participant institutions, which waived the requirement for obtaining informed patient consent stipulated in the Japanese government guidelines to ensure participant anonymity.

Subjects

Adult patients with OHCA who were judged by the attending EMS as having a nonshockable rhythm at the

time of the first pulse check were included in this study. The patients with missing data of their time to return of spontaneous circulation or initial pulse check time were excluded.

Definition of Timing of Rhythm Change

The JAAM-OHCA registry does not include a record of the identified rhythm(s) at the time of each pulse check, except for the initial rhythm. Therefore, we defined the time of rhythm change from nonshockable to shockable as the time at which the patient was defibrillated during the resuscitation process.

Statistical Analysis

All eligible patients were divided into a derivation cohort (patients seen from June 2014 to December 2016) and a validation cohort (patients seen from January 2017 to December 2017). A multivariable analysis was performed using data from the derivation cohort to identify predictors of a spontaneous rhythm change from nonshockable rhythm to a shockable rhythm and develop a predictive score. The predictive accuracy of the proposed score was evaluated in the validation cohort.

Multivariable analysis using a Cox regression model was performed on the derivation cohort to identify predictors of a spontaneous shockable rhythm change. The primary outcome was the time to shockable rhythm change from the initial pulse check. Patients who arrived at the hospital before the rhythm change were treated as censored. The covariates included in the analysis were those that could be assessed by the time EMS arrived at the site because we aimed to establish a predictive score that can be calculated upon arrival at the scene. In a sensitivity analysis, the variables of advanced airway management and epinephrine injection were included as time-dependent covariates, which we believe allow individual hazard change before and after their procedures.

Ridge penalized Cox regression was applied to the entire derivation cohort to devise a predictive model. The linear predictor of the estimated model was proposed as the prediction score. The value of the score predicting an event rate of 5% at 60 minutes was obtained from the estimated baseline hazard. We proposed a risk classification using this value as the threshold for the developed score. The time point of 60 minutes was determined as the time when the survival curve reached a plateau, based on the findings that most patients (>99%, 17 693 out of 17 743 in the derivation cohort) arrived at the hospital within 60 minutes, and in most cases, the spontaneous rhythm change (>99%, 723/724 in the derivation cohort) was observed within 60 minutes (Figure S1).

For internal validation of the sequence of procedures used to develop the proposed score, we evaluated the

prediction accuracy using a nested cross validation (CV)¹⁰ in the derivation cohort. In the nested CV, the predictive accuracy of the score, whose ridge penalization parameter was optimized in the inner CV loop, was evaluated in the outer CV loop. For external validation, the predictive accuracy of the proposed score was evaluated in the validation cohort. For both the internal and external validations, Harrell's concordance index for the predictive score was estimated, and its 95% CI was evaluated using 10 000 bootstrap samples. The survival curves in the 2 risk groups were estimated by the Kaplan-Meier method, and the difference in the time to the shockable rhythm change between the 2 risk groups was compared by the log-rank test.

All reported *P* values are 2-sided, and *P*<0.05 was regarded as denoting a statistically significant difference. All analyses were conducted using R version 4.1.1 (R Foundation for Statistical Computing, Vienna, Austria) and SAS version 9.4 (SAS Institute, Cary, NC). We used the "survival" package for Cox regression (<https://CRAN.R-project.org/package=survival>) and the "glmnet" package for the ridge regression (<https://www.jstatsoft.org/v33/i01/> and <https://www.jstatsoft.org/v39/i05/>).

RESULTS

The selection flow diagram for patients included and excluded from our retrospective analysis is shown in Figure 1. Among 26 034 patients with OHCA with a nonshockable rhythm at the initial pulse check, 230 patients were excluded because they had missing values for the time until return of spontaneous circulation or time until spontaneous rhythm change. The remaining 25 804 patients were included in the present analysis. We divided the patients into derivation (17 743 cases) and validation (8061 cases) cohorts to develop and validate our predictive score. Before developing the score, the derivation cohort was also used to identify the variables that can characterize the predictor(s) of a spontaneous rhythm change. The baseline characteristics of patients included in the analysis are summarized in Table 1 with the standardized difference of each variable summarized in Figure S2. The event rates (a spontaneous rhythm change from nonshockable to shockable before hospital arrival) were 4.1% (1050/25 804) in the derivation cohort and 4.1% (724/17 743) in the validation cohort, respectively. In the derivation cohort, the survival rate and the proportion of patients with a favorable neurological outcome at 30 days were 3.2% (815/25 804) and 0.8% (216/25 804), respectively. Of the 25 804 cases, 4.1% (1050/25 804) showed a spontaneous rhythm change from nonshockable to shockable. The estimated odds ratio of survival and favorable neurological outcomes at 30 days for rhythm change were 2.38 (95% CI: 1.85–3.06) and 3.28 (95% CI: 2.17–4.97), respectively.

