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New computer model for prediction of individual 10-year mortality on the basis of conventional atherosclerotic risk factors

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ABSTRACT

Background: Large cohort studies have revealed that subjects with atherosclerotic risk factors have high mortality. However, there has been no method to predict individual mortality based on these risk factors. Accordingly, we developed a computer model predicting the 10-year mortality of an individual with atherosclerotic risk factors.
Methods: We enrolled two different cohorts in Japan. One was from Tanushimaru-town and the other was from Uku-town. Residents over the age of 40 underwent baseline examinations and were followed-up for ten years. 1851 Subjects in Tanushimaru-town were randomly divided into 1486 training samples and 365 test samples. We applied supervised statistical pattern recognition (SSPR) techniques to develop, using the training samples, a computer model to predict the 10-year mortality of an individual based on 6 conventional risk factors. The test samples were then used to evaluate the predictive accuracy.
Results: There were 49 deaths and 316 survivors in the test samples in Tanushimaru-town. The correctly simulated number of deaths and survival was 36 and 250, respectively. The predictive accuracy of death was 73.5% (36/49) and that of survival was 79.1% (250/316) with *c*-statistics of 0.827. In order to verify our model, we predicted death and survival for the other test samples (Uku-town, $n = 170$). The predictive accuracy of death was 72.9% (35/48) and that of survival was 76.2% (93/122) with *c*-statistics of 0.848.
Conclusions: This is the first computer model to use SSPR methods to estimate individual 10-year mortality based on conventional risk factors with high accuracy.

1. Introduction

Identification of risk factors contributing to cardiovascular disease and death is one of the major accomplishments of 20th century epidemiology. Various statistical models have been utilized over the decades to investigate atherosclerotic risk factors [1–7], and they have identified risk factors such as old age, male gender, hypertension, dyslipidemia, smoking, diabetes mellitus, family history of coronary artery disease, sedentary life style, and so on. Thus persons with these risk factors have high mortality. However, there has been no method available to predict individual mortality on the basis of these risk factors. Suppose a 60-year-old male smoker has systolic blood pressure of 160 mmHg, total cholesterol of 260 mg and hemoglobin A1c of 6.0%. Until now it has not been possible to predict his survival status at 10 years because no computer model has been developed for this purpose.

Accordingly, we used supervised statistical pattern recognition (SSPR) [8] to develop a new computer model for prediction of individual 10-year mortality based on six important conventional atherosclerotic risk factors (age, sex, systolic blood pressure, hemoglobin A1c, total cholesterol, and smoking). SSPR is an established method applied to resolve various issues, including document classification, speech recognition, biometric recognition remote sensing and statistical method [8]. We enrolled two population-based cohorts and followed the residents for 10 years. We divided one cohort into training samples and test samples. From the training samples, we developed a computer model for the

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prediction of individual 10-year mortality on the basis of the six important conventional risk factors mentioned above. We then used the computer model with the test samples to evaluate the accuracy of our predicted individual 10-year mortality. To verify our model, we predicted individual 10-year mortality in the test samples of the second cohort and compared the results with actual mortality.

2. Methods

2.1. Data collection

We enrolled two different cohorts from the south-west part of Japan. One was from Tanushimaru-town (the cohort of Seven Countries Study in Japan) [9] and the other was from Uku-town. These two cohorts are 200 km apart and both are located in Kyushu Island. As reported previously, the demographic backgrounds of the subjects in the two cohorts are similar to those of the general Japanese population [10]. Residents of the two cohorts aged over 40 years underwent baseline examination and were followed-up every year for ten years. We invited residents over 40 years in Tanushimaru-town ($n = 3470$) and Uku-town ($n = 2113$) to participate in the present study. We enrolled only subjects who gave informed consent. A general medical history including smoking, alcohol intake, and current medication was taken. The body mass index (BMI) was calculated from measurements of height and body weight. Blood pressure (BP) was measured twice with participants in the supine position. The second BP was taken after five deep breaths and systolic and fifth-phase diastolic pressures were used for analysis. Blood samples obtained from antecubital vein in the morning in a fasting state were centrifuged and frozen. From these, we measured fasting plasma glucose (FPG), serum hemoglobin A1c [HbA1c (NGSP)], lipid profiles (total cholesterol, LDL-cholesterol, HDL-cholesterol, and triglycerides), creatinine, uric acid, albumin, and white blood cell counts. Survival or death was determined based on a review of obituaries, medical records, death certificates, hospital charts, and interviews with primary care physicians, families of the deceased and other witnesses. Of the initially enrolled 1920 subjects in Tanushimaru-town, 62 subjects were lost to follow-up and were excluded from the analysis. The remaining 1858 subjects (follow-up rate = 97%) were randomly divided into 1486 training samples and 372 test samples (Table 1). Of 372 test samples, 7 test samples were excluded because of missing data, and 365 test samples were used. Of the initially enrolled 866 subjects in Uku-town, 833 subjects underwent complete follow-up (follow-up rate = 96%). We used 122 survivors and 48 deaths as test samples (Table 1). The remaining 663 samples were survivors before the elapse of 10 years or were missing data. All participants gave informed consent. This study was approved by the Ethics Committee of Kurume University.

