IJC Heart & Vasculature 34 (2021) 100762

Contents lists available at ScienceDirect

IJC Heart & Vasculature

journal homepage: www.journals.elsevier.com/ijc-heart-and-vasculature

Risk prediction for new-onset atrial fibrillation using the Minnesota code electrocardiography classification system

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ARTICLE INFO

Article history:
Received 31 January 2021
Received in revised form 6 March 2021
Accepted 14 March 2021

Keywords:
Atrial fibrillation
Epidemiology
Risk factors
Risk score
Minnesota code

ABSTRACT

Background: Few risk models are available to predict future onset of atrial fibrillation (AF) in workers. We aimed to develop risk prediction models for new-onset AF, using annual health checkup (HC) data with electrocardiogram findings.

Methods and Results: We retrospectively included 56,288 factory or office workers (mean age = 51.5 years, 33.0% women) who underwent a HC at a medical center and fulfilled the following criteria; age ≥ 40 years, no history of AF, and **greater than 1** annual follow-up HC in 2013–2016. Using Cox models with the Akaike information criterion, we developed and compared prediction models for new-onset AF with and without the Minnesota code information. We externally validated the discrimination accuracy of the models in a general Japanese population cohort, the Hisayama cohort. During the median 3.0-year follow-up, 209 (0.37%) workers developed AF. Age, sex, waist circumference, blood pressure, LDL cholesterol, and γ-GTP were associated with new-onset of AF. Using the Minnesota code information, the AUC significantly improved from 0.82 to 0.84 in the derivation cohort and numerically improved from 0.78 to 0.79 in the validation cohort, and from 0.77 to 0.79 in the Hisayama cohort. The NRI and IDI significantly improved in all and male subjects in both the derivation and validation cohorts, and in female subjects in both the validation and the Hisayama cohorts.

Conclusions: We developed useful risk model with Minnesota code information for predicting new-onset AF from large worker population validated in the original and external cohorts, although study interpretation is limited by small improvement of AUC.

1. Introduction

Atrial fibrillation (AF) is one of the most common types of arrhythmias, affecting 33.5 million people worldwide in 2010 [1], and contributes to significant mortality, morbidity, and impaired quality of life. The number of patients with AF has been increasing worldwide, and the prevalence and incidence of AF increases with aging of the society. Therefore, it is important to effectively predict new-onset AF [2]. In Japan, under the Industrial Safety and Health Act, employees are obliged to undergo a general health checkup (HC) at least once a year, including physical examination, laboratory tests, chest X-ray, and electrocardiogram (ECG), which provides a unique opportunity to assess the prevalence, incidence, and risk factors for the development of AF. For the prediction of AF, previous studies proposed several risk models incorporating ECG [3–9]. However, most risk models employed only a part of ECG findings, such as the P wave [3–6,9], PR intervals [7,8], QT intervals [4], and left ventricular hypertrophy findings [4,7,8], resulting in incomprehensive evaluation and misclassification of the risk with over- or underestimation. The Minnesota code ECG classification system was developed to objectively confirm ECG findings [10]. In the present study, we thus aimed to develop a risk

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https://doi.org/10.1016/j.ijcha.2021.100762
2352-9067/

prediction model for new-onset AF, using the Minnesota code ECG classification system and HC data.