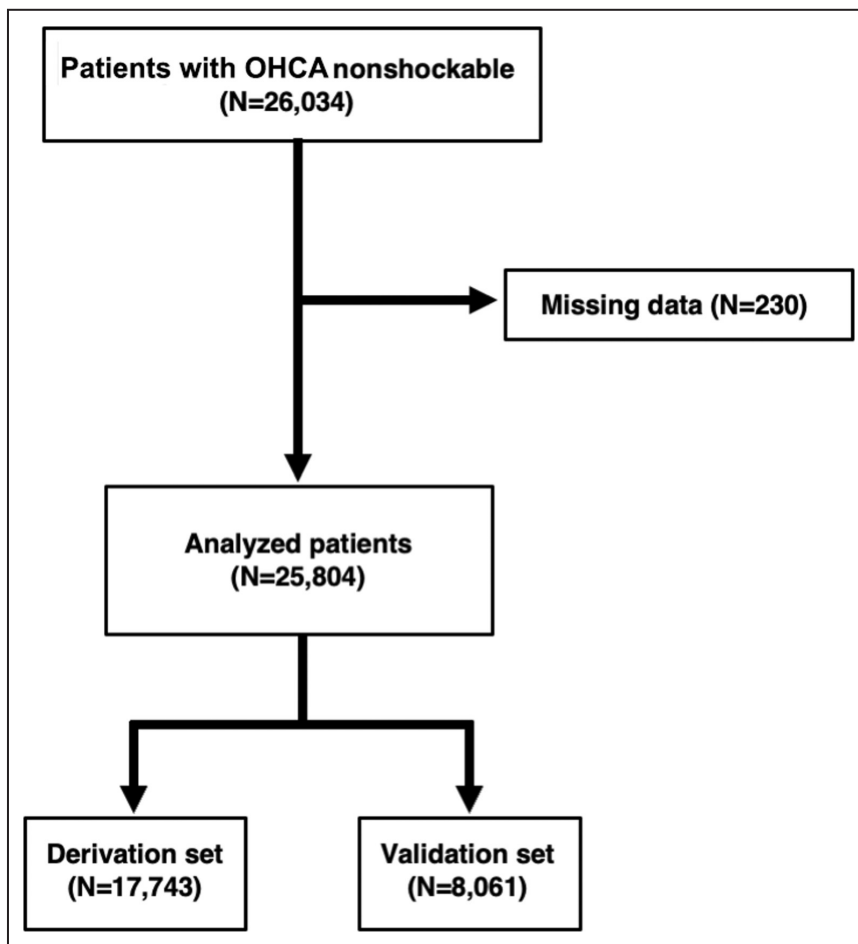


Figure 1. Flow diagram for patient distribution for the development of a predictive score.

OHCA indicates out-of-hospital cardiac arrest.

The results of the multivariable analysis using a Cox proportional hazards model of the 17 743 cases in the derivation cohort are shown in [Table 2](#). The analysis identified the following variables as being associated with a significantly increased hazard for spontaneous rhythm change: presence of a witness, pulseless electrical activity as the initial rhythm, shock with an automated external defibrillator (AED) by a bystander, and a nonexogenous cause of CA. Conversely, age >65 years, female sex, chest compression by bystander, and trauma and asphyxiation as the cause of the CA were associated with a significantly decreased hazard for spontaneous rhythm change. Initiation of mouth-to-mouth resuscitation by a bystander had no statistically significant influence on the likelihood of spontaneous rhythm change. As a sensitivity analysis, we performed a Cox proportional hazards regression analysis by adding the variables of advanced airway management and epinephrine injection as time-dependent adjustment factors, neither of which were included in our predictive score. However, as both

variables have been considered important clinical factors for favorable outcomes, we decided to analyze with these factors. We confirmed that the addition of these parameters did not appreciably alter the results from our original analysis ([Table S1](#)).

Based on the data of the derivation cohort, we developed our predictive score, the Rhythm Change Before Hospital Arrival for Nonshockable (CHANS) score, for spontaneous rhythm change using all variables that would be available at the time of the initial pulse check. The coefficient for each variable in the score is summarized in [Table 3](#). Using the cutoff value of the CHANS score of -1.523 , corresponding to an event rate of 5% within 60 minutes, we created a risk classification that could differentiate between patients with a high probability (CHANS score ≥ -1.523) and low probability (CHANS score < -1.523) for spontaneous rhythm change ([Table 3](#)).

In the internal validation, the Harrell's concordance index of the predictive score obtained by the nested CV in the derivation cohort was 0.71 (95% CI: 0.69–0.73).

