

Prediction for risk of ischemic heart disease (IHD) in aged 30 or older Korean using national health insurance service-national sample cohort (NHIS-NSC)

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Abstract

The mortality rate of ischemic heart disease (IHD) was the highest rate of any heart diseases in South Korea. In this study, we predict the absolute risk factors of IHD according to individual characteristics or health status. Cox proportional hazards regression models were fitted to estimate hazard ratio of risk. Stepwise method was used to select a final model. After predictors were selected, the results were used to estimate the absolute 10-year IHD risk using Framingham risk score function and to calculate a simple point system. The total observation period for 106,167 subjects was 1,071,584 person-years. During the observation period, 4,627 subjects (4.4%) developed IHD with incidence rate of 431.79 per 100,000 person-year. Sex, age, smoking, drink, blood pressure, fasting blood sugar and total cholesterol were included in the final model. A Harrell's c-index was 0.7321 as a measure of discrimination and the overall O/E ratio was 0.972 (95% CI 0.944-1.000). We have predicted a model for 10-year risk of IHD related to risk factors using NHIS-NSC. Using these results, if you have your health information, you will be able to predict your risk of IHD.

Keywords: Absolute risk factor, Cox proportional hazards regression, Framingham risk score, ischemic heart disease.

1. Introduction

In 2015, the total number of deaths in South Korea was 275,895, and the three leading causes were malignant neoplasms (cancer), heart disease, and cerebrovascular disease. The heart disease was the third leading cause of death 10 years ago, and now it is second only to cancer. The mortality rate of ischemic heart disease (IHD) was 28.9 per 100,000 population, which was the highest rate of any heart diseases (Statistics Korea, 2016). IHD is a commonly caused by atherosclerosis affecting the coronary arteries, which limits the flow of oxygen-rich

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blood to myocardium. Age and IHD mortality rate were highly correlated, IHD mortality rate significantly increasing in older age groups (Statistics Korea, 2016). Therefore, it is expected that IHD mortality rate will increase drastically in the near future due to the rapidly ageing population.

In Europe and the United States, large-scale cohort studies on IHD were done, identifying major risk factors and developing disease prevention prediction models (D'Agostino *et al.* 2001). Major risk factors for IHD include hypertension, high cholesterol, diabetes, and smoking. Studies suggest that moderate alcohol intake may reduce the risk of IHD (Ko *et al.*, 2010, Ji *et al.*, 2004, Hines, 2001).

However, most studies focus on measuring the relative risk of a risk factor and comparing its magnitude to other risk factors; thus, it is difficult for a clinician or an individual to accurately predict the risk of a disease according to the patient's or individual's health condition. The purpose of this study was to identify the risk factors of IHD and to predict the absolute risk of IHD according to individual characteristics or health status.

2. Method

2.1. Data

In this study, we used Republic of Korea National Health Insurance Service-National Sample Cohort (NHIS-NSC) Database from 2002 to 2013. NHIS-NSC is a population-based cohort established by the National Health Insurance Service (NHIS) in South Korea. The database consists of a qualification DB, a diagnosis DB, and a checkup DB. 2.2% of total population was selected by stratified sampling using proportional allocation method was conducted (Kyu-Jin Kim *et al.*, 2017). NHIS-NSC had records of 585,795 (male 285,560, women 300,235) individuals over 30 years of age. We excluded subjects who deceased or were hospitalized for malignant neoplasm, cerebrovascular disease, and/or IHD from 2002 to 2003. Subjects with missing data on selected risk factors were also excluded, leaving a total of 106,167 individuals (men 57,187, women 48,980) for the study.

2.2. Response variable

Incidence of IHD during follow-up (2004 to 2013) were identified by death or hospitalization from IHD (ICD 10, I20-I25). If a death or hospitalization from IHD was identified, the period from the beginning of the research to the onset of the disease was calculated. If the subject was free of IHD, we calculated the survival period from the beginning of the research to the end of research or censored time.

2.3. Risk factor

Based on previous studies, risk factors of IHD used in our study are sex, age, smoking history, alcohol drinking, physical exercise, family medical history, Body mass Index, blood pressure, fasting blood glucose, and total cholesterol (Ko *et al.*, 2010, Shin *et al.*, 2012, Ji *et al.*, 2004).

