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ORIGINAL RESEARCH ARTICLE

Sudden cardiac death after acute decompensation in heart failure patients: implications of discharge haemoglobin levels

Ryoma Fukuoka[1,2], Shun Kohsaka[1]*, Yasuyuki Shiraishi[1], Mitsuaki Sawano[1], Takayuki Abe[3], Wayne C. Levy[4], Yuji Nagatomo[5], Yosuke Nishihata[6], Ayumi Goda[7], Takashi Kohno[7], Akio Kawamura[2], Keiichi Fukuda[1] and Tsutomu Yoshikawa[8]

[1]*Department of Cardiology, Keio University School of Medicine, Tokyo, Japan;* [2]*Department of Cardiology, International University of Health and Welfare, School of Medicine, Chiba, Japan;* [3]*School of Data Science, Yokohama City University, Yokohama, Japan;* [4]*Division of Cardiology, University of Washington, Seattle, WA, USA;* [5]*Department of Cardiology, National Defense Medical College, Tokorozawa, Japan;* [6]*Department of Cardiology, Cardiovascular Centre, St. Luke's International Hospital, Tokyo, Japan;* [7]*Department of Cardiovascular Medicine, Kyorin University School of Medicine, Tokyo, Japan; and* [8]*Department of Cardiology, Sakakibara Heart Institute, Tokyo, Japan*

Abstract

Aims Heart failure (HF) patients have a high risk of mortality due to sudden cardiac death (SCD) and non-SCD, including pump failure death (PFD). Anaemia predicts more severe symptomatic burden and higher morbidity, as noted by markedly increased hospitalizations and readmission rates, and mortality, underscoring its importance in HF management. Herein, we aimed to determine whether haemoglobin (Hb) level at discharge affects the mode of death and influences SCD risk prediction.

Methods We evaluated the data of 3020 consecutive acute HF patients from a Japanese prospective multicentre registry. Patients were divided into four groups based on discharge Hb levels. SCD was defined as an unexpected and otherwise unexplained death in a previously stable patient or death due to documented or presumed cardiac arrhythmia without a clear non-cardiovascular cause. The mode of death (SCD, PFD or other cause) was adjudicated by a central committee. Finally, we investigated whether adding Hb level to the Seattle Proportional Risk Model (SPRM; established risk score utilized to estimate 'proportion' of SCD among death events) would affect its performance.

Results The mean age of studied patients was 74.3 ± 12.9 years, and 59.8% were male. The mean Hb level was 12.0 ± 2.1 g/dL (61.3% of patients had anaemia defined by World Health Organization criteria). During the 2-year follow-up, 474 deaths (15.7%) occurred, including 93 SCDs (3.1%), 171 PFDs (5.7%) and 210 other deaths (7.0%; predominantly non-cardiac death). Absolute risk of PFD ($P < 0.001$) or other death ($P < 0.001$) increased along with the severity of anaemia, whereas the incidence of SCD was low but remained consistent across all four groups ($P = 0.440$). As a proportion of total deaths in each Hb level group, the contributions from non-SCD increased and from SCD decreased along with anaemia severity ($P = 0.007$). Adding Hb level to the SPRM improved the overall discrimination (c-index: 0.62 [95% confidence interval (CI) 0.56–0.69] to 0.65 [95% CI 0.59–0.71]), regardless of the baseline ejection fraction (EF) (c-index: 0.64 [95% CI 0.55–0.73] to 0.67 [95% CI 0.58–0.75] for reduced EF and 0.55 [95% CI 0.45–0.66] to 0.61 [95% CI 0.52–0.70] for preserved EF).

Conclusions The discharge Hb level provides information about both absolute and proportional risks for each mode of death in acute HF patients, and the addition of Hb level improves the performance of SPRM by identifying more non-SCD cases. Future 'proportional' SCD risk models should incorporate Hb level as a covariate to meet this high performance.

Keywords Heart failure; Haemoglobin level; Anaemia; Sudden cardiac death; Risk prediction model

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**Correspondence to: Shun Kohsaka, Department of Cardiology, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo, Japan. Tel: 81-3-5843-6702; Fax: 81-3-5363-3875. Email: sk@keio.jp*

Introduction

Heart failure (HF) is a complex condition with increased co-morbidities. As HF patients age, co-morbid conditions become more prevalent, and the long-term risk of hospitalization for acute HF increases.[1,2] Recent guidelines recognize anaemia as one of the most common co-morbidities in HF patients,[1] and haemoglobin (Hb) level is considered a general marker, along with renal condition, of overall condition in HF patients.[3] Although several recent studies suggest that a lower Hb level is associated with an increased risk of all-cause death in HF patients,[4–6] little is known about the modes of death in these patients.[7]

The modes of death in HF patients vary widely, such that some die suddenly (sudden cardiac death [SCD]), whereas others die from progressive failure of cardiac function (pump failure death [PFD]) or from non-cardiac reasons. The ability to predict each mode of death may aid in providing information to clinicians, patients and families when choosing specific HF medications or devices.[8,9] The use of an implantable cardioverter-defibrillator (ICD) for primary prevention of SCD in HF patients is supported by relevant evidence,[10,11] and current guidelines propose an algorithm of SCD risk stratification based on ejection fraction (EF).[1,12] Furthermore, the administration and uptitration of guideline-directed medical therapy (GDMT) in HF with reduced EF (HFrEF) patients are also recommended to reduce HF hospitalizations and premature PFD.[1] Therefore, it is crucial for medical care providers treating HF to predict the risk and mode of death accurately. However, limited information is available to discriminate among modes of death for risk prediction in individual HF patients.

We hypothesized that Hb level would also affect the mode of death in HF patients and may aid in improvement of SCD prediction. Previously, the Seattle Proportional Risk Model (SPRM) was developed to predict the relative proportional risk of SCD over that of non-SCD for each patient.[13] The model has been validated in HF populations in Western countries[14] and more recently in Japanese HF cohort despite significant differences in the patients' backgrounds.[15] Hence, the aims of the present study were (i) to investigate the relationship between the Hb level at discharge and mode of death of patients in the contemporary Japanese HF registry and (ii) to evaluate whether adding the Hb level to the SPRM improves the accuracy of SCD prediction.