Table 1. Baseline Characteristics of All Subjects

Variable	Total (n=25 804)		Derivation cohort (n=17 743)		Validation cohort (n=8061)	
	Rhythm changed (n=1050)	Rhythm not changed (n=24 754)	Rhythm changed (n=724)	Rhythm not changed (n=17 019)	Rhythm changed (n=326)	Rhythm not changed (n=7735)
Age, y	73.0 (62.0–82.0)	77.0 (64.0–85.0)	72.0 (62.0–82.0)	76.0 (64.0–85.0)	73.0 (61.3–83.0)	77.0 (65.0–85.0)
Sex, female, n (%)	327 (31.1)	10 463 (42.3)	210 (29.0)	7174 (42.2)	117 (35.9)	3289 (42.5)
Witness, n (%)	556 (76.0)	9846 (83.0)	400 (77.2)	6776 (82.6)	156 (72.9)	3070 (83.9)
Chest compression by bystander, n (%)	442 (42.1)	11 071 (44.7)	281 (38.8)	7391 (43.4)	161 (49.4)	3680 (47.6)
AED by bystander, n (%)	43 (4.1)	168 (0.7)	29 (4.0)	102 (0.6)	14 (4.3)	66 (0.9)
Mouth-to-mouth resuscitation by bystander, n (%)	63 (6.0)	1228 (5.0)	42 (5.8)	855 (5.0)	21 (6.4)	373 (4.8)
Initial rhythm, PEA, n (%)	502 (47.8)	7025 (28.4)	351 (48.5)	4872 (28.6)	151 (46.3)	2153 (27.8)
Cause for CA						
Trauma, n (%)	23 (2.2)	1909 (7.7)	20 (2.8)	1376 (8.1)	3 (0.9)	533 (6.9)
Hanging, n (%)	25 (2.4)	1267 (5.1)	16 (2.2)	905 (5.3)	9 (2.8)	362 (4.7)
Drowning, n (%)	24 (2.3)	926 (3.7)	19 (2.6)	635 (3.7)	5 (1.5)	291 (3.8)
Asphyxiation, n (%)	34 (3.2)	1806 (7.3)	20 (2.8)	1230 (7.2)	14 (4.3)	576 (7.4)
Addiction, n (%)	3 (0.3)	155 (0.6)	3 (0.4)	108 (0.6)	0 (0)	47 (0.6)
Unknown exogenous, n (%)	16 (1.5)	480 (1.9)	9 (1.2)	350 (2.1)	7 (2.1)	130 (1.7)
Nonexogenous, n (%)	795 (75.7)	14 868 (60.1)	550 (76.0)	10 143 (59.6)	245 (75.2)	4725 (61.1)
Unknown (exogenous or nonexogenous), n (%)	130 (12.4)	3343 (13.5)	87 (12.0)	2272 (13.3)	43 (13.2)	1071 (13.8)
Duration of resuscitation effort, min	30.0 (21.0–43.0)	28.0 (19.0–37.0)	30.0 (21.0–42.0)	28.0 (19.0–38.0)	32.0 (20.0–45.0)	28.0 (19.0–37.0)
Prehospital epinephrine administration, n (%)	527 (50.2)	6537 (26.4)	355 (49.0)	4300 (25.3)	172 (52.8)	2237 (28.9)
Ventilation, n (%)	627 (59.7)	13 068 (52.8)	424 (58.6)	8872 (52.1)	203 (62.3)	4196 (54.2)
Drug injections, n (%)	526 (50.1)	6509 (26.3)	354 (48.9)	4272 (25.1)	172 (52.8)	2237 (28.9)
PCI, n (%)	52 (5.0)	168 (0.7)	39 (5.4)	96 (0.6)	13 (4.0)	72 (0.9)
ROSC, n (%)	415 (39.5)	7376 (29.8)	302 (41.7)	5032 (29.6)	113 (34.7)	2344 (30.3)
Outcome at 30 d						
Survival, n (%)	72 (6.9)	743 (3.0)	51 (7.0)	508 (3.0)	21 (6.4)	235 (3.0)
Good (CPC ≤2), n (%)	26 (2.5)	190 (0.8)	18 (2.5)	134 (0.8)	8 (2.5)	56 (0.7)

Data are presented as the median and interquartile ranges (25th–75th percentile) or as absolute frequencies with percentages. AED indicates automated external defibrillator; CA, cardiac arrest; CPC, cerebral performance category; CPR, cardiopulmonary resuscitation; PCI, percutaneous coronary intervention; PEA, pulseless electrical activity; and ROSC, return of spontaneous circulation.

The Kaplan-Meier curve by the nested CV in the derivation cohort suggested that the risk classification based on the score was a good predictor of the time to rhythm change in the internal validation (log-rank test; $P < 0.001$). In the external validation, the predictive accuracy of the proposed CHANS score was 0.67 (95% CI: 0.64–0.70). The Kaplan-Meier curves were significantly different between the 2 groups divided according to the proposed risk classification in the validation cohort (log-rank test; $P < 0.001$) (Figure 2 and Figure S3).

DISCUSSION

The proportion of survivors and those with a favorable neurological outcome are known to be much lower in patients with OHCA with an initial nonshockable

rhythm than in those with an initial shockable rhythm. However, a previous study showed that spontaneous conversion of the initial rhythm from nonshockable to shockable during emergency medical resuscitation efforts was associated with a high likelihood of a favorable neurological outcome if defibrillation was performed quickly,^{7,11} which implies that prompt identification of a spontaneous rhythm change is critical. In fact, in our current patient series, a spontaneous rhythm change occurred in ≈4% of the patients, and prompt and appropriate management could have potentially increased the number of survivors with favorable neurological outcomes.

Our analysis of data from a large-scale, multicenter registry in Japan identified age, sex, initial rhythm, chest compression by bystander, shock with AED, and

Table 2. Estimated Coefficients and P Values Between Each Variable and Future Rhythm Change in the Derivation Cohort

Variable	β	HR (95% CI)	P value
Age, >65 y	-0.408	0.67 (0.56–0.78)	<0.001
Sex, female	-0.472	0.62 (0.53–0.73)	<0.001
Witnessed	0.401	1.49 (1.27–1.76)	<0.001
PEA	0.716	2.05 (1.74–2.40)	<0.001
Chest compression by bystander	-0.227	0.80 (0.68–0.94)	0.006
AED by bystander	1.378	3.97 (2.67–5.89)	<0.001
Mouth to mouth resuscitation by bystander	0.092	1.10 (0.79–1.52)	0.586
Cause for CA			
Trauma	-1.137	0.32 (0.20–0.53)	<0.001
Hanging	-0.526	0.59 (0.34–1.02)	0.059
Drowning	0.188	1.21 (0.73–2.00)	0.465
Asphyxiation	-0.927	0.40 (0.24–0.64)	<0.001
Addiction	-0.238	0.79 (0.25–2.51)	0.687
Unknown exogenous	-0.425	0.65 (0.33–1.30)	0.227
Nonexogenous	0.362	1.44 (1.14–1.80)	0.002

AED indicates automated external defibrillator; CA, cardiac arrest; HR, hazard ratio; and PEA, pulseless electrical activity.

cause of CA as being independent predictors of spontaneous rhythm change. We subsequently developed and validated a predictive score, the CHANS score, for facilitating prediction of a potential spontaneous rhythm change in the prehospital setting by the attending EMS who have to multitask to save the patients' lives. The Harrell's concordance index of the CHANS score was ≈ 0.70 , which suggests that while the score may have great potential, future studies are needed to further improve its predictive performance.¹² This is the first study to explore means for prehospital prediction of a spontaneous rhythm change in patients with OHCA to facilitate the development of improved strategies for resuscitation management in the prehospital setting for improved outcomes of patients with CA.