The age was categorized by 10 years. Smoking status was categorized as non-smoker, ex-smoker, and smoker. Alcohol consumption was categorized as yes or no instead of almost never, 2-3time/month, 1-2time/week, 3-4time/week and daily. Exercise was categorized as

never, 1-2time/week, over 3time/week. Family history category was considered positive if subject had a family history of heart disease, stroke, and/or cancer according to the self-report. Body mass index(kg/m²) was categorized as underweight (<18.5), normal (18.5-23), overweight (23-25), obese class I (25-30), obese class II (30-35) and obese class III (\geq 35) based on classification from Korean Society for the Study of Obesity. Blood pressure(mmHg) was categorized as normal (<120 and <80), prehypertension I (systolic as 120-129 or diastolic as 80-84), prehypertension II (systolic as 130-139 or diastolic as 85-89), hypertension I (systolic as 140-159 or diastolic as 90-99) and hypertension II (systolic as 160 or diastolic as 100) (ESH/ESC Guidelines, 2013). Fasting blood sugar(mg/dL) was categorized as normal (<100), impaired fasting glucose (100-125) and diabetes (\geq 126) (KDA, 2015). Total cholesterol(mg/dL) was categorized as <200, 200-239, and \geq 240 (ATP III, 2001).

2.4. Statistical analysis

Cox proportional hazards regression models were fitted to estimate hazard ratio of risk factors(Taeseob Lee *et al.*, 2017). We evaluated univariate models to check relation between IHD and each risk factors and multivariate models. All models are adjusted for sex and age. Stepwise method was used to select a final model. After predictors were selected, the results were used to estimate the absolute 10-year IHD risk, which was calculated from the following formula by Framingham heart study (D'Agostino *et al.*, 2001).

$$P = 1 - S(t)^{\exp(f(x,M))}; f(x, M) = \sum_{i=1}^p \beta_i (x_i - M_i).$$

Here, β_i are the regression coefficients of Cox model, x_i are dichotomous values (1 and 0) of the dummy variables for each category. M_i is the proportion of the category of variable. $S(t)$ is a baseline survival rate.

Let W_{ij} denote the reference value for the j th category of the i th risk factor. The reference value of the base category is denoted W_{iRef} for each of the i risk factors. The points for each category of each risk factor are determined by the following:

$$Points_{ij} = \beta_i(W_{ij} - W_{iRef})/B,$$

where the constant, B, is the number of regression units that reflect 1 point in the final points system (Sullivan *et al.*, 2004).

Discrimination and calibration were conducted for model validation. Discrimination was evaluated with Harrell's c-index. An internal validation of our model was also conducted with a bootstrapping method (Harrell *et al.*, 1996, Michikawa *et al.*, 2012). The model was applied to each bootstrap sample (1000 random samplings) and the c-index was estimated each time. We calculated the mean difference between the original c-index and the c-index of each sample was calculated; the c-index was corrected by subtracting the mean difference from the original c-index. For calibration, the ratio of observed and expected IHD cases (O/E ratio) with 95% CIs was calculated from the following formula (Park *et al.*, 2009, Michikawa *et al.*, 2012).

Finally, we calculated a simple point system to make the risk estimation model easy to use for primary prevention of IHD (Sullivan *et al.*, 2004, Michikawa *et al.*, 2012). All analyses were conducted using both SAS version 9.3 and R version 3.2.5

3. Results

The total observation period for 106,167 subjects was 1,071,584 person-years (mean follow-up period: 10.09 years). During the observation period, 4,627 subjects (4.4%) developed IHD with incidence rate of 431.79 per 100,000 person-year. For men, 2,707 cases (4.7%) of IHD were newly diagnosed out of 57,187 subjects, and IHD incidence rate per 100,000 person-year was 472.80. For women, 1,920 cases (3.9%) of IHD cases were newly diagnosed out of 48,980 subjects, and IHD incidence rate per 100,000 person-year was 384.74. The baseline characteristics of study subjects are described in Table 3.1.