Table 1
Baseline characteristics of subjects in 1999 in the training and test samples in Tanushimaru-town, and test sample in Uku-town.

Characteristics	Tanushimaru-town		Uku-town
	Training samples	Test samples	Test samples
Number (no. of deaths)	1486 (204)	365 (49)	170 (48)
Age (yr)	63 ± 11	62 ± 11	64 ± 10
Sex (% male)	625 (42)	146 (40)	67 (39)
BMI (kg/m^2)	23.1 ± 3.2	22.9 ± 3.0	23.7 ± 3.5
Waist (cm)	77.3 ± 9.3	76.4 ± 9.3	81.5 ± 9.7
Systolic BP (mmHg)	134 ± 21	133 ± 21	135 ± 20
Diastolic BP (mmHg)	79 ± 12	78 ± 11	78 ± 10
FPG (mg/dl)	97.8 ± 20.1	96.6 ± 16.3	97.0 ± 17.2
HbA1c (%)	5.6 ± 0.8	5.5 ± 0.7	5.5 ± 0.5
BUN (mg/dl)	16.4 ± 4.2	15.9 ± 4.0	17.3 ± 5.0
Creatinine (mg/dl)	0.86 ± 0.20	0.84 ± 0.17	0.91 ± 0.21
Uric acid (mg/dl)	5.0 ± 1.4	4.9 ± 1.4	5.1 ± 1.5
Total cholesterol (mg/dl)	200 ± 35	199 ± 32	202 ± 33
HDL-cholesterol (mg/dl)	55.9 ± 14.1	54.9 ± 13.1	59.1 ± 14.3
Triglycerides (mg/dl)[a]	97.8	98.4	87.6
Range	28–1284	30–963	37–777
LDL-cholesterol (mg/dl)	122.1 ± 31.2	121.8 ± 29.1	121.0 ± 28.6
Smoking (%yes)	255 (17)	57 (16)	19 (11)
Alcohol (%yes)	333 (22)	28 (21)	24 (14)
Medication			
Hypertension (%yes)	296 (20)	68 (19)	57 (33)
Hyperlipidemia (%yes)	74 (5)	13 (4)	12 (7)
Diabetes (%yes)	50 (3)	8 (2)	6 (3)

Data are mean ± standard deviation, geometric mean, range, or percent.
Abbreviation: BMI; body mass index, BP; blood pressure, FPG; fasting plasma glucose, BUN; blood urea nitrogen, LDL; low-density lipoprotein, HDL; high-density lipoprotein.
[a] These variables were represented as original scale after analysis by log (natural) transformed values.

2.2. Statistical analysis

2.2.1. Supervised learning in statistical pattern recognition method

A predictive model of 10-year death or survival was developed by the SSPR [8] method based on six major conventional risk factors (age, sex, systolic BP, HbA1c, total cholesterol, and smoking). Training samples were used to develop the model, and test samples were used to evaluate the predictive performance of the model (Fig. 1).