Among the variables associated with spontaneous rhythm change, the hazard ratio of shock with AED was especially high (3.97 [95% CI: 2.67–5.89]) as compared with other variables. This result is consistent with reports from clinical practice because defibrillating a patient with an AED before the arrival of paramedics is suggestive of a cardiogenic component to the CA, in which case the patient has a higher probability of a spontaneous rhythm change. On the other hand, asphyxiation and trauma as the causes of CA were associated with a lower probability of spontaneous rhythm change. Although future studies are needed, at present the data suggest that patients with CA most likely caused by the above mechanisms may still be able to achieve return of spontaneous circulation, irrespective of a spontaneous rhythm change. In fact, a direct

Table 3. Proposed CHANS Score and Risk Classification for Prediction of Rhythm Change From Nonshockable to Shockable

Variable	Coefficients*
Age, >65 y (X_1)	-0.368 (β_1)
Sex, female (X_2)	-0.436 (β_2)
Witnessed (X_3)	0.382 (β_3)
PEA (X_4)	0.678 (β_4)
CPR by bystander (X_5)	-0.208 (β_5)
AED by bystander (X_6)	1.376 (β_6)
Mouth-to-mouth resuscitation by bystander (X_7)	0.081 (β_7)
Reason for CA	
Trauma (X_8)	-0.904 (β_8)
Hanging (X_9)	-0.428 (β_9)
Drowning (X_{10})	0.174 (β_{10})
Choke (X_{11})	-0.760 (β_{11})
Addiction (X_{12})	-0.183 (β_{12})
Unknown exogenous (X_{13})	-0.339 (β_{13})
Nonexogenous (X_{14})	0.380 (β_{14})
Calculation formula	<p>Score (S) = $\beta_1 X_1 + \beta_2 X_2 \dots + \beta_{14} X_{14}$ β_i: coefficient of ith variable ($i = 1, \dots, 14$) X_i: value of ith variable ($i = 1, \dots, 14$) $X_i = 1$ if the subject is in the category, $X_i = 0$ otherwise.</p> <p>Risk class (R) = $\begin{cases} \text{High } (S \geq -1.523) \\ \text{Low } (S < -1.523) \end{cases}$</p>

AED indicates automated external defibrillator; CA, cardiac arrest; CHANS, Rhythm Change Before Hospital Arrival for Nonshockable; CPR, cardiopulmonary resuscitation; and PEA, pulseless electrical activity.

*Coefficients were estimated by ridge penalized Cox regression.

treatment option for these etiologies may more easily alleviate the CA, such as mitigating the causal agent in asphyxiation, or hydration and blood transfusion after an accident.

The Harrell's concordance index used for evaluating the predictive accuracy in our study is the index of a score for predicting the "time" of the event occurrence and is likely to show lower values compared with the values of area under the curve. The value of ≈ 0.70 is regarded as acceptable^{13,14} but may need to be improved for optimal performance. To improve the predictive performance of the prediction model, we considered that it may be effective to add other clinical variables to the model. Most of the variables included in our registry were those that are known to be strongly related to the outcome of patients with CA, such as the presence of a witness, the initial rhythm, and so on, and there were few variables directly associated with the electrophysiology of the heart, such as the electrical frequency of pulseless electrical activity.¹⁵ Variables associated with the quality of bystander CPR before the initial pulse check, such as the depth of chest compression, can also improve the performance of