Methods

Data sources

The West Tokyo Heart Failure (WET-HF) registry is a large, ongoing, prospective, multicentre cohort registry designed to collect data on clinical backgrounds and outcomes of patients hospitalized for acute HF.[15] The complete data set includes over 400 variables, including patient status at the time of admission, type of treatment and medical intervention during the hospitalization and their status and medications at the time of discharge. Individual cardiologists at each institution made the clinical diagnosis of acute HF according to the Framingham criteria.[16] Specifically, patients presenting with acute coronary syndrome were not included. To obtain a robust assessment of the care and patient outcome, patient-level data and outcome were collected by dedicated clinical research coordinators, and on-site treating physicians were queried directly when the information was not clear from the medical records. Data were entered into an electronic data-capturing system, which also has a data query engine and system validations for data quality. Furthermore, exclusive on-site auditing by the investigators (Y.S. and S.K.) ensured proper registration of each patient. The objectives and detailed design are provided on the University Hospital Medical Information Network (UMIN000001171). The study protocol was approved by each centre's ethics review committee, and the study complies with the Declaration of Helsinki. All patients provided informed consent.

Definitions of mode of death

Mortality and mode of death were extracted from the individual medical records by the primary investigator (R.F.) and adjudicated by the study committee members (S.K., Y.S., T.K. and T.Y.). Mode of death was classified as SCD, PFD or other death in the present study. SCD was defined as unexpected death in a clinically stable patient, typically within 1 h of symptom onset, from documented or presumed cardiac arrhythmia and without a clear non-cardiovascular cause; therefore, the electrocardiogram recordings of terminal events were not required. Patients who were comatose and then died after attempted resuscitation were classified as SCD. Those who died after having been out of direct personal contact for more than 24 h were classified as unknown death.[17] We also performed individual analysis including the resuscitated events in patients with ICD or cardiac-resynchronization therapy defibrillator (CRTD), and they were discussed separately. PFD was defined as death associated with clinically worsening symptoms and/or signs of HF.[17] Other death was defined as death not adjudicated as either SCD or PFD. Furthermore, death other than SCD was defined as non-SCD to validate the SPRM and the modified model in the present analysis.

Study cohort and SPRM score calculation

From January 2009 to December 2016, 3468 consecutive acute HF patients from five teaching hospitals within the

metropolitan Tokyo area were registered in the WET-HF registry. We excluded 154 patients who died during the index hospitalization, 209 patients who were lost to follow-up and 69 patients who died from unknown causes. We also excluded 16 patients whose Hb values at discharge were not available. After these exclusions, data of 3020 patients who were stable and discharged after index hospitalization were analysed (*Figure S1*).

According to the criteria of the World Health Organization, anaemia was defined as Hb levels of $<$13 g/dL for men and $<$12 g/dL for women.[18] The study patients were categorized into four groups based on their Hb level at discharge: severe anaemia ($<$10.0 g/dL), mild/moderate anaemia (10.0–12.9 g/dL for men and 10.0–11.9 g/dL for women), normal Hb (13.0–14.9 g/dL for men and 12.0–14.9 g/dL for women) and high Hb ($\geq$15.0 g/dL). Chronic kidney disease (CKD) was defined as an estimated glomerular filtration rate (eGFR) value of $<$60 mL/min/1.73 m^2, according to the National Kidney Foundation KDOQI guidelines.[19]

Originally, the SPRM variables were identified by multivariate logistic regression from the clinical variables within the five separate validation cohorts of 9985 Western ambulatory systolic HF patients without an ICD; within the cohort, 2552 died (1225 SCDs) during an average 2.3-year follow-up.[13] The model found that the proportion of SCD was greater with younger age, male gender, lower EF, better New York Heart Association (NYHA) functional class (i.e. I or II vs. III or IV), higher body mass index (BMI) and use of digoxin. Conversely, diabetes mellitus (DM), hyper-/hypotension, renal dysfunction and hyponatraemia reduce relative SCD likelihood.[13] The SPRM score was calculated to predict proportional risk of SCD for each patient using above variables at discharge. For the present study, individual SPRM score was calculated to predict proportional risk of SCD for each patient. In addition, the Seattle Heart Failure Model (SHFM) score to predict annual all-cause mortality for each patient was calculated in accordance to the statistical model described in the original article.[20]

Statistical analysis

Continuous variables are presented as means and standard deviations or as medians and interquartile ranges, and categorical variables are presented as absolute values and percentages. For comparisons of patient demographics across the four Hb level groups, we used one-way analysis of variance or the Kruskal–Wallis test for continuous variables and the Pearson chi-squared test for categorical variables, as appropriate.

The cumulative incidence of all-cause death was estimated using the Kaplan–Meier method, and differences across the four Hb level groups were assessed with the log-rank test. Using the normal Hb group as the reference group, the risk of severe anaemia, mild/moderate anaemia and high Hb for all-cause death was estimated using the Cox proportional hazard model. Variables that were entered into the model are listed in *Table S1*. Furthermore, we evaluated the cause-specific mortality determined by the Hb level at discharge. For each mode of death (SCD and non-SCD), patients who died of other causes were censored as non-events at the time of death. We also constructed Cox proportional hazard analyses to estimate adjusted hazard ratio (HR) for each mode of death according to Hb level at discharge, and the variables that were entered into the model are listed in *Table S2*.

To evaluate the relationship between anaemia and CKD, alone or combined, and all-cause death, the Kaplan–Meier method and the log-rank test were constructed as subgroup analysis. Using the neither anaemia nor CKD group as the reference group, the risks of CKD alone, anaemia alone and both anaemia and CKD for all-cause death were estimated using the Cox proportional hazard model. We also assessed the cause-specific mortality (SCD and non-SCD) and their estimated HR according to the four subgroups. Variables that were entered into each model are listed in *Tables S3* and *S4*.

Finally, we evaluated the association of the Hb level at discharge on SCD risk stratification for acute HF patients and assessed the performance of the SPRM after including the Hb level into a logistic regression model. Discrimination of the original SPRM- or modified model-predicted proportional risk of SCD was assessed by calculating the c-index or the area under the receiver operating characteristic curve (AUC) for SCD vs. non-SCD among non-survivors. A c-index $\geq$ 0.6 was considered modest. The calibration of the original SPRM- or modified model-predicted proportional risk of SCD among non-survivors was evaluated using the Hosmer–Lemeshow statistic and visual plotting. We also performed a further subgroup analysis to investigate the relationship between Hb level at discharge and mode of death as well as SCD predictive ability of the modified model in HFrEF patients (EF $<$ 40%) and HF with preserved EF (HFpEF: EF $\geq$ 40%). All statistical analyses were performed using SPSS version 24.0 (SPSS Inc., Chicago, IL, USA), and $P < 0.05$ was considered statistically significant.