The SSPR method aims to provide a reasonable answer to all inputs. We used SSPR to construct a prognostic model, consisting of six conventional risk factors, with a minimum distance classifier [11]. The minimum distance classifier assigns a blinded sample $x = (x_1, x_2, \ldots, x_d)$ to survival if $f_A(x) < f_B(x)$, and to death if $f_A(x) < f_B(x)$. A and B mean survival and death, respectively. The function $f_i(x)$ is given by:

$$f_i(x) = \sum_{j=1}^{d} \frac{\left(x_j - \hat{\mu}_{ij}\right)^2}{2\hat{\sigma}_j^2}, \quad i = A, B$$

$\hat{\mu}_{ij}$ is the jth sample mean of group i and $\hat{\sigma}_j^2$ is the jth common variance:

$$\hat{\mu}_{ij} = \frac{1}{n_i} \sum_{k=1}^{n_i} \hat{x}_{ij}^k$$

$$\hat{\sigma}_j^2 = 0.5\hat{\sigma}_{Aj}^2 + 0.5\hat{\sigma}_{Bj}^2$$

where n_i is the number of training samples of group i, $\hat{x}_{ij}^k$ is the jth factor of the kth training sample of group i, $\hat{\sigma}_{ij}^2$ is the jth sample variance of group i:

$$\hat{\sigma}_{ij}^2 = \frac{1}{n_i - 1} \sum_{k=1}^{n_i} \left(\hat{x}_{ij}^k - \hat{\mu}_{ij}\right)^2$$

The sample mean and the sample variance are estimated using only the training samples. We used this model to predict survival status and death status in 365 available test samples and compared the results with the actual survival and death in order to calculate predictive accuracy. c-Statistics is the area under the curve created by plotting the fraction of correctly predicted subjects out of the deaths (sensitivity) and the fraction of incorrectly predicted subjects out of the survivors (1-specificity), at various threshold settings.

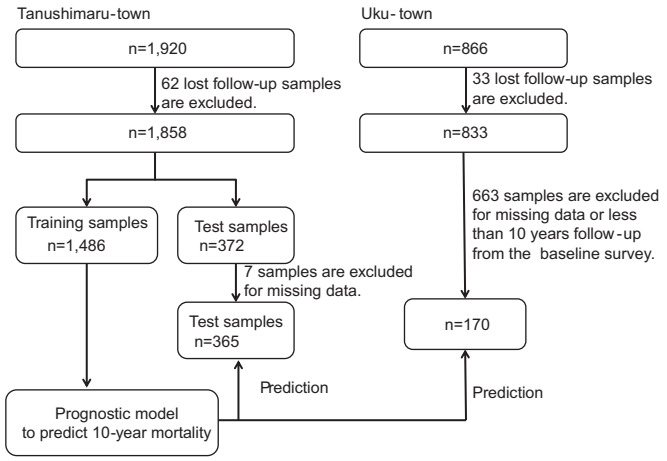

Fig. 1. Participants from Tanushimaru-town were randomly divided into training samples or test samples. The prognostic computer model was developed using only the training samples. In the same cohort, predictive accuracy of the computer model was evaluated using the test sample. The predictive accuracy of the computer model was then verified using the test samples from Uku-town.

In order to verify the model performance, we then applied it to test samples of the second cohort, Uku-town. Similarly, we calculated predictive accuracy and *c*-statistics. Because we decided to adopt 6 major conventional risk factors (age, sex, systolic blood pressure, HbA1c, total cholesterol, and smoking) for computer modeling, we used Cox proportional hazards regression to confirm that these factors really were risk factors in the training samples of Tanushimaru-town (Table 2). In this analysis, sex and smoking habits were used as dummy variables. Statistical significance was defined as $p < 0.05$. All statistical analyses were performed using the SAS system (Release 9.3, SAS Institute, Cary, NC) or R (www.r-project.org).

3. Results

3.1. Backgrounds of the two cohorts and risk factors for death

As shown in Table 1, baseline characteristics of the training samples of Tanushimaru-town, test samples of Tanushimaru-town and test samples of Uku-town were very similar. In the training samples of Tanushimaru-town, there were 204 deaths and 1282 survivors at 10 years. Age, male gender, systolic blood pressure, HbA1c, total cholesterol, and smoking were all significantly ($p < 0.001$) associated with death. Although BMI and waist were significant predictors, they were not so strong compared to the other predictors (Table 2).

Table 2
Regression coefficients from a Cox's proportional hazards model for all-cause death in the training sample in Tanushimaru-town.