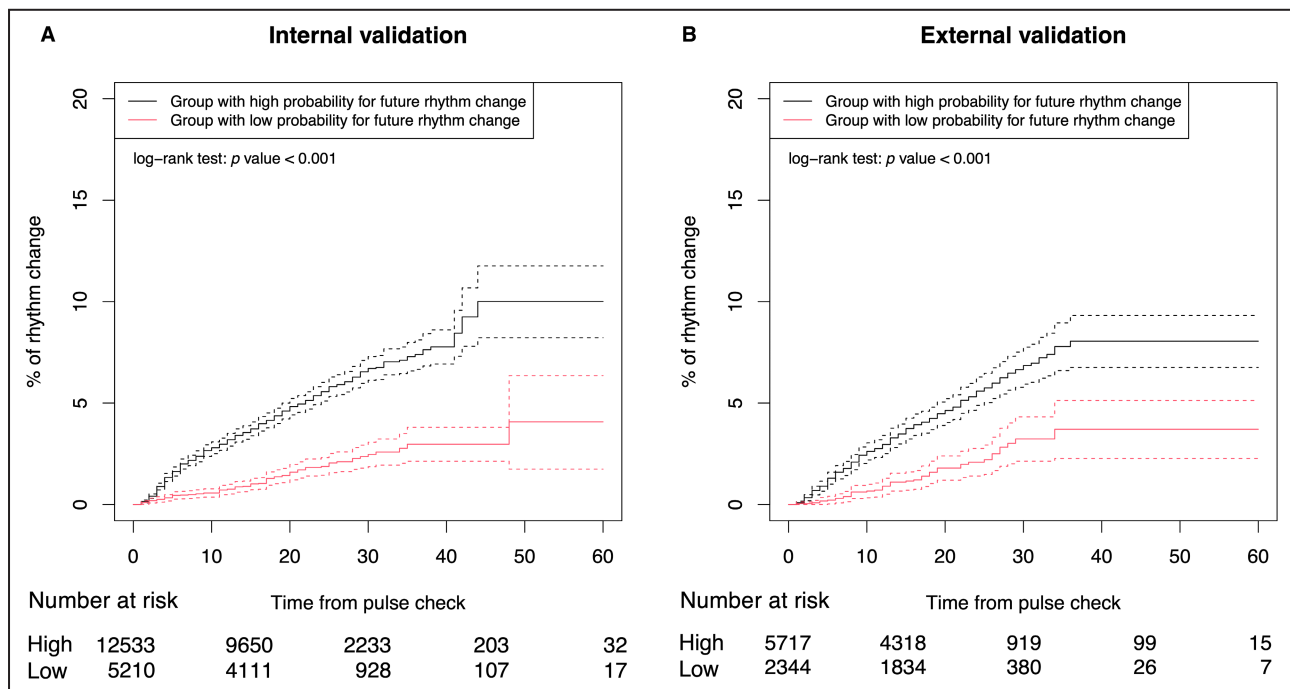


Figure 2. Kaplan-Meier analysis in the internal and external validation cohorts up to 60 minutes after initial pulse check. Kaplan-Meier curves were plotted for the internal (A) and external (B) validation cohorts. The black line shows the curve for the group with a high probability of spontaneous rhythm change, while the red line denotes the curve for the group with a low probability of spontaneous rhythm change.

our score, but are more challenging to accurately ascertain. In future studies, addition of such data may be considered to further improve the predictive accuracy of the CHANS score.

There were several limitations of our study. First, we used a multicenter, prospective registry of patients with OHCA in Japan. Accurate validation of our predictive score requires larger, more heterogeneous populations from other countries. Second, in this study, we divided available data into the derivation and validation cohorts based on the date of visit. Although no large differences in baseline characteristics were observed between the 2 cohorts, there is a possibility that these differences can influence the assessment of the predictive accuracy in our study. Third, we used the timing of defibrillation as the timing of the rhythm change from nonshockable to shockable. Although all the EMS were following the Japanese resuscitation guidelines¹⁶ and were expected to perform defibrillation immediately upon recognition of a shockable rhythm, with the numerous tasks that must be performed simultaneously when performing resuscitation, there could have been some lag time before attempts at defibrillation or even recognition of a shockable rhythm. Finally, we used a 5% event occurrence before hospital arrival (or within 60 minutes after initial pulse check), which helped us develop the threshold for dividing the groups into one with a high

probability and another with a lower probability of spontaneous rhythm change; however, it is imperative to evaluate whether 5% is the appropriate cutoff point or needs to be adjusted according to the population in which the analysis is being conducted.

Guidelines on CPR recommend a rhythm check every 2 minutes, based on the results of a few randomized clinical trials performed about 2 decades ago.^{17,18} Today, with the development of new resuscitation technologies, such as mechanical CPR devices that enable continuous CPR without user fatigue¹⁹ and devices that can detect shockable rhythm during CPR,²⁰ it remains unclear if the appropriate interval for pulse check should still be every 2 minutes. Our results suggest the potential for varying the interval for pulse checks according to the risk of change of the rhythm. For example, if the risk of change of the rhythm is low, the pulse could be checked less frequently, like every 3 minutes, which could reduce the total time of no flow because of pulse check. On the other hand, if the risk of change of the rhythm is high, the pulse may need to be checked more frequently than every 2 minutes. Evidence from our current study alone is not sufficient, and further prospective studies are required to validate our findings. However, we believe that our current study may pave the way for individualization of the interval for pulse checks according to the risk of change of the rhythm in individual patients.

CONCLUSIONS

Seven factors (age, sex, the presence of a witness, initial rhythm, chest compression by a bystander, shock with AED by a bystander, and cause of CA) were identified as predictors of a spontaneous rhythm change from nonshockable at initial pulse check to shockable before hospital arrival. A predictive score to identify a high probability of a rhythm change was developed and validated, although further studies may be needed for improving the predictive accuracy.

ARTICLE INFORMATION

Received December 13, 2021; accepted May 16, 2022.

Affiliations

Department of Biostatistics (R.E., K.N., S.M.) and Department of Emergency and Critical Care Medicine (M.N.), Nagoya University Graduate School of Medicine, Nagoya, Japan; Department of Emergency and Critical Care Medicine, Graduate School of Biomedical and Health Sciences, Hiroshima University, Hiroshima, Japan (M.N., K.K., S.O., N.S.); Laboratory for Critical Care Physiology, The Feinstein Institutes for Medical Research, Manhasset, NY (M.N., M.S., K.H.); Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hempstead, NY (M.S.); and Department of Preventive Services, School of Public Health, Graduate School of Medicine, Kyoto University, Kyoto, Japan (T.I.).

Acknowledgments

The authors thank the residents, fellows, and paramedical staff of the participant intensive care units and emergency departments for data collection and treatment support.

Sources of Funding

This research was supported by a Grant-in-Aid for Scientific Research (21H04874 and JST CREST: JPMJCR21D3) from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

Disclosures

None.