Table 3.1 Baseline characteristics

Variables	Category	Total	No case of IHD	IHD cases
		(N=106,167) n (%)	(N=101,540) n (%)	(N=4,627) n (%)
Sex	Men	57,187 (53.9)	54,480 (53.7)	2,707 (58.5)
	Women	48,980 (46.1)	47,060 (46.3)	1,920 (41.5)
Age group, years	30-39	24,294 (22.9)	24,028 (23.7)	266 (5.7)
	40-49	34,703 (32.7)	33,829 (33.3)	874 (18.9)
	50-59	23,011 (21.7)	21,692 (21.4)	1,319 (28.5)
	60-69	17,263 (16.3)	15,782 (15.5)	1,481 (32.0)
	70-79	5,979 (5.6)	5,375 (5.3)	604 (13.1)
	80-	917 (0.9)	834 (0.8)	83 (1.8)
Smoking	Non-smoker	71,900 (67.7)	68,806 (67.8)	3,094 (66.9)
	Ex-smoker	5,175 (4.9)	4,976 (4.9)	199 (4.3)
	Smoker	29,092 (27.4)	27,758 (27.3)	1,334 (28.8)
Alcohol	Yes	47,370 (44.6)	45,549 (44.9)	1,821 (39.4)
	No	58,797 (55.4)	55,991 (55.1)	2,806 (60.6)
Exercise	Never	61,301 (57.7)	58,502 (57.6)	2,799 (60.5)
	1-2 times/week	26,024 (24.5)	25,044 (24.7)	980 (21.2)
	more than 3 times/week	18,842 (17.7)	17,994 (17.7)	848 (18.3)
Family history	Yes	18,404 (17.3)	17,683 (17.4)	721 (15.6)
	No	87,763 (82.7)	83,857 (82.6)	3,906 (84.4)
Body mass index, kg/m ²	<18.5	2,882 (2.7)	2,785 (2.7)	97 (2.1)
	18.5-22.9	39,521 (37.2)	38,229 (37.7)	1,292 (27.9)
	23-24.9	28,280 (26.6)	27,016 (26.6)	1,264 (27.3)
	25-29.9	32,464 (30.6)	30,688 (30.2)	1,776 (38.4)
	30-34.9	2,834 (2.7)	2,649 (2.6)	185 (4.0)
	≥35	186 (0.2)	173 (0.2)	13 (0.3)
Blood pressure, mmHg	Normal	29,671 (27.9)	28,853 (28.4)	818 (17.7)
	Prehypertension I	43,715 (41.2)	41,952 (41.3)	1,763 (38.1)
	Prehypertension II	14,128 (13.3)	13,407 (13.2)	721 (15.6)
	Hypertension I	15,299 (14.4)	14,233 (14.0)	1,066 (23.0)
	Hypertension II	3,354 (3.2)	3,095 (3.1)	259 (5.6)
Fasting blood sugar, mg/dL	Normal	75,796 (71.4)	72,992 (71.9)	2,804 (60.6)
	Impaired fasting glucose	23,309 (22.0)	22,110 (21.8)	1,199 (25.9)
	Diabetes	7,062 (6.7)	6,438 (6.3)	624 (13.5)
Total Cholesterol, mg/dL	<200	58,380 (55.0)	56,269 (55.4)	2,111 (45.6)
	200-239	33,783 (31.8)	32,208 (31.7)	1,575 (34.0)
	≥240	14,004 (13.2)	13,063 (12.9)	941 (20.3)

Almost all risk factors except for exercise and family history were associated with increased IHD risk in the age and sex adjusted univariate. However, some categories in certain variables were not statistically significant compare to the reference category. As a result of stepwise

model selection, exercise and family history showed no statistically significant association with IHD; Therefore they were excluded in final model (Table 3.2). Some categories of certain variables were merged if there was no statistically significant difference from reference categories. We merged ‘non- smoker and ex-smoker’ in smoking, as well as ‘< 18.5 kg/m2 and 18.5 - 22.9 kg/m2’ in BMI. In this model, baseline survival function at 10 years was 0.9706 by Framingham Study risk score function.