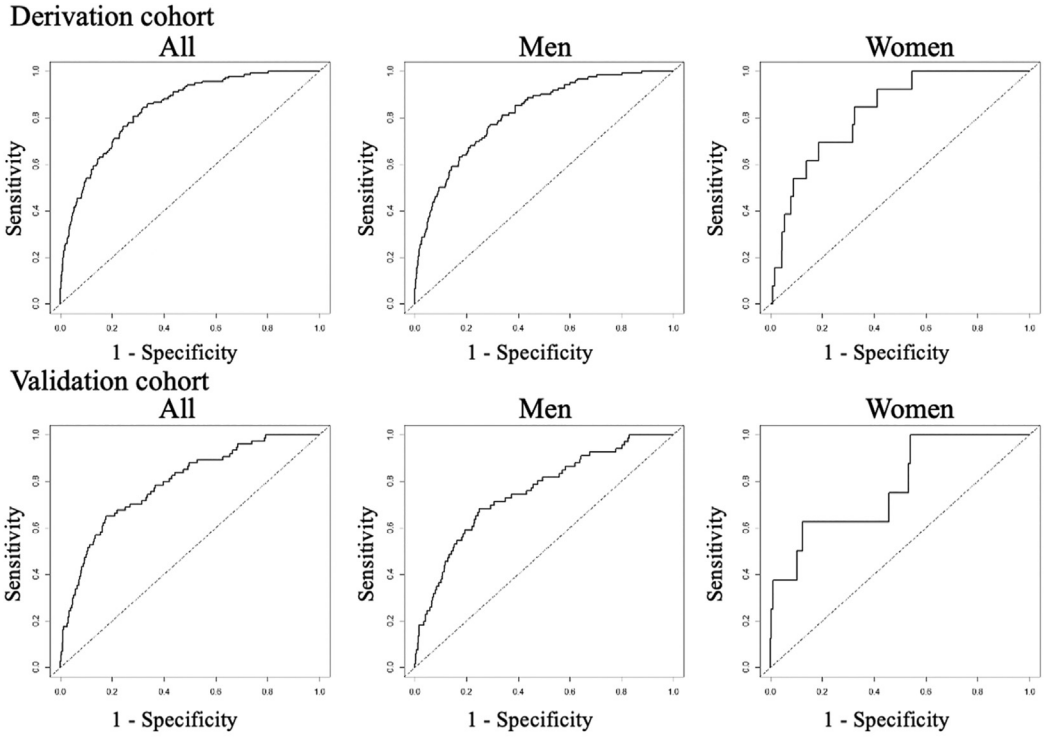
2. Methods

2.1. Study setting and subjects

We used the database of a HC organization (Morinomiyako Occupational Health Center) in Miyagi prefecture, Japan, with over 150,000 factory or office workers in 7,000 companies. After the review of 96,957 HC records in 2013. After excluding the subjects without any HC records from 2013 to 2016 (N = 20,299), those with a prior history of AF (N = 398), and those aged under 40 years (N = 19,972), we finally included 56,288 participants in the present study (**Supplemental** Fig. 1). This research protocol was approved by Ethics Review Committee of the Tohoku University Graduate School of Medicine (approval number 2017–1-555). Written informed consent was obtained from all participants regarding the secondary use of the data at the time of the health screening visit. Opt-out was not possible because the data were obtained after full anonymization by the HC organization (Morinomiyako Occupational Health Center).

2.2. Study measurements

We collected the following variables from the records; height, body weight, waist circumference, blood pressure (BP), hemoglobin, red blood cell (RBC) count, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglyceride, aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyl transpeptidase (γ-GTP), fasting blood sugar level, HbA1c, and ECG. Body weight was measured after removing excess clothing using a digital weight scale (BWB-800, Tanita, Tokyo, Japan). Waist circumference was measured at the level of the umbilicus in a standing position using a tape measure after normal expiration. If the umbilical level was displaced downward due to the accumulation of abdominal fat, waist circumference was measured at the midpoint between the superior border of the iliac crest and the inferior margin of the twelfth rib. BP was measured at the upper arm twice after at least 5 min rest with the participant seated using an automated BP measurement device (HBP-300,



cohort	subjects	new AF	AUC	(95%CI)
Derivation cohort	all (n=37,526)	135	0.84	(0.81-0.87)
	men (n=25,131)	122	0.82	(0.78-0.85)
	women (n=12,395)	13	0.83	(0.73-0.92)
Validation cohort	all (n=18,762)	74	0.79	(0.74-0.84)
	men (n=12,609)	66	0.75	(0.69-0.81)
	women (n=6,153)	8	0.78	(0.61-0.95)
Hisayama cohort	all (n=2,705)	63	0.79	(0.74-0.83)
	men (n=1,115)	39	0.72	(0.64-0.79)
	women (n=1,590)	24	0.83	(0.76-0.89)

AUC, area under the curve; CI, confidence interval

Fig. 1. ROC (receiver operating characteristic) curves for each prediction models in overall, men, and women.

Omron, Kyoto, Japan). If the result of the first measurement was more than 130 mmHg in systolic or more than 85 mmHg in diastolic BP, a second measurement was taken. We used the first measurement of BP. A standard 12-lead ECG was recorded at a paper speed of 25 mm per second in a supine position using CardioMax FCP-8221 (FUKUDA DENSHI, Tokyo, Japan), which automatically evaluated the electrical waveform and reported the Minnesota codes. Blood test biochemistry was determined using AU5800 or AU680 (Beckman Coulter Inc. CA, USA) except for blood sugar, which was determined using BM-9130 (NIHON DENSHI, Tokyo, Japan), while blood cell counts were determined using XN-1000 or XN-9100 (Sysmex, Hyogo, Japan).