Supplemental Material

Table S1

Figures S1–S3

REFERENCES

- Riess ML. New developments in cardiac arrest management. *Adv Anesth*. 2016;34:29–46. doi: 10.1016/j.aan.2016.07.003
- Nolan JP, Berg RA, Andersen LW, Bhanji F, Chan PS, Donnino MW, Lim SH, Ma MH, Nadkarni VM, Starks MA, et al. Cardiac arrest and cardiopulmonary resuscitation outcome reports: update of the Utstein resuscitation registry template for in-hospital cardiac arrest: a consensus report from a Task Force of the International Liaison Committee on Resuscitation (American Heart Association, European Resuscitation Council, Australian and New Zealand Council on Resuscitation, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Council of Southern Africa, Resuscitation Council of Asia). *Resuscitation*. 2019;144:166–177. doi: 10.1016/j.resuscitation.2019.08.021
- Wang HE, Schmicker RH, Daya MR, Stephens SW, Idris AH, Carlson JN, Colella MR, Herren H, Hansen M, Richmond NJ, et al. Effect of a strategy of initial laryngeal tube insertion vs endotracheal intubation on 72-hour survival in adults with out-of-hospital cardiac arrest: a randomized clinical trial. *JAMA*. 2018;320:769–778. doi: 10.1001/jama.2018.7044
- Ong MEH, Perkins GD, Cariou A. Out-of-hospital cardiac arrest: pre-hospital management. *Lancet*. 2018;391:980–988. doi: 10.1016/S0140-6736(18)30316-7
- Geri G, Gilgan J, Wu W, Vijendra S, Ziegler C, Drennan IR, Morrison L, Lin S. Does transport time of out-of-hospital cardiac arrest patients matter? A systematic review and meta-analysis. *Resuscitation*. 2017;115:96–101. doi: 10.1016/j.resuscitation.2017.04.003
- Kleinman ME, Goldberger ZD, Rea T, Swor RA, Bobrow BJ, Brennan EE, Terry M, Hemphill R, Gazmuri RJ, Hazinski MF, et al. 2017 American Heart Association focused update on adult basic life support and cardiopulmonary resuscitation quality: an update to the American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation*. 2018;137:e7–e13. doi: 10.1161/CIR.0000000000000539
- Goto Y, Maeda T, Nakatsu-Goto Y. Prognostic implications of conversion from nonshockable to shockable rhythms in out-of-hospital cardiac arrest. *Crit Care*. 2014;18:528. doi: 10.1186/s13054-014-0528-7
- Kitamura T, Iwami T, Atsumi T, Endo T, Kanna T, Kuroda Y, Sakurai A, Tasaki O, Tahara Y, Tsuruta R, et al. The profile of Japanese Association for Acute Medicine—out-of-hospital cardiac arrest registry in 2014–2015. *Acute Med Surg*. 2018;5:249–258. doi: 10.1002/ams2.340
- Perkins GD, Jacobs IG, Nadkarni VM, Berg RA, Bhanji F, Biarent D, Bossaert LL, Brett SJ, Chamberlain D, de Caen AR, et al. Cardiac arrest and cardiopulmonary resuscitation outcome reports: update of the Utstein resuscitation registry templates for out-of-hospital cardiac arrest: a statement for healthcare professionals from a Task Force of the International Liaison Committee on Resuscitation (American Heart Association, European Resuscitation Council, Australian and New Zealand Council on Resuscitation, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Council of Southern Africa, Resuscitation Council of Asia); and the American Heart Association Emergency Cardiovascular Care Committee and the Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation. *Circulation*. 2015;132:1286–1300. doi: 10.1161/CIR.000000000000144
- Varma S, Simon R. Bias in error estimation when using cross-validation for model selection. *BMC Bioinformatics*. 2006;7:91. doi: 10.1186/1471-2105-7-91
- Zhang W, Luo S, Yang D, Zhang Y, Liao J, Gu L, Li W, Liu Z, Xiong Y, Idris A. Conversion from nonshockable to shockable rhythms and out-of-hospital cardiac arrest outcomes by initial heart rhythm and rhythm conversion time. *Cardiol Res Pract*. 2020;2020:3786408. doi: 10.1155/2020/3786408
- Aggarwal R, Ranganathan P. Understanding diagnostic tests—part 3: receiver operating characteristic curves. *Perspect Clin Res*. 2018;9:145–148. doi: 10.4103/picr.PICR_87_18
- Moeckelmann N, Ebrahimi A, Tou YK, Gupta R, Low TH, Ashford B, Ch'ng S, Palme CE, Clark JR. Prognostic implications of the 8th edition American Joint Committee on Cancer (AJCC) staging system in oral cavity squamous cell carcinoma. *Oral Oncol*. 2018;85:82–86. doi: 10.1016/j.oraloncology.2018.08.013
- Uno H, Cai T, Pencina MJ, D'Agostino RB, Wei LJ. On the C-statistics for evaluating overall adequacy of risk prediction procedures with censored survival data. *Stat Med*. 2011;30:1105–1117. doi: 10.1002/sim.4154
- Weiser C, Poppe M, Sterz F, Herkner H, Clodi C, Schriefl C, Warenits A, Vossen M, Schwameis M, Nurnberger A, et al. Initial electrical frequency predicts survival and neurological outcome in out of hospital cardiac arrest patients with pulseless electrical activity. *Resuscitation*. 2018;125:34–38. doi: 10.1016/j.resuscitation.2018.01.041
- Japan Resuscitation Council. *2015 Japanese Guidelines for Emergency Care and Cardiopulmonary Resuscitation*. Igaku-Shoin; 2016
- Wik L, Hansen TB, Fylling F, Steen T, Vaagenes P, Auestad BH, Steen PA. Delaying defibrillation to give basic cardiopulmonary resuscitation to patients with out-of-hospital ventricular fibrillation: a randomized trial. *JAMA*. 2003;289:1389–1395. doi: 10.1001/jama.289.11.1389
- Baker PW, Conway J, Cotton C, Ashby DT, Smyth J, Woodman RJ, Grantham H; Clinical I. Defibrillation or cardiopulmonary resuscitation first for patients with out-of-hospital cardiac arrests found by paramedics to be in ventricular fibrillation? A randomised control trial. *Resuscitation*. 2008;79:424–431. doi: 10.1016/j.resuscitation.2008.07.017
- Zhu N, Chen Q, Jiang Z, Liao F, Kou B, Tang H, Zhou M. A meta-analysis of the resuscitative effects of mechanical and manual chest compression in out-of-hospital cardiac arrest patients. *Crit Care*. 2019;23:100. doi: 10.1186/s13054-019-2389-6
- Aramendi E, de Gauna SR, Irueta U, Ruiz J, Arcocha MF, Ormaetxe JM. Detection of ventricular fibrillation in the presence of cardiopulmonary resuscitation artefacts. *Resuscitation*. 2007;72:115–123. doi: 10.1016/j.resuscitation.2006.05.017