Parameters	β	SE	HR (95% C.I.)	p Value
Age (yr)	0.111	0.008	1.118 (1.101–1.135)	<0.001
Male gender	−0.770	0.144	0.463 (0.349–0.614)	<0.001
Systolic BP (mmHg)	0.017	0.003	1.018 (1.011–1.024)	<0.001
HbA1c (%)	0.264	0.067	1.302 (1.142–1.484)	<0.001
Total cholesterol (mmol/l)	−0.011	0.002	0.989 (0.985–0.993)	<0.001
Smoking (%yes)	0.668	0.157	1.950 (1.433–2.653)	<0.001
Alcohol (%yes)	−0.230	0.179	0.795 (0.560–1.127)	0.198
BMI (kg/m^2)	−0.076	0.024	0.927 (0.885–0.971)	0.009
Waist (cm)	0.016	0.007	1.016 (1.002–1.031)	0.030

Abbreviation: β; regression coefficients, SE; standard error, HR; hazard ratio, C.I.: confidence interval, BP; blood pressure, BMI; body mass index.

3.2. New computer model for prediction of individual 10-year mortality

Our new computer model $f(x)$ for predicting 10-year survival and death from 1486 training samples is as follows.

$$\begin{aligned} f(x) &= f_A(x) - f_B(x) \\ &= 0.123978 \times \text{age} - 0.856709 \times \text{gender} + 0.018992 \\ &\quad \times \text{systolic BP} - 0.011564 \times \text{total cholosterol} \\ &\quad + 0.249791 \times \text{HbA1c} + 0.748658 \times \text{smoker} \\ &\quad - 8.871682 \underset{\text{Survival}}{\overset{\text{death}}{\gtrless}} 0 \end{aligned}$$

where male = 1, female = 0, smoker = 1, and non-smoker = 0. The formula assigns a given test sample x to death and survivor when $f(x) > 0$ and $f(x) < 0$, respectively.

3.3. Predictive performance of death and survival in test samples from Tanushimaru-town

There were 316 survivors and 49 deaths in 365 test samples of Tanushimaru-town at 10 years. The number of survivors simulated by our computer model was 250, with 36 deaths. The predictive accuracy was 79.1% (250/316) for survival and 73.5% (36/49) for death, as shown in Fig. 2a. *c*-Statistics for predicting survival and death was 0.827 as shown in Fig. 2b.

3.4. Predictive performance of deaths and survivors in test samples of Uku-town

In the test sample from Uku-town, there were 122 survivors and 48 deaths. The predictive accuracy of survival was 76.2% (93/122) and that of death 72.9% (35/48) as shown in Fig. 3a. *c*-Statistics for predicting survival and death was 0.848 as shown in Fig. 3b.

4. Discussion

This report is the first to present a computer model to predict individual survival and death based on six conventional atherosclerotic risk factors, using the SSPR method. With this model, we were able to predict the survival/death status of an individual subject by putting the actual values of their risk factors into the formula. The predictive value was fairly reasonable, as shown by the *c*-statistics.

With conventional models such as the Framingham score or the QRISK, we are able to estimate individual risk of cardiovascular events but are not able to predict death in the small training sample size [7,12,13]. Accordingly, we adopted the SSPR method in this study to predict individual 10-year mortality. There are several powerful SSPR techniques, like the support vector machine, the neural network, and the quadratic classifier. However, they are not always optimal in terms of predictive performance in test samples [8,12,13]. Generally, the optimal model is selected based on properties of subjects and comparison of performance in plural models. In this study, we developed a simple model that clinicians can easily use by inputting actual values of conventional risk factors. First, we used the training samples from Tanushimaru-town to confirm that the six conventional factors we chose were really risk factors of death in this population. We found by Cox's proportional hazards model that age, sex, systolic BP, HbA1c, and smoking were associated with death in this cohort, which is consistent with many published reports from Western countries. Thus, development of