2.3. Outcome

The study outcome was new-onset AF. All ECG findings were reviewed, and the diagnosis of AF was confirmed by cardiologists.

2.4. Statistical analysis

All continuous variables are expressed as mean ± standard deviation (SD). Categorical variables are expressed as numbers (percentage of the total). The baseline characteristics of the subjects were compared using an unpaired *t*-test or χ^2-test, as appropriate. Age, waist circumference, BMI, systolic and diastolic BP, hemoglobin, RBC, LDL cholesterol, HDL cholesterol, triglyceride, AST, ALT, γ-GTP, and Minnesota codes were potential risk factors in the model. We log-transformed γ-GTP because of the skewness of its distribution. When performing the risk assessment of AF, we employed the Minnesota code using the first and second categories of the coding system.

We randomly divided the overall cohort into the derivation (N = 37,562; age, 51.5 years; 33.0% women) and validation cohorts (N = 18,762; age, 51.6 years; 32.8% women). In the derivation cohort, the risk factors were assessed using Cox regression. The proportional hazard assumption for each factor in the Cox model was confirmed using the linearity of the additive Cox proportional hazard model [11] using scaled Schoenfeld residuals. Model fitness was assessed using the Akaike information criterion (AIC) [12]. We assigned each point to the selected variables, corresponding to the number of coefficients of the Cox regression. The predictive accuracy of the models was assessed by the area under the curve (AUC) of the receiver operating characteristic (ROC) in all men and women. We further examined the improvement of reclassification of the model, using the net reclassification index (NRI) and integrated discrimination improvement (IDI) by comparing the prediction model with and without the Minnesota code [13]. We analyzed the incidence rates of AF in 1000 person-years stratified by age and sex, and stratified by score groups of the risk model in each cohort. For external validation, to evaluate whether the model developed by workers can apply to the general population, we further applied the model to a population-based prospective cohort study, the Hisayama study [14]. The Hisayama cohort is a representative sample of the typical Japanese population from the town of Hisayama, Japan; the study has been performed since 1961 and is still ongoing [14]. Of the 3,328 subjects who attended the town health examination in 2002, 2,705 subjects were included in this cohort, excluding the following subjects; those who did not consent to participate, those with a prior history of AF, those with missing follow-up data, and those with no data on ECG or other factors included in our model. The baseline characteristics of the 2,705 subjects in the Hisayama cohort are shown in Supplemental Table 1. ECG was repeated at the health examinations in 2007 and/or in 2012 to determine whether a participant experienced a new-onset AF. A 2-sided P value of < 0.05 was considered significant. Statistical analyses were performed using R software ver. 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria) [15] and SAS 9.4 (SAS Institute, Cary, NC, the United States).

3. Results

3.1. Baseline characteristics

The baseline characteristics of the 56,288 participants are shown in Table 1. The mean age was 51.5 years and women accounted for 33.0% of the study population. Mean systolic and diastolic BP were 130.2 mmHg and 80.7 mmHg, respectively. The mean waist circumference was 83.3 cm and the mean LDL cholesterol and fasting blood sugar levels were 124.8 mg/dl and 96.0 mg/dl, respectively. The rates of medication use for hypertension, diabetes, and dyslipidemia were 16.3%, 4.6%, and 4.2%, respectively. The proportion of current smokers was 39.7%, and excessive alcohol intake was reported in 3.5%. Between the derivation and validation cohorts, baseline characteristics did not differ significantly or clinically, except diastolic BP.