SUPPLEMENTAL MATERIAL

Table S1. Sensitivity analysis

Variable	β	HR (95% CI)	<i>P</i>
Age, > 65 yrs	-0.429	0.65 (0.55-0.77)	< 0.001
Sex, female	-0.467	0.63 (0.53-0.74)	< 0.001
Witnessed	0.346	1.41 (1.20-1.67)	< 0.001
PEA	0.647	1.91 (1.63-2.24)	< 0.001
CPR by bystander	-0.257	0.77 (0.66-0.91)	0.002
AED by bystander	1.361	3.90 (2.63-5.78)	< 0.001
Mouth to mouth resuscitation by bystander	0.104	1.11 (0.80-1.54)	0.533
Cause for CA			
Trauma	-1.009	0.36 (0.22-0.60)	< 0.001
Hanging	-0.487	0.61 (0.36-1.06)	0.081
Drowning	0.236	1.27 (0.77-2.09)	0.359
Asphyxiation	-0.873	0.42 (0.26-0.68)	< 0.001
Addiction	-0.163	0.85 (0.27-2.70)	0.783
Unknown exogenous	-0.335	0.72 (0.36-1.43)	0.341
Non-exogenous	0.400	1.49 (1.19-1.87)	< 0.001
Advanced airway management	0.096	1.10 (0.92-1.32)	0.292
Epinephrin injections	1.205	3.34 (2.71-4.10)	< 0.001

PEA; pulseless electrical activity, CPR; cardiopulmonary resuscitation, AED; automated external defibrillator, CA; cardiac arrest, HR; hazard ratio, 95% CI, 95% confidence interval.

Figure S1. Distribution of the time until hospital arrival after the initial pulse check and the time to shockable rhythm change after the initial pulse check.

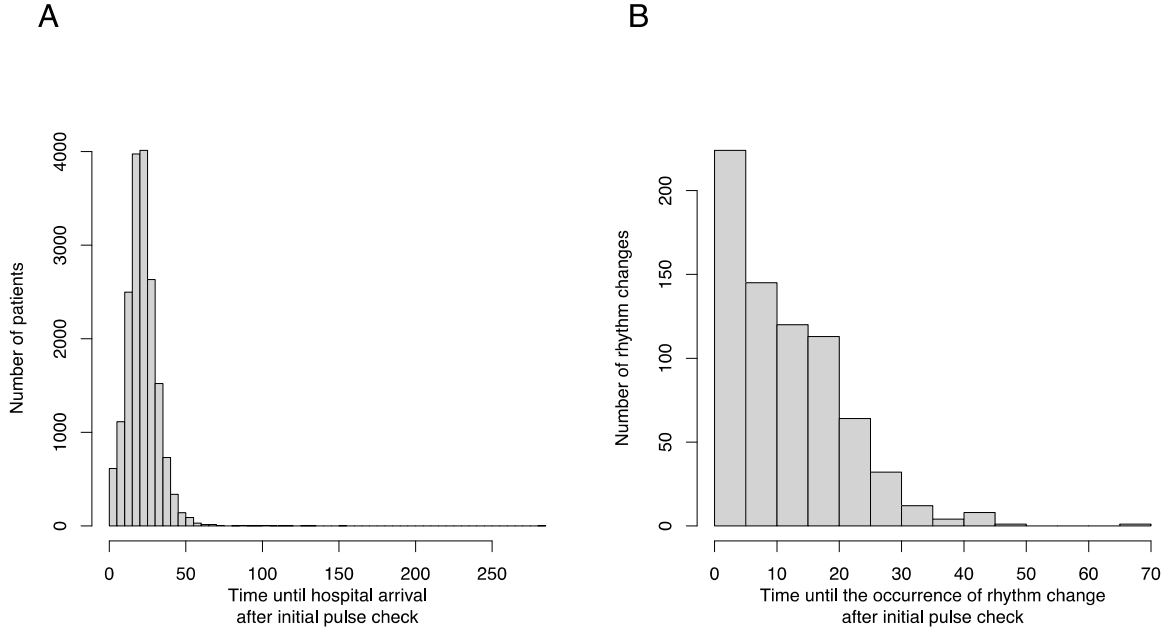


Figure S2. Standardized difference between the derivation and validation cohorts.