Results

Patient characteristics

Patients in the present cohort were predominantly male (59.8%), with a mean age of 74.3 ± 12.9 years. The distribution of the Hb level is shown in *Figure S2*. The mean Hb level was 12.0 ± 2.1 g/dL, and 61.3% of patients had anaemia. Furthermore, 141 patients received ICD or CRTD in the present study. The clinical characteristics of patients

Table 1 Clinical characteristics of the patients according to Hb level at discharge

	Severe anaemia *n* = 513	Mild/moderate anaemia *n* = 1337	Normal Hb *n* = 868	High Hb *n* = 302	*P*-value
Age, year	78.0 ± 10.7	77.3 ± 11.2	71.9 ± 13.1	61.8 ± 13.4	<0.001
Male, *n* (%)	259 (50.4)	853 (63.8)	442 (50.9)	253 (83.8)	<0.001
BMI, kg/m^2	20.7 ± 3.6	21.3 ± 4.0	22.1 ± 4.2	23.6 ± 4.4	<0.001
ICD or CRTD, *n* (%)	14 (2.7)	77 (5.8)	39 (4.5)	11 (3.6)	0.034
Ischemic aetiology, *n* (%)	166 (32.4)	460 (34.4)	191 (22.0)	61 (20.2)	<0.001
EF, %	51 (40–60)	48 (34–60)	45 (31–58)	34 (26–45)	<0.001
DM, *n* (%)	200 (39.0)	503 (37.6)	255 (29.4)	99 (32.8)	<0.001
Previous HF admission, *n* (%)	195 (38.0)	430 (32.2)	195 (22.5)	53 (17.5)	<0.001
History of stroke, *n* (%)	77 (15.0)	207 (15.5)	103 (11.9)	32 (10.6)	0.028
Atrial fibrillation or flutter, *n* (%)	208 (40.5)	614 (45.9)	454 (52.3)	171 (56.6)	<0.001
Chronic lung disease, *n* (%)	28 (5.5)	74 (5.5)	33 (3.8)	13 (4.3)	0.259
Sodium, mEq/L	139 (136–141)	139 (136–141)	140 (138–141)	139 (137–141)	<0.001
eGFR, mL/min/1.73 m^2	34.7 (20.4–52.8)	46.0 (31.5–61.8)	56.8 (44.9–70.6)	58.0 (47.3–68.9)	<0.001
ACEI/ARB, *n* (%)	306 (59.6)	821 (61.4)	584 (67.3)	223 (73.8)	<0.001
Beta-blocker, *n* (%)	358 (69.8)	997 (74.6)	699 (80.5)	263 (87.1)	<0.001
MRA, *n* (%)	118 (23.0)	454 (34.0)	365 (42.1)	135 (44.7)	<0.001
Digoxin, *n* (%)	25 (4.9)	73 (5.5)	77 (8.9)	40 (13.2)	<0.001
SBP, mmHg	118 (102–130)	111 (100–124)	108 (98–120)	108 (98–118)	<0.001
NYHA functional Class I or II, *n* (%)	400 (78.0)	992 (74.2)	710 (81.8)	267 (88.4)	<0.001
SHFM-predicted annual all-cause mortality, %	13.6 (8.9–21.0)	9.7 (6.3–16.0)	5.8 (3.7–9.1)	4.9 (3.2–7.7)	<0.001
SPRM-predicted proportional risk of SCD, %	21.9 (16.3–28.4)	26.8 (20.2–34.5)	33.1 (25.6–42.4)	45.9 (35.8–56.7)	<0.001

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; CRTD, cardiac-resynchronization therapy defibrillator; DM, diabetes mellitus; EF, ejection fraction; eGFR, estimated glomerular filtration rate; Hb, haemoglobin; HF, heart failure; ICD, implantable cardioverter-defibrillator; MRA, mineralocorticoid receptor antagonists; NYHA, New York Heart Association; SBP, systolic blood pressure; SCD, sudden cardiac death; SHFM, Seattle Heart Failure Model; SPRM, Seattle Proportional Risk Model.

according to the four Hb groups are presented in *Table 1*. The proportions of patients in the four Hb groups were as follows: severe anaemia, 17.0%; mild/moderate anaemia, 44.3%; normal Hb, 28.7%; and high Hb, 10.0%. Compared with patients with no anaemia, patients in the two anaemia groups were older, had a lower BMI and eGFR as well as a higher EF and had a greater degree of ischaemic aetiology and NYHA functional Class III or IV. The prevalence of DM and the history of stroke were higher in the two anaemia groups, whereas atrial fibrillation or flutter was more common in the no anaemia groups. Angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs), beta-blockers, mineralocorticoid receptor antagonists (MRAs) and digoxin were prescribed less in the two anaemia groups. In addition, SHFM-predicted risk of annual all-cause mortality increased and SPRM-predicted proportional risk of SCD decreased with increasing severity of anaemia.