3.2. Risk factors for AF

During the 3-year follow-up checkups, 135 subjects (0.36%) developed AF in the derivation cohort. In the multivariable Cox model, age (hazard ratio [HR], 1.11; 95% confidence interval [CI], 1.08–1.13; p < 0.01), male sex (HR, 2.13; 95% CI, 1.17–3.87; p = 0.01), waist circumference (HR, 1.05; 95% CI, 1.03–1.07; p < 0.01), diastolic BP (HR, 1.02; 95% CI, 1.00–1.03; p = 0.04), logγ-GTP (HR, 1.49; 95% CI, 1.15–1.92; p < 0.01) and the following Minnesota codes were associated with an increased risk of AF; Minnesota code 2–3 (HR, 4.74; 95% CI, 1.71–13.12; p < 0.01), 2–4 (HR, 21.84; 95% CI, 2.97–160.41; p < 0.01), 3–1 (HR, 1.99; 95% CI, 1.30–3.05; p < 0.01), 4–3 (HR, 2.21; 95% CI, 0.89–5.52; p = 0.09), 5–3 (HR, 2.04; 95% CI, 1.02–4.08; p = 0.04), 8–1 (HR, 3.00; 95% CI, 1.87–4.82; p < 0.01), 8–2 (HR, 10.35; 95% CI, 1.92–55.84; p = 0.01), 8–8 (HR, 2.65; 95% CI, 1.28–5.48; p = 0.01), and 9–3 (HR, 2.44; 95% CI, 0.89–6.72; p = 0.08). In contrast, LDL cholesterol (HR, 0.99; 95% CI, 0.98–1.00; p < 0.01) and 9–4 (HR, 0.74; 95% CI, 0.52–1.05; p = 0.09) were associated with a decreased risk of AF (Table 2). Of note, there was no significant association between new-onset AF and taking cholesterol-lowering medication (p = 0.75) (**Supplemental** Fig. 2).

3.3. Risk model and prediction accuracy

The AUC of the risk model without the Minnesota code, comprising age, sex, waist circumference, diastolic BP, LDL cholesterol, and logγ-GTP was 0.82 (men: 0.79, women: 0.80) in the derivation cohort, 0.78 (men: 0.73, women: 0.80) in the validation cohort, and 0.77 (men: 0.72, women: 0.80) in the Hisayama cohort. The AUC of the risk model including Minnesota codes was 0.84 (men: 0.82, women: 0.83) in the derivation cohort, 0.79 (men: 0.75, women: 0.78) in the validation cohort, and 0.79 (men: 0.72, women: 0.83) in the Hisayama cohort (Supplemental Table 2). The final model was as follows; 0.103×(age) + 0.755×(male sex) + 0.046×(waist circumference) + 0.016×(diastolic BP)+(-0.010)×(LDL cholesterol) + 0.397×(log [γ-GTP]) + 1.557×(Minnesota code; MC2-3) + 3.084×(MC2-4) + 0.689×(MC3-1) + 0.794×(MC4-3) + 0.714×(MC5-3) + 1.099×(MC8-1) + 2.337×(MC8-2) + 0.973×(MC8-8) + 0.892×(MC9-3)+(-0.298)×(MC9-4). The model including the Minnesota code variables had a significantly higher predictive accuracy for all and male subjects in the derivation cohort, as compared with the model without them. When conducting a 5-fold cross validation, average AUC with the Minnesota code was numerically higher (0.81) than that without the code (0.80). The

Table 1
Baseline characteristics of the office and factory workers in the derivation and validation cohorts.

Variables	Over all (N = 56,288)	Derivation cohort (N = 37,526)	Validation cohort (N = 18,762)	P value
Age (years)	51.5 ± 7.7	51.5 ± 7.7	51.6 ± 7.6	0.07
Women (%)	33.0	33.0	32.8	0.07
Waist circumference (cm)	83.3 ± 9.9	83.3 ± 9.9	83.3 ± 9.9	0.91
BMI (kg/m^2)	23.6 ± 3.7	23.6 ± 3.7	23.6 ± 3.7	0.75
Systolic BP (mmHg)	130.2 ± 18.4	130.2 ± 18.4	130.0 ± 18.5	0.13
Diastolic BP (mmHg)	80.7 ± 12.0	80.8 ± 12.1	80.5 ± 12.0	0.01
LDL cholesterol (mg/dl)	124.8 ± 31.7	124.9 ± 31.7	124.6 ± 31.7	0.27
HDL cholesterol (mg/dl)	64.7 ± 17.8	64.7 ± 17.8	64.7 ± 17.9	0.86
Triglyceride (mg/dl)*	96 (67,145)	97 (67,145)	95 (67,144)	0.10
AST (mg/dl)	24.4 ± 15.9	24.4 ± 15.8	24.4 ± 16.2	0.63
ALT (mg/dl)	25.1 ± 18.9	25.2 ± 19.0	25.1 ± 18.7	0.52
γ-GTP (mg/dl)*	29 (19,50)	29 (19,50)	29 (19,50)	0.31
Fasting blood sugar (mg/dl)	96.1 ± 21.3	96.0 ± 21.1	96.1 ± 21.7	0.38
HbA1c (%)	5.7 ± 0.7	5.7 ± 0.7	5.7 ± 0.7	0.22
Medication				
Hypertension, N (%)	9193 (16.3)	6095 (16.2)	3098 (16.5)	0.40
Diabetes, N (%)	2588 (4.6)	1718 (4.6)	870 (4.6)	0.74
Dyslipidemia, N (%)	2377 (4.2)	1604 (4.3)	773 (4.1)	0.40
Current smoking status, N (%)	22,366 (39.7)	14,962 (39.9)	7404 (39.5)	0.38
Excessive alcohol intake, N (%)	1984 (3.5)	1336 (3.6)	648 (3.5)	0.39