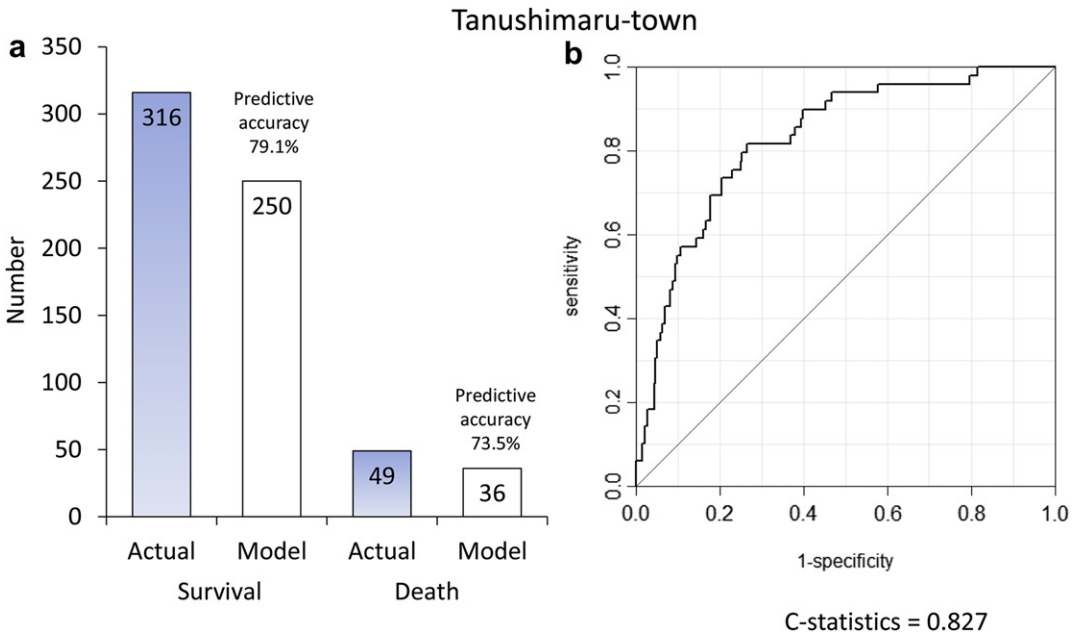

Fig. 2. Left (a): comparison of actual survival or death with predicted actual survival or death, respectively, for the test samples from Tanushimaru-town. Gray bars indicate the actual number of survivors or deaths. Right (b): *c*-statistic for prediction in Tanushimaru-town

a prognostic model based on these conventional risk factors was reasonable. In this population, total cholesterol was inversely associated with death, which may be puzzling to readers in Western countries. However, it has been repeatedly shown in Japan that low cholesterol is associated with risk of death [14–17].

Some discussion is needed with regard to the coefficients in our formula. As described above, the coefficient of total cholesterol was negative. Thus, the coefficient of total cholesterol must be changed to positive when this formula is used in western countries where high cholesterol is definitely associated with risk of death. Although the value of the age coefficient was not very large, it was apparent from the formula that age was the strongest risk factor for death. The predictive accuracy based on age alone was 71.2% for survival and 69.4% for death in the test samples of Tanushimaru-town. Thus, although age was the strongest risk factor in this model, the predictive accuracy of death based on age alone was lower in younger subjects of this cohort (data not shown). In any case, it is well known that old age is the strongest risk factor for death.

We verified the predictive accuracy of our computer model in two ways. First was by *c*-statistics. Second was by applying our model to test samples from a different cohort, Uku-town. In that cohort, the predictive accuracy of survival or death was 76.2% and