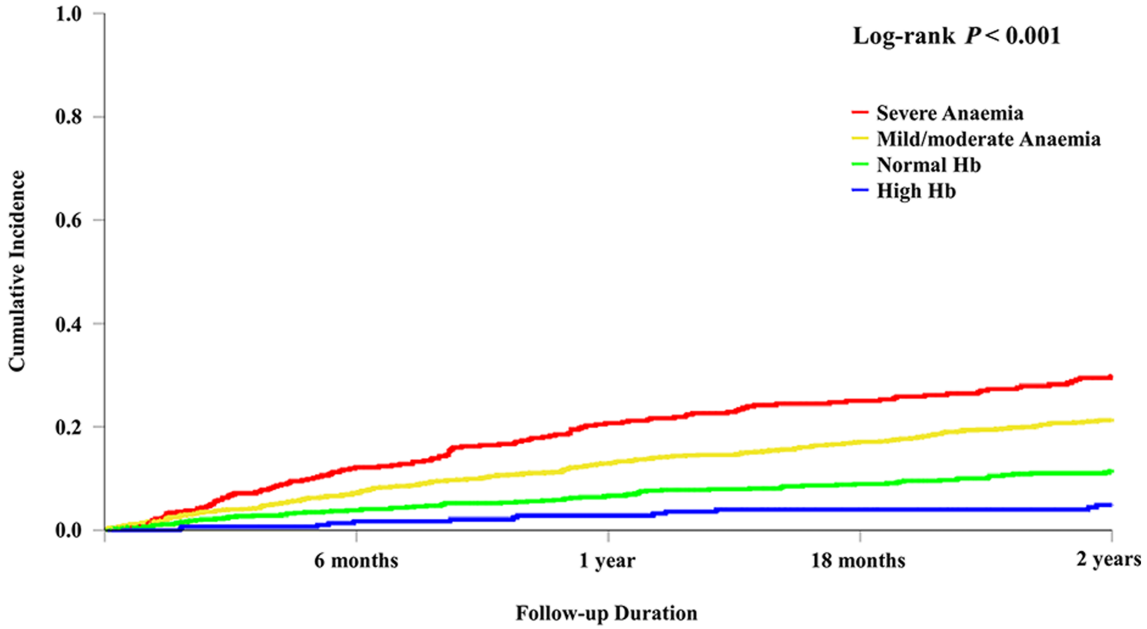
All-cause death and mode of death in overall cohort

During the 2-year follow-up, 474 deaths (15.7%) occurred, including 93 SCDs (3.1%), 171 PFDs (5.7%) and 210 other deaths (7.0%; 5 myocardial infarction and 205 non-cardiac deaths). Among 141 patients received ICD or CRTD, 6 SCDs, 22 PFDs and 11 other deaths occurred. Furthermore, 18 patients had appropriate ICD shock, which was not included as SCD event.

The cumulative 2-year incidence of all-cause death increased with increasing severity of anaemia (5.4%, 11.4%, 21.7% and 29.8% in the high Hb, normal Hb, mild/moderate anaemia and severe anaemia groups, respectively; $P < 0.001$; *Figure 1*). Even after adjusting for potential confounders, the excess risk of the severe and mild/moderate anaemia groups relative to the normal Hb group for all-cause death remained significant (HR: 2.32; 95% confidence interval [CI]: 1.73–3.10; $P < 0.001$ and HR: 1.50; 95% CI: 1.16–1.94; $P = 0.002$, respectively); however, the risk of death in the high Hb group remained non-significant (HR: 0.61; 95% CI: 0.34–1.08; $P = 0.091$; *Table 2*). With regard to cause-specific mortality, adjusted risk for non-SCD was similarly greater in the severe anaemia group (HR: 2.81; 95% CI: 2.03–3.89; $P < 0.001$), followed by the mild/moderate anaemia group (HR: 1.73; 95% CI: 1.29–2.33; $P < 0.001$). In contrast, the adjusted risk for SCD was no longer significant across all four groups (*Table 2*).

Figure 2A shows the absolute risk of each mode of death categorized by anaemia severity. Absolute risk of PFD or other death increased as Hb decreased ($P < 0.001$ for each), whereas the absolute incidence of SCD was low across all four groups ($P = 0.440$). As a proportion of total deaths in each Hb level group, the contributions from non-SCD increased and from SCD decreased along with the severity of anaemia ($P = 0.001$; *Figure 2B*). When 18 patients resuscitated from

Figure 1 Kaplan–Meier curves for all-cause death according to Hb level at discharge.



Number at risk	0 months	6 months	1 year	18 months	2 years
Severe Anaemia	513	401	330	265	215
Mild/moderate Anaemia	1337	1115	985	829	690
Normal Hb	868	764	700	593	498
High Hb	302	272	263	224	195

Table 2 Adjusted HR for all-cause death, SCD and non-SCD according to Hb level at discharge

	Adjusted HR (95% CI)	*P*-value
All-cause death		
Severe anaemia	2.32 (1.73–3.10)	<0.001
Mild/moderate anaemia	1.50 (1.16–1.94)	0.002
Normal Hb	Reference	—
High Hb	0.61 (0.34–1.08)	0.091
SCD		
Severe anaemia	1.01 (0.51–1.98)	0.985
Mild/moderate anaemia	1.06 (0.64–1.74)	0.833
Normal Hb	Reference	—
High Hb	0.72 (0.29–1.79)	0.474
Non-SCD		
Severe anaemia	2.81 (2.03–3.89)	<0.001
Mild/moderate anaemia	1.73 (1.29–2.33)	<0.001
Normal Hb	Reference	—
High Hb	0.52 (0.25–1.10)	0.089

CI, confidence interval; Hb, haemoglobin; HR, hazard ratio; SCD, sudden cardiac death.

ventricular tachycardia (VT) or ventricular fibrillation (VF) by appropriate ICD shock were included as SCD patients, absolute risk of PFD or other death ($P < 0.001$ for each) also increased along with the severity of anaemia, whereas the incidence of SCD was low but remained consistent across all four groups ($P = 0.156$). As a proportion of total deaths in each Hb level group, the contributions from non-SCD increased and from SCD decreased along with the severity of anaemia ($P < 0.001$).

Mode of death in HFrEF and HFpEF patients

Similar to the overall cohort, the absolute risk of PFD and other death increased as Hb decreased ($P < 0.001$ for each), whereas the absolute incidence of SCD was low across all four groups ($P = 0.472$) in HFrEF patients (*Figure S3A*). As a proportion of total deaths in each Hb level group, the contributions from non-SCD increased and from SCD decreased along with the severity of anaemia ($P = 0.002$; *Figure S3B*).

Among HFpEF patients, absolute risk of PFD and other death also increased as Hb decreased ($P = 0.031$ for PFD and $P < 0.001$ for other death), whereas the absolute incidence of SCD was low across all four groups ($P = 0.584$; *Figure S3C*). As a proportional risk, the number of total deaths was too small to estimate risk in the high Hb group; however, the contributions from non-SCD gradually increased and from SCD decreased along with the severity of anaemia ($P = 0.563$; *Figure S3D*).