* Median (interquartile range). BMI, body mass index; BP, blood pressure; LDL, low-density lipoprotein; HDL, high-density lipoprotein; AST. Aminotransferase; ALT, alanine aminotransferase; γ-GTP, γ-glutamyl transpeptidase

Table 2
Variables and scores in the prediction models.

Variables	Score	Variables	Score
Age	0.103	Sex, men	0.755
Waist circumference	0.046	Diastolic BP	0.016
LDL cholesterol	−0.010	Log·γ-GTP	0.397
M.C.2–3	1.557	M.C.2–4	3.084
M.C.3–1	0.689	M.C.4–3	0.794
M.C.5–3	0.714	M.C.8–1	1.099
M.C.8–2	2.337	M.C.8–8	0.973
M.C.9–3	0.892	M.C.9–4	−0.298

BP, blood pressure; LDL, low-density lipoprotein; γ-GTP, γ-glutamyl transpeptidase; M.C., Minnesota Code

NRI and IDI showed that reclassification with the addition of the Minnesota codes significantly improved the model in all and male subjects in the derivation and validation cohorts, and in female subjects in the validation and Hisayama cohorts (**Supplemental Table 3**). The ROC curves are shown in Fig. 1. The ROC curves showed that the sensitivity and specificity of the optimal cut-off point were 76.3% (men, 76.2%; women, 69.2%), and 75.7% (men, 71.4%; women, 81.5%) in the derivation cohort, and 67.6% (men, 68.2%; women, 62.5%), and 78.1% (men, 75.0%; women, 87.6%) in the validation cohort.

3.4. Incidence rates of AF

Of 56,288 participants, 209 (0.36%) developed AF in the overall cohort (1.4/1,000 person-years, 1.9 in men, 0.4 in women), of which 188 (90.0%) were men. **Supplemental Figure 3** shows that the incidence rates of AF increased with age and were higher in men than in women across all age categories. Fig. 2 shows the occurrence rates of AF stratified by score groups of the risk model in each cohort. The occurrence rates in all subjects and men increased with higher scores, and women had a steep rise in the high score group compared to men in both cohorts.

4. Discussion

Using data from 56,288 workers, we were able to develop a risk model for predicting the 3-year incidence of new-onset AF, which was externally validated in the Hisayama cohort, which is representative of the general Japanese population. To the best of our knowledge, this model is the first comprehensive and generalizable risk model with Minnesota code and HC data, which can be used in occupational and residential settings.

4.1. Risk factors for developing AF

In the present study, age, sex, waist circumference, BP, LDL cholesterol, and γ-GTP were identified as risk factors for the development of AF. Age, sex, and hypertension were validated risk factors for AF [16]. Obesity is also reportedly associated with AF development [17–19]. Several mechanisms have been described that link obesity to AF development, where left atrial remodeling and ventricular diastolic dysfunction may be a substantial aspect of the association between obesity and AF development [20,21]. Obesity could cause AF through increased oxidative stress, inflammation [22,23], and sleep apnea [24,25]. Some studies reported that higher levels of LDL cholesterol were associated with a lower incidence of AF [24–27]. Indeed, several mechanisms of AF development have been described in relation to cholesterol. First, cholesterol is known to affect the composition of cell membranes and cellular electrophysiological properties [28–30]. Second, subclinical hyperthyroidism is associated with low cholesterol levels and increased incidence of AF, which may be confounding factors or reflections of the hidden link between cholesterol and AF [27,31]. Third, the link between cholesterol and AF is accelerated by inflammation. Inflammation is associated with the initiation and perpetuation of AF [32]. LDL cholesterol levels are known to be lower in inflammation due to the action of inflammatory cytokines [33]. Thus, lower levels of cholesterol could reflect the level of inflammation. In the present study, cholesterol-lowering medication showed no significant relationship between LDL cholesterol and the incidence of AF, a consistent finding with the previous studies [34,35]. It is uncertain whether LDL cholesterol could be protective against developing AF or whether lowering LDL cholesterol levels increases the risk of AF. However, it is also important to note that statins exert anti-inflammatory effects that may decrease the incidence of AF [36].