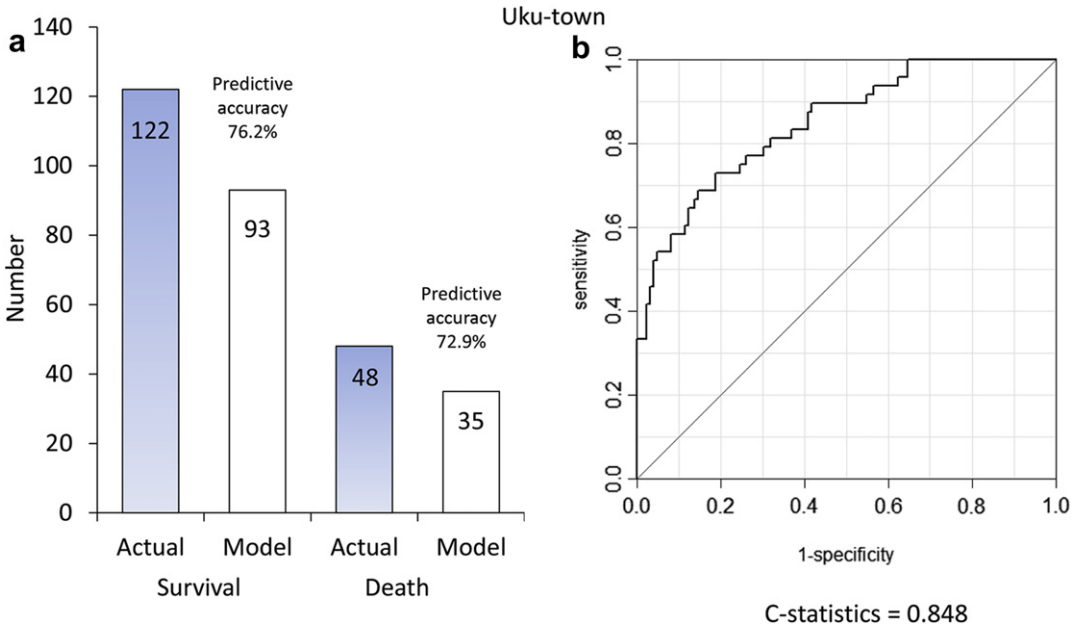

Fig. 3. Left (a): comparison of actual survival or death with predicted actual survival or death, respectively, for the test samples from Uku-town. Gray bars indicate the actual number of survivors or deaths. Right (b): *c*-statistic for prediction in Uku-town

72.9%, respectively, with high *c*-statistics. Although the predictive accuracy was high in the test samples of Uku-town, it was slightly inferior to that of the test samples of Tanushimaru-town. We do not know the reason for the small difference of predictive accuracy between the two test samples. Both are located in Kyushu Island and subject backgrounds are very similar between the two cohorts. One difference was the prevalence of hypertension medication, which could have caused the slightly lower predictive accuracy in the test samples from Uku-town.

We constructed a Cox regression model with the same predictor variables. In the Cox model, *c*-statistics for Tanushimaru-town and Uku-town were 0.821 and 0.853, respectively. In our model, *c*-statistics for Tanushimaru-town and Uku-town were 0.827 and 0.848, respectively. Our model is approximately equal to the Cox model in terms of the *c*-statistics.

NIPPON DATA 80 Risk score and our new computer model are similar. However, NIPPON DATA 80 Risk Charts are for cause-specific death probability, i.e., the probability of death from coronary heart disease, stroke, and all cardiovascular diseases. In contrast, our new computer model predicts the probability of all-cause death. Moreover, NIPPON DATA 80 Risk Charts were constructed by sex and 10-year age groups whereas our new computer model prediction was based on combinations of all conventional risk factors, including age and sex.

In order to illustrate the usefulness of our computer model, we look at two death cases from the test samples. Case 1 was a male aged 65 years with 218 mmHg in systolic BP, 201 mg/dl in total cholesterol, 4.8% in HbA1c, and non-smoker. We put these values into the formula and $f(x)$ was $1.345068 > 0$. The computer prediction was death and he actually died. However, if his systolic BP had been less than 140 mmHg, his $f(x)$ would have been $-0.15530 < 0$. The prediction would have changed from death to survival.

Case 2 was a female aged 61 years with 160 mmHg in systolic BP, 164 mg/dl in total cholesterol, 5.1% in HbA1c, and a current smoker. We put these values into the formula and $f(x)$ was $0.999083 > 0$. The computer prediction was death and she actually died. However, if her systolic BP had been less than 140 mmHg and she had been a non-smoker, her $f(x)$ would have been $-0.148407 < 0$. The prediction would have changed from death to survival. These cases illustrate not only the accuracy of the prediction but also the importance of risk factor control.

5. Limitations

Although the predictive accuracy was relatively high with high *c*-statistics, it was not 100%. It is not clear whether the six conventional atherosclerotic risk factors we adopted are the best combination for predicting 10-year mortality. It may be necessary to include other risk factors in order to improve predictive accuracy [11,18]. Second, we adopted only atherosclerotic risk factors other than age and smoking for prediction because we did not have detailed information on causes of death. Thus, the predictive accuracy may have been skewed by death unrelated to cardiovascular diseases. Third, because we had follow-up data for only 10 years, the prediction was limited to 10-year mortality. Fourth, we do not have any data on physical activity and respiratory fitness, which are predictors of death [19,20].

6. Perspectives

First of all, our new computer model may be useful to an individual with some risk factors who wants to know whether he is likely to still be alive in 10 years. Second, SSPR techniques allow us to construct a prognostic model using only means and variances without having to know individual baseline data. In contrast, to construct a prognostic model by Cox regression, means and variances alone are not sufficient; individual data are necessary. Thus, the SSPR method reported here can be applied to other cohorts if means and variances have been reported.

7. Conclusions

In summary, this is the first computer model to accurately predict individual 10-year mortality based on conventional atherosclerotic risk factors, using the SSPR method.

Conflicts of interest

None declared.

Statement of originality

To our knowledge, this is the first computer model by the SSPR method to estimate individual 10-year mortality based on conventional atherosclerotic risk factors.

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