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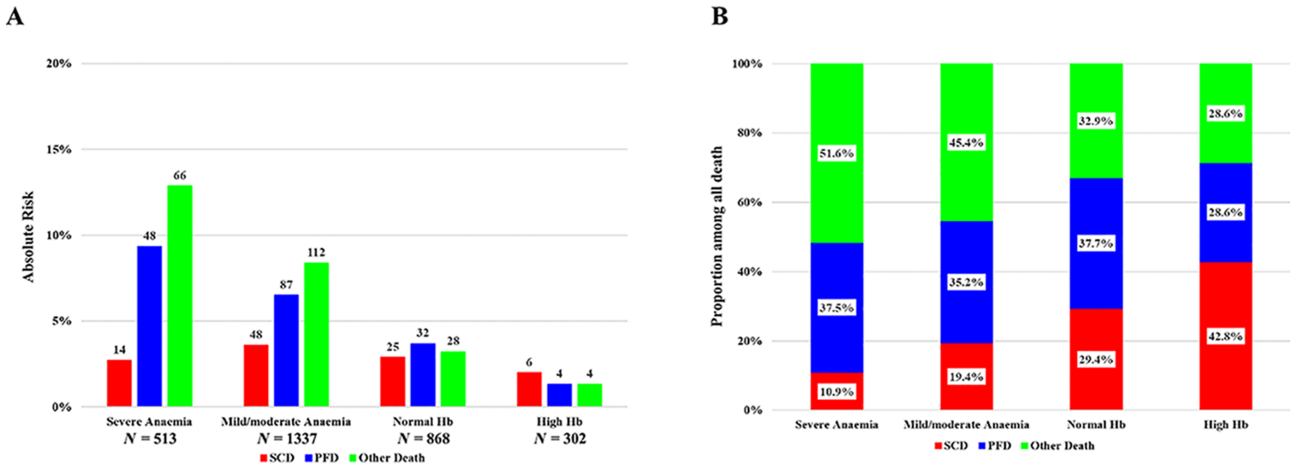
Figure 2 Risks for each mode of death according to Hb level at discharge in the entire cohort. (A) Absolute risk of each mode of death according to Hb level at discharge. The numbers shown above the coloured bars indicate the absolute number of cases of each mode of death. (B) Proportional risk of each mode of death according to Hb level at discharge. The numbers within the stacked bars indicate the percentage of each mode of death among all deaths according to Hb level at discharge.



Subgroup analysis according to the presence of anaemia and CKD at discharge

The cumulative 2-year incidence of all-cause death was 6.0%, 12.9%, 16.5% and 26.3% in the neither anaemia nor CKD, CKD alone, anaemia alone and both anaemia and CKD groups, respectively ($P < 0.001$). Both adjusted risks for all-cause death and non-SCD were greater in the both anaemia and CKD group, followed by the anaemia group. In contrast, the adjusted risk for SCD was no longer significant across all four groups (*Table 3*).

Absolute risk of PFD or other death increased from neither anaemia nor CKD to both anaemia and CKD groups ($P < 0.001$ for each), whereas the absolute incidence of SCD was low across all four groups ($P = 0.280$; *Figure 3A*). As a proportion of total deaths, the contributions from non-SCD increased and from SCD decreased from neither anaemia nor CKD to the both anaemia and CKD groups ($P = 0.005$; *Figure 3B*).

Table 3 Adjusted HR for all-cause death, SCD and non-SCD in four groups according to the presence of anaemia and CKD

	Adjusted HR (95% CI)	P-value
All-cause death		
Anaemia −/CKD −	Reference	—
Anaemia −/CKD +	1.57 (1.00–2.47)	0.050
Anaemia +/CKD −	1.86 (1.17–2.96)	0.008
Anaemia +/CKD +	2.85 (1.89–4.29)	<0.001
SCD		
Anaemia −/CKD −	Reference	—
Anaemia −/CKD +	1.63 (0.74–3.59)	0.228
Anaemia +/CKD −	1.59 (0.67–3.78)	0.290
Anaemia +/CKD +	1.59 (0.75–3.39)	0.228
Non-SCD		
Anaemia −/CKD −	Reference	—
Anaemia −/CKD +	1.67 (0.97–2.88)	0.066
Anaemia +/CKD -	2.13 (1.22–3.69)	0.008
Anaemia +/CKD +	3.71 (2.23–6.07)	<0.001

CI, confidence interval; CKD, chronic kidney disease; HR, hazard ratio; SCD, sudden cardiac death.

Association of the discharge Hb level on SCD risk stratification

Compared with non-SCD patients, SCD patients had a higher Hb level at discharge (11.8 ± 1.8 g/dL vs. 10.9 ± 1.8 g/dL, $P < 0.001$). According to multivariate logistic regression analysis, both the SPRM (odds ratio [OR]: 1.72; 95% CI: 1.11–2.68, $P = 0.016$) and Hb level at discharge (OR: 1.21; 95% CI: 1.06–1.39, $P = 0.005$) were significantly associated with SCD in non-survivors. The modified model was developed by the SPRM after including the Hb level into the logistic regression model. *Figure 4A,B* shows the scatter plot of original SPRM- or modified model-predicted proportional risk of SCD and SHFM-predicted annual all-cause mortality in the overall cohort. An inverse relationship was observed between both original SPRM- or modified model-predicted proportional risk of SCD and the SHFM-predicted annual all-cause mortality, and the plot displays a separate distribution among the four Hb groups in the modified model compared with those in the original SPRM model.

Figures 5 and *S4* show the AUC and calibration plot for the original SPRM and modified model. The modified model demonstrated improved discrimination from the original SPRM (c-index: 0.62 [95% CI 0.56–0.69] to 0.65 [95% CI 0.59–0.71]). In addition, the Hosmer–Lemeshow test showed adequate calibration, and the calibration plot also showed

Figure 3 Risks for each mode of death in the four groups according to the presence of anaemia and CKD. (A) Absolute risk of each mode of death in the four groups according to the presence of anaemia and CKD. The numbers shown above the coloured bars indicate the absolute number of cases of each mode of death. (B) Proportional risk of each mode of death in the four groups according to the presence of anaemia and CKD at discharge. The numbers within the stacked bars indicate the percentage of each mode of death among all deaths according to the presence of anaemia and CKD at discharge.