Recent clinical studies have shown that elevated circulating levels of γ-GTP increase the incidence of AF [37–39]. In the present study, we identified γ-GTP as a model component in both sexes. γ-GTP is known as an indicator of alcohol consumption but is inde-

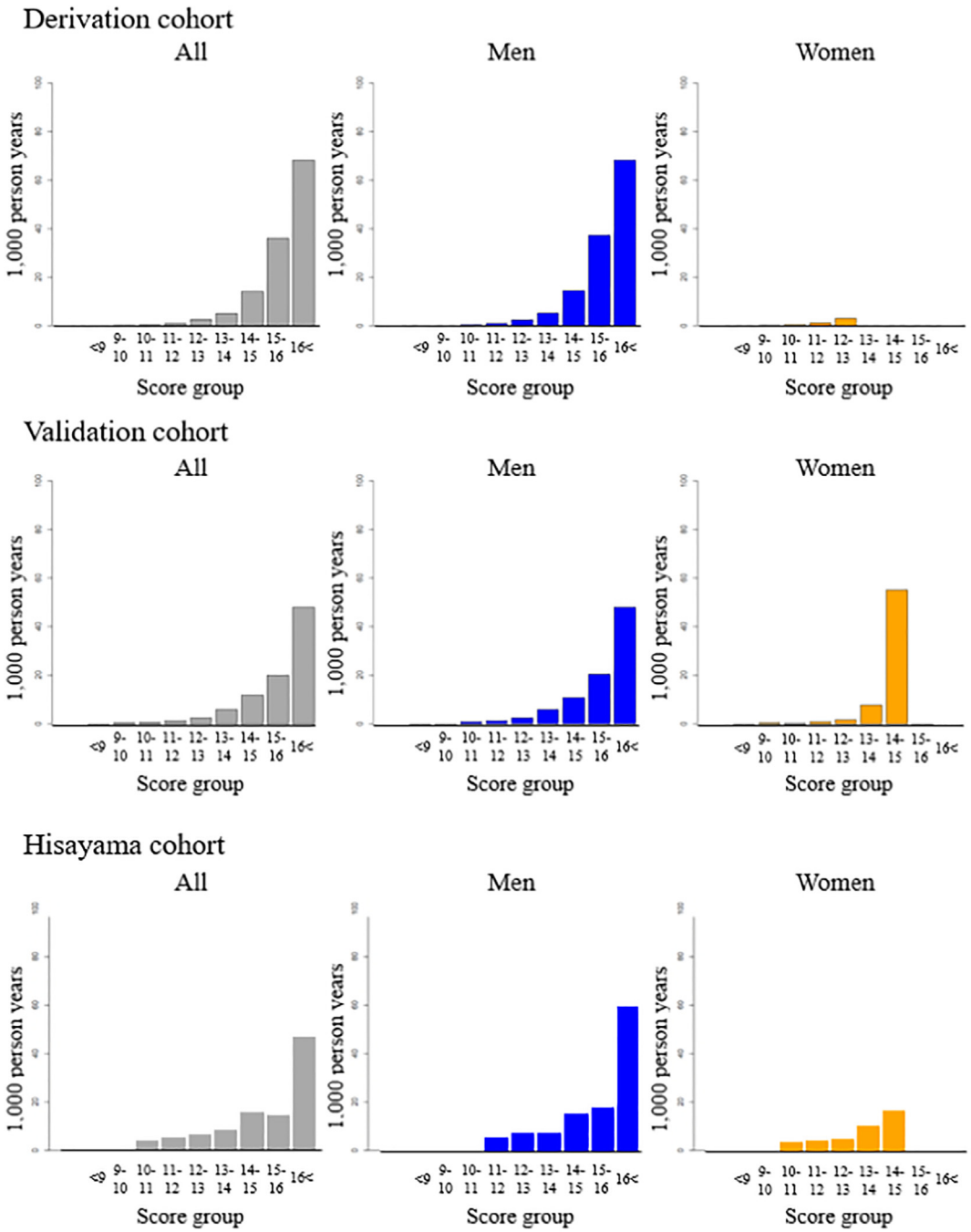


Fig. 2. Event rates stratified by the score groups in the derivation, validation, and Hisayama cohorts.