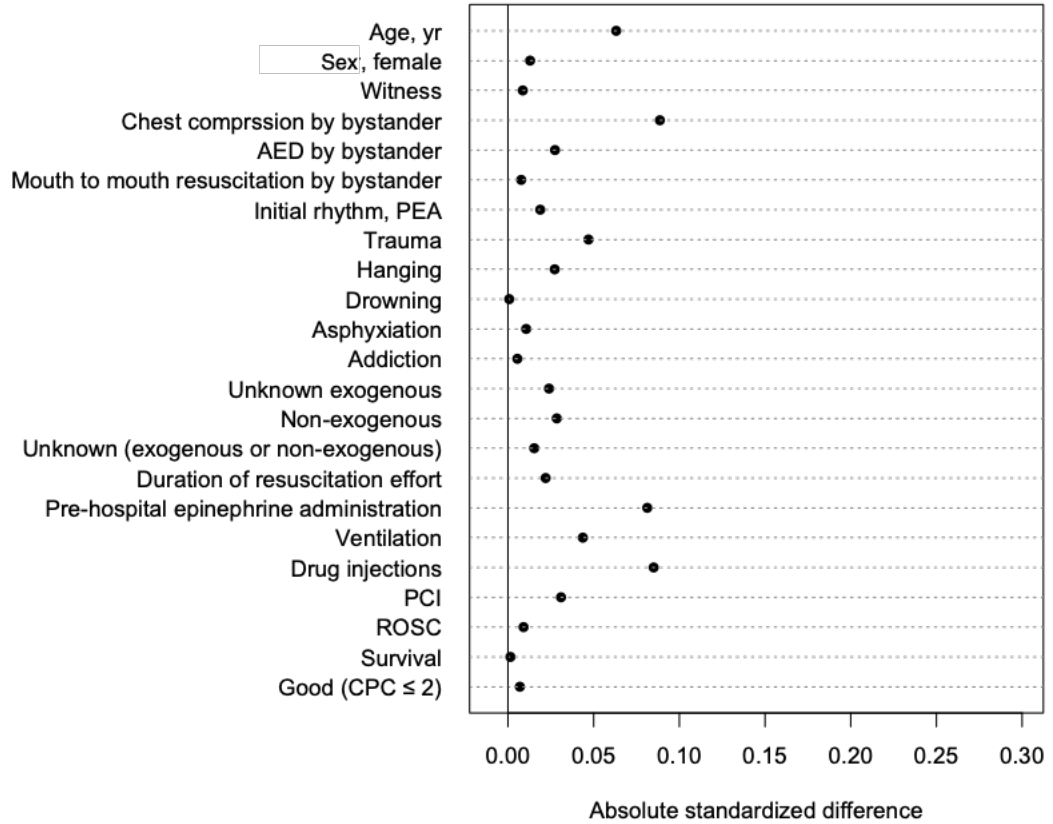
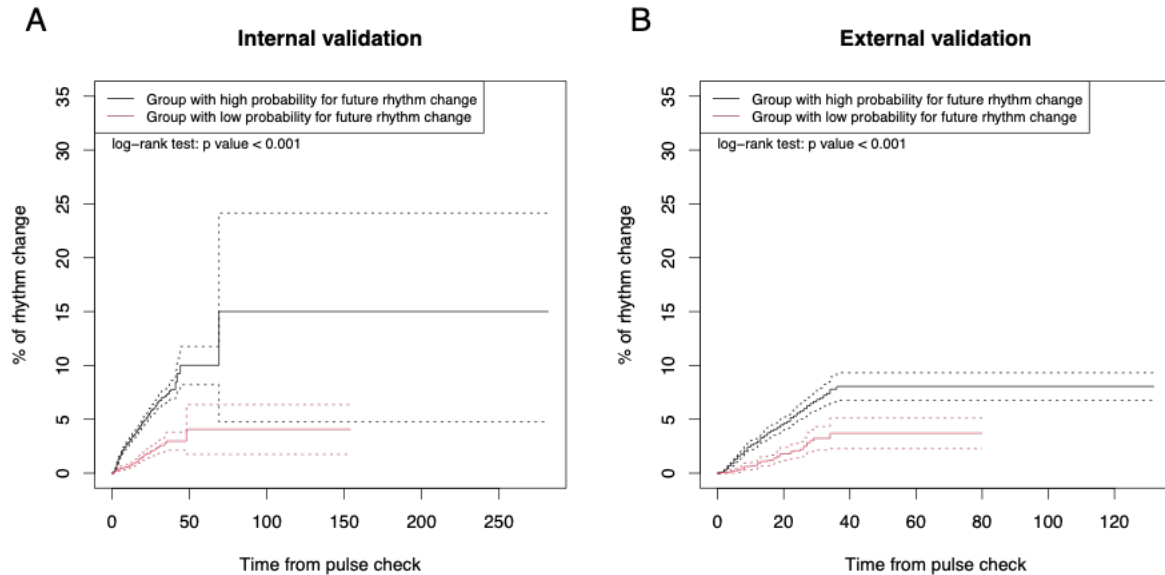


Figure S3. Kaplan-Meier analysis in the internal and external validation cohorts without time restrictions.



Kaplan-Meier curves were plotted for the internal (A) and external (B) validation cohorts. The black line shows the curve for the group with high probability of spontaneous rhythm change, while the red line denotes the curve for the group with a low probability of spontaneous rhythm change.