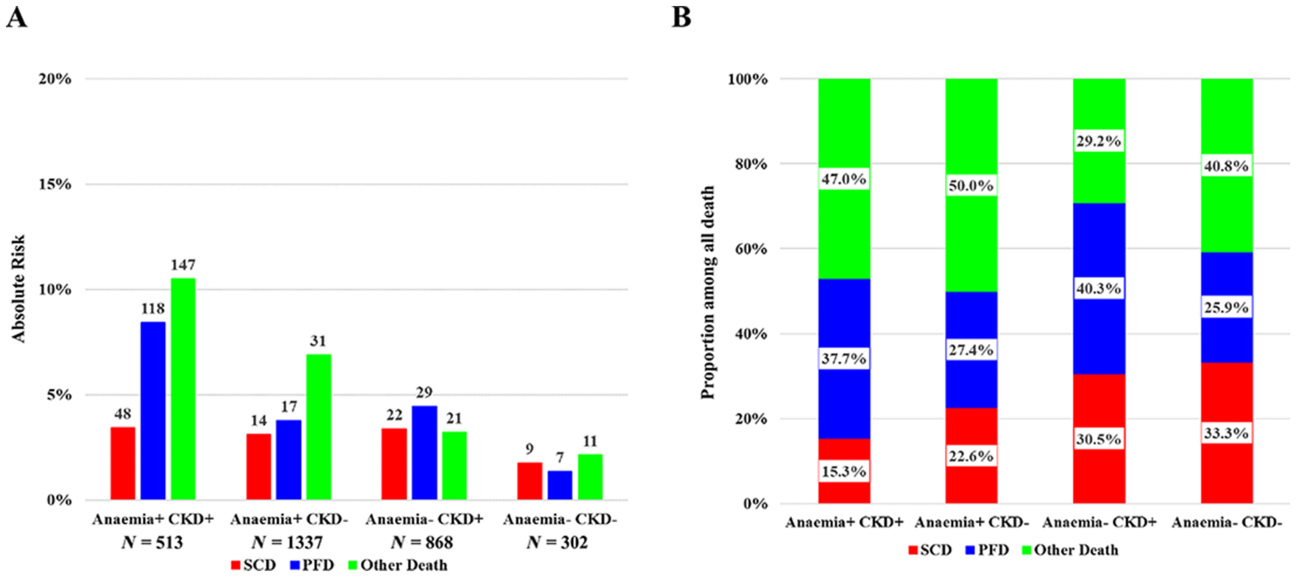
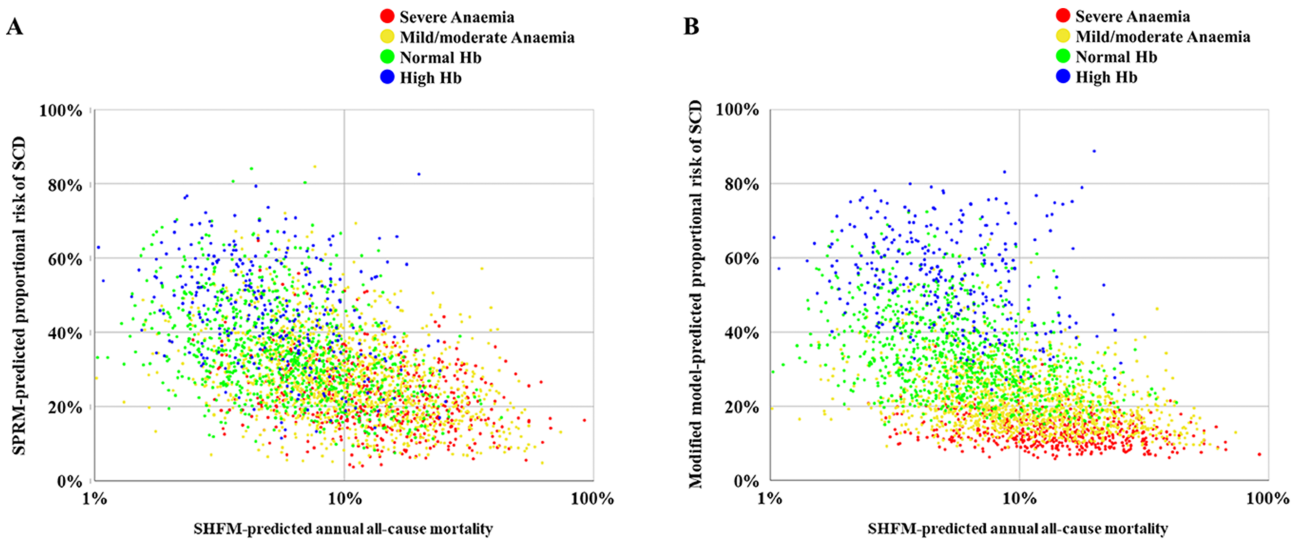


Figure 4 Scatter plots of the original SPRM- or modified model-predicted proportional risk of SCD and SHFM-predicted annual all-cause mortality among the entire cohort. (A) Original SPRM. (B) Modified model.



reasonable conformance. The modified model also demonstrated improved discrimination compared with the original SPRM in both cases when 141 patients with ICD or CRTD implantation were excluded (c-index: 0.63 [95% CI 0.56–0.70] to 0.66 [95% CI 0.60–0.73]) and when 18 patients resuscitated from VT or VF by appropriate ICD shock were included as SCD patients (c-index: 0.65 [95% CI 0.59–0.71] to 0.67 [95% CI 0.61–0.73]). Furthermore, the modified model showed the improved SCD predictive performance regardless of HF phenotype (c-index: 0.64 [95% CI 0.55–0.73] to 0.67 [95% CI 0.58–0.75] for HFrEF patients and 0.55 [95% CI 0.45–0.66] to 0.61 [95% CI 0.52–0.70] for HFpEF patients).