pendently associated with the incidence of AF [37–39]. The pathophysiological mechanism of the association between γ-GTP and the incidence of AF may be explained by the fact that γ-GTP is an indicator of metabolic abnormalities, inflammation, and oxidative stress [40,41].

4.2. Predictive ability of the risk models

In the previous studies, the predictive ability of the risk models developed from 3 large cohorts in the United States was 0.765 (0.748–0.781) as the C-statistic in the derivation cohort and 0.664 (0.632–0.697) and 0.705 (0.663–0.747) in the age, gene and environment—Reykjavik study [42] and the Rotterdam Study [43] in the external validation cohort, respectively. The Suita Study in Japan reported that the C-statistic for internal validation of the risk model was 0.75 (0.72–0.77) [44]. The Hamamatsu Study in Japan reported that the C-statistic was 0.78 (0.76–0.80) in the derivation cohort, and the validation of the C-statistic in bootstrap sampling was 0.79 (0.78–0.80) [8]. The AUC of our model was 0.79 (0.74–0.84) in the validation cohorts for internal validation and 0.79 (0.74–0.83) in the Hisayama cohort for external validation. The predictive ability of the model was comparable to that of other models.

4.3. Utility of the models

In Japan, approximately 19 million Japanese individuals in the community and 56 million workers undergo annual HCs, including

ECG, following the law. Our risk model can be directly implemented without any additional cost to HC and can stratify the risk of developing AF. Therefore, it is theoretically possible to apply the present risk model widely in Japan. The risk model may help us prevent new-onset AF by identifying individuals at high risk and by modifying their risk through appropriate management of their risk factors (e.g., hypertension, obesity, sleep-disordered breathing, smoking, and alcohol consumption), health guidance, and education [45]. Early detection of AF could be possible by using self-palpation [46], ECG, Holter ECG monitoring, and wearable healthcare devices [47,48]. Given the rapid aging of the society worldwide, the number of older workers aged 55 or above is estimated to increase from 270 million in 2020 to 750 million in 2030, which will correspond to more than 18% of the total global labor force [49]. To sustain working safety and health for older workers, the prediction of AF is important in the global labor force.

4.4. Strengths and limitations

One of the most important strengths of the present study is the development of a risk model from a large worker population using the Minnesota code that can comprehensively and objectively assess ECG. Another strength is the high predictive accuracy of the risk model, which was externally validated in the Hisayama cohort, a representative sample of the typical Japanese population and has a high potential for social implementation.

The present study has some limitations. First, paroxysmal AF might have been overlooked because HC was conducted only once a year. Second, due to the limited information about past medical history, we were unable to include coronary artery disease, heart failure, valvular disease, or thyroid disease, which are reportedly risk factors for AF, into the derivation of the risk models. Third, the number of women who developed new-onset AF was small, and thus it is possible that we were unable to evaluate the risk model in women sufficiently. Forth, the population in the present study comprised all workers, which might have caused a healthy worker bias; they were able to be hired into the workforce (Healthy Hire Effect) and continue to work for at least 2 years (Healthy Worker Survivor Effect). Furthermore, they could also get access to healthcare for routine disease screening and physical exercise, which is considered a beneficial effect of work (Advantage of Working) [50].

5. Conclusions

We developed a risk model for predicting 3-year incidence of new-onset AF using the Minnesota code and HC data with externally validated in the Hisayama cohort from a representative population study in Japan, although study interpretation is limited by small improvement of AUC. Further studies may be needed to improve risk stratifications in HC.

Acknowledgments

The authors are deeply grateful to all participants and Mr. Shigeo Kunii at Morinomiyako Occupational Center for assembling the database.

Funding

This study was supported in part by the Agency for Medical Research and Development, Tokyo, Japan (grant number 19ek0210083h0003).

Disclosures

The authors declare that there is no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2021.100762.

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