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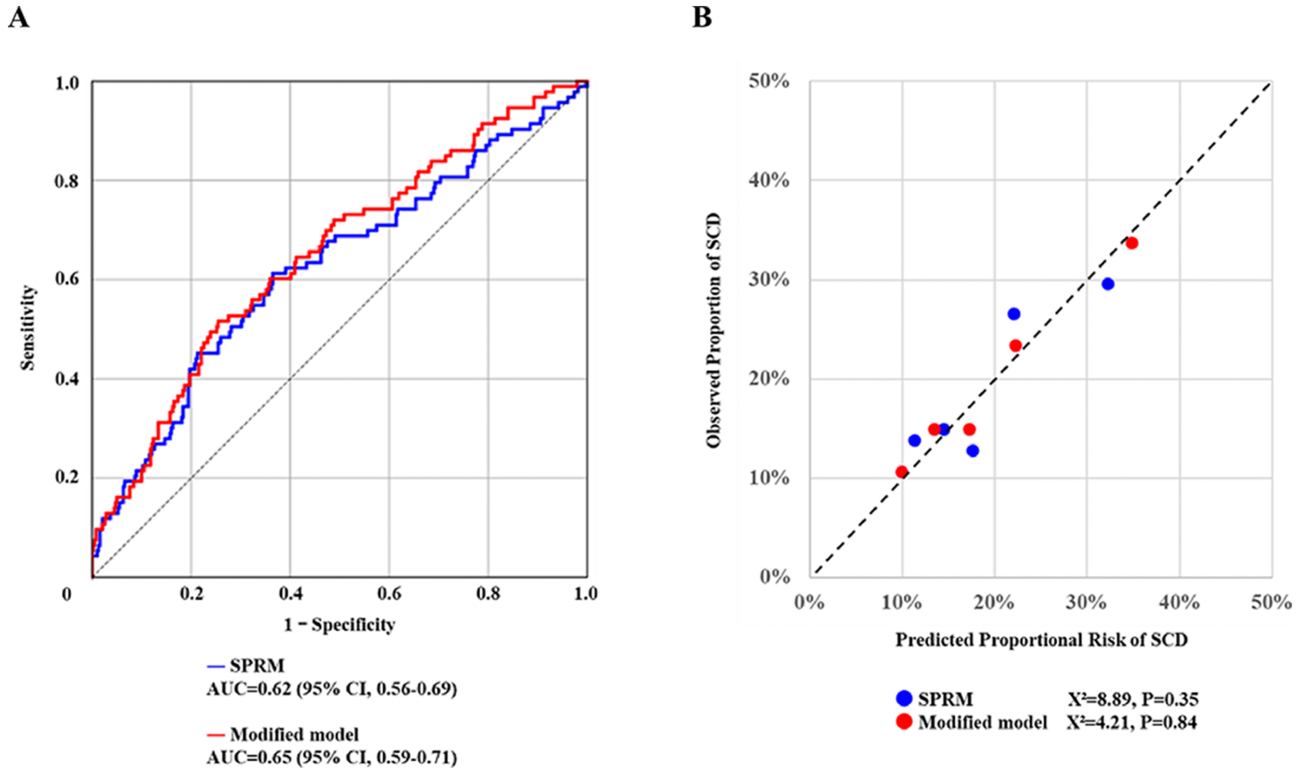
Figure 5 AUC and calibration plot for the original SPRM and the modified model among non-survivors. (A) AUC for the original SPRM- or modified model-predicted proportional risk of SCD. (B) Calibration plot for the original SPRM and the modified model. The original SPRM- or modified model-predicted proportional risk of SCD, divided into deciles, was plotted against the observed proportion of SCD. The line indicates the ideal calibration line.



Discussion

The major findings of this study were as follows: (i) More than 60% acute HF patients had anaemia at discharge, and anaemia, regardless of its severity, was associated with increased risks of all-cause death; (ii) the absolute risk of non-SCD (PFD and other death, predominantly non-cardiac death) increased along with the severity of anaemia (lower discharge Hb level), whereas the incidence of SCD was low but remained consistent; (iii) as a proportion of total deaths in each Hb level group, the contributions from non-SCD increased and from SCD decreased along with the severity of anaemia; (iv) the addition of Hb level improved the performance of classic 'proportional' SCD prediction model (SPRM) by identifying more non-SCD cases; and (v) the improvement of its predictive performance was seen more in HFrEF patients and particularly in those with HFpEF.

In our study, the absolute risk of non-SCD (e.g. PFD and non-cardiac death) increased with the severity of anaemia, which was in accordance with previous reports from the MUSIC (*MUerte Subita en Insuficiencia Cardiaca*)[21] and ATTEND (Acute Decompensated Heart Failure Syndromes)[22] studies. Anaemia could be due to volume overload, and subsequent haemodilution due to reduced cardiac output, which could be associated with PFD.[23] In addition, anaemia can also be a surrogate of malignancy, chronic infection, collagen disease, gastrointestinal bleeding and advanced CKD, which may increase the risk of non-cardiac death. Unlike the SPRM derivation cohort, which did not find Hb level to be an independent predictor in a mainly ambulatory HFrEF population, our study included patients with severe anaemia (mean Hb level in the SPRM cohort: 13.4 g/dL and in our Japanese cohort: 12.0 g/dL), reflecting real-world patients hospitalized for acute HF. Furthermore, in non-survivors, both SPRM and Hb level at discharge were significantly associated with SCD over that non-SCD, and the addition of the Hb level enabled the improvement of the classic 'proportional' SCD prediction model (SPRM) performance. These findings of the present study seem to be opposite to the relationship between SCD and Hb levels in a recent report from the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist) trial.[24] The main difference from this previous study was that we used a novel methodology to identify anaemia as an independent factor

associated with an increased 'proportional' SCD or non-SCD risk rather than with the 'absolute' risk of SCD. Notably, the prevalence of HF patients with anaemia in Asia has been reported to be higher than that in Western countries, ranging from 57% to 61% in Japan[25] and 53% in the US registry (Acute Decompensated Heart Failure National Registry [ADHERE]).[26] This difference might be related to the higher prevalence of CKD; its prevalence was 68% in our study, whereas in the ADHERE registry, it was 30%.[26] A previous study has also reported that Japanese patients, in particular, were at a higher odds for having both CKD and anaemia,[27] suggesting that CKD is a major driving factor for the occurrence of anaemia, and this might be a possible explanation for the higher prevalence of anaemia in Japanese HF patients.[27]

Despite favourable outcomes in large-scale randomized controlled trials,[10] recent reports have suggested that ICDs may be significantly underused—only 16% of patients eligible for primary prevention of ICD received it in a population-based study in Canada,[28] 10.8% in Japanese cohort study[29] and 10% in a most recent Swedish HF registry.[30] The prognosis of HF has also drastically improved over the last two decades, and the rates of SCD declined significantly owing to the implementation of GDMT in HFrEF (i.e. ACEIs or ARBs, beta-blockers and MRAs).[31] These therapies may possibly reduce the need for an ICD. Although SCD still contributes to a relevant proportion of deaths in this population, accurate risk stratification for SCD and the benefit–risk ratio of primary prevention ICD is often questioned.[30] In our study, Hb level at discharge affected the mode of death in HF patients. Furthermore, improved SPRM performance in our study with the addition of Hb levels made it possible to stratify patients at a higher proportional risk for SCD more accurately and might improve the appropriate use of this effective but expensive therapy. In addition, information on the mode of death will assist in the design of future HF clinical trials, where the tested medications or devices could be specifically targeted at reducing SCD (or PFD).[9,32]

In our cohort, patients with severe anaemia were older, had a lower BMI and eGFR and had a greater degree of NYHA functional Class III or IV. These factors are considered in a recent study to reflect non-use/suboptimal dosing according to GDMTs,[33] and indeed, the prescription rate of GDMTs was low in these patients compared with patients with high Hb levels. Furthermore, higher observed all-cause mortality and a lower observed proportion of SCD over non-SCD were noted in this group. We anticipate that the ideal ICD candidate will have a disproportionately increased SCD risk, as well as a low predicted all-cause mortality. In the present study, patients with high Hb levels meet these criteria; however, the ICD/CRTD implantation rate was the lowest in this group. We speculate this phenomenon due to the risk of SCD in this particular group might have been underappreciated. We believe that the prediction of the proportional SCD risk by the original SPRM or the modified model can support clinicians in their decision-making regarding ICD/CRTD implantation and, thereby, contribute to addressing this life-threatening event.

Though HF is a complex clinical syndrome, a single biomarker might not reflect all its characteristics.[13] Thus, a combined approach is required for accurate clinical decision-making. Furthermore, the SPRM was constructed with the use of data from the Prospective Randomized Amlodipine Survival Evaluation (PRAISE) and several other cohorts from the early 1990s to the early 2000s.[13] Thus, we hypothesized that several modifications may be required to adjust for the low incidence of SCD in modern HF patients.[34] The above may be particularly pertinent in patients with HFpEF because limited data are available among this patient population. Our study showed that adding the Hb level to SPRM improves SCD prediction in patients with HFpEF, although the discrimination was modest. Therefore, further study is needed to improve the accuracy of SCD prediction.

There are several limitations to the present study. First, we did not have the data to assess the effect of changes in the Hb level after discharge on outcomes. We also did not obtain information about the aetiology of anaemia. Second, the present cohort was recruited using broad inclusion criteria. Therefore, the study cohort had a high prevalence of co-morbid conditions, and other measured and unmeasured factors might have affected our findings. Third, the number of clinical events (SCD) was limited; therefore, our modified model was not validated in a separate data set, and further evaluation using larger HF cohorts is warranted. Moreover, this registry was geographically limited to the metropolitan Tokyo area, and the results might not be applicable to other countries or even other areas in Japan, particularly rural areas. However, patient characteristics and demographics in our cohort were similar to those in the ATTEND registry, which included the entire Japanese population and is thus suggested to be representative of the general population of acute HF patients, with the adjudication of clinical outcomes, including SCD. Finally, the present study included only patients who could be followed up and whose data for the mode of death were obtained, which might have led to substantial selection bias. Additionally, the modes of death might have been misclassified, with potential resulting bias.

Conclusions

The Hb level at discharge provides information about both the absolute and proportional risks for each mode of death in acute HF patients, and the addition of Hb level to the classic SCD prediction proportional risk model improved its performance by identifying more non-SCD cases. Future risk models should consider addition of the Hb level as a covariate to meet this high performance.

Conflict of interest

S.K. received an unrestricted research grant for the Department of Cardiology, Keio University School of Medicine, from Bayer Pharmaceutical Co., Ltd., Daiichi Sankyo Co., Ltd., and Novartis Pharma Co., Ltd. Y.S. is affiliated with an endowed department by Nippon Shinyaku Co., Ltd., Medtronic Japan Co., Ltd., and BIOTRONIK JAPAN Inc., and received research grants from the SECOM Science and Technology Foundation and the Uehara Memorial Foundation and honoraria from Otsuka Pharmaceuticals Co., Ltd., and Ono Pharmaceuticals Co., Ltd. W.C.L. is a member of the Steering Committee; Cardiac Dimensions, Respicardia and Clinical Endpoint Committee: Abbott, Siemens, Beckman Coulter and EBR Systems. He is a consultant to Medtronic and Impulse Dynamics. Other authors have no conflicts of interest to disclose. There are no patents, products in development or marketed products to declare. Seattle Proportional Risk Model copyright is owned by the University of Washington CoMotion.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. List of adjusting variables in the Cox proportional hazard model to estimate adjusted HR for all-cause death according to Hb level at discharge.

Table S2. List of adjusting variable in the Cox proportional hazard model to estimate adjusted HR for each mode of death according to Hb level at discharge.

Table S3. List of adjusting variable in the Cox proportional hazard model to estimate adjusted HR for all-cause death according to according to the presence of anaemia and CKD.

Table S4. List of adjusting variable in the Cox proportional hazard model to estimate adjusted HR for each mode of death according to the presence of anaemia and CKD.

Figure S1. Study population.

Abbreviations: WET-HF, West Tokyo Heart Failure.

Figure S2. Distribution of Hb levels.

Figure S3. Risks of each mode of death according to Hb level at discharge among HFrEF (A and B), and HFpEF (C and D) patients.

(A and C) Absolute risk of each mode of death according to Hb level at discharge. The numbers shown above the coloured bars indicate the absolute number of cases of each mode of death.

(B and D) Proportional risk of each mode of death according to Hb level at discharge. The numbers within the stacked bars indicate the percentage of each mode of death among all deaths according to Hb level at discharge.

Figure S4. AUC and calibration plot for the original SPRM and the modified model among all non-survivors with HFrEF (A and B) and those with HFpEF (C and D).

(A and C) AUC for the original SPRM- or modified model-predicted proportional risk of SCD.

(B and D) Calibration plot for the original SPRM and modified model. The original SPRM- or modified model-predicted proportional risk of SCD, divided into deciles, was plotted against the observed proportion of SCD. The line indicates the ideal calibration line.

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