Table 3.2 Cox regression coefficient and hazard ratio for IHD risk factor

Variables	Category	Univariate model (sex and age group adjusted)			Final model using stepwise (sex and age group adjusted)		
		β	se	HR (95% CI)	β	se	HR (95% CI)
Sex	Men	0.4864	0.0301	1.63 (1.53-1.73)	0.4551	0.0364	1.58 (1.47-1.69)
Age group, years	40-49	0.9248	0.0703	2.52 (2.20-2.89)	0.8851	0.0705	2.42 (2.11-2.78)
	50-59	1.7769	0.0676	5.91 (5.18-6.75)	1.6501	0.0685	5.21 (4.55-5.96)
	60-69	2.2466	0.0671	9.46 (8.29-10.78)	2.0888	0.0688	8.08 (7.06-9.24)
	70-79	2.5405	0.0742	12.69 (10.97-14.67)	2.4034	0.0764	11.06 (9.52-12.85)
	80-	2.6968	0.1261	14.83 (11.58-18.99)	2.5698	0.1279	13.06 (10.17-16.79)
Smoking	Ex-smoker*	-0.0687	0.0760	0.93 (0.80-1.08)			
	Smoker	0.1841	0.0382	1.20 (1.12-1.30)	0.2555	0.0379	1.29 (1.20-1.39)
Alcohol	Yes	-0.1058	0.0341	0.90 (0.84-0.96)	-0.1830	0.0353	0.83 (0.78-0.89)
Exercise	1-2 times/week	-0.0198	0.0381	0.98 (0.91-1.06)			
	more than 3 times week	-0.0674	0.0395	0.94 (0.87-1.01)			
Family history	Yes	0.0159	0.0409	1.02 (0.94-1.10)			
Body mass index kg/m2	<18.5*	-0.0630	0.1056	0.94 (0.76-1.16)			
	23-24.9	0.2260	0.0397	1.25 (1.16-1.36)	0.1852	0.0393	1.20 (1.11-1.30)
	25-29.9	0.4104	0.0367	1.51 (1.40-1.62)	0.3294	0.0370	1.39 (1.29-1.50)
	30-35	0.6655	0.0788	1.95 (1.67-2.27)	0.5105	0.0795	1.67 (1.43-1.95)
	≥35	0.8342	0.2789	2.30 (1.33-3.98)	0.6472	0.2792	1.91 (1.11-3.30)
Blood pressure, mmHg	Normal	ref.			ref.		
	Prehypertension I	0.1711	0.0426	1.19 (1.09-1.29)	0.1061	0.0429	1.11 (1.02-1.21)
	Prehypertension II	0.3154	0.0515	1.37 (1.24-1.52)	0.2250	0.0520	1.25 (1.13-1.39)
	Hypertension I	0.4649	0.0474	1.59 (1.45-1.75)	0.3524	0.0482	1.42 (1.29-1.56)
	Hypertension II	0.4736	0.0722	1.61 (1.39-1.85)	0.3398	0.0729	1.41 (1.22-1.62)
Fasting glucose	Impaired fasting glucose	0.1349	0.0347	1.14 (1.07-1.23)	0.0762	0.0349	1.08 (1.01-1.16)
	Diabetes	0.5346	0.0448	1.71 (1.56-1.86)	0.4425	0.0450	1.56 (1.43-1.70)
Total Cholesterol mg/dL	200-239	0.1355	0.0334	1.15 (1.07-1.22)	0.0853	0.0336	1.09 (1.02-1.16)
	≥240	0.4362	0.0396	1.55 (1.43-1.67)	0.3327	0.0401	1.40 (1.29-1.51)
Baseline survival function at 10-year, S(10)				-	0.9706		

* Categories combined in the final model, ref.: reference

Prediction model for incident IHD showed a Harrell’s c-index of 0.7323 as a measure of discrimination. In the bootstrap simulation, the corrected c-index was 0.7314. In the calibration analysis, the overall O/E ratio was 0.972 (0.944 - 1.000). Although there was a slight overestimation or underestimation in each category of risk factors, the O/E ratios were generally acceptable (min-max is 0.933 - 1.390 in O/E ratio of all categories).

Using Sullivan’s point system, we evaluated how individual total points relate to specific absolute risk of IHD in 10 years (Table 3.3). Sullivan’s points system is a scoring system that can easily and simply calculate the risk of developing individual characteristics by scoring risk factors for IHD. The total score range ranged from -2 to 65, and the risk of IHD for all

possible scores is shown in Table 3.4. The lowest risk score of -2 indicates that the risk of IHD is approximately 0.42%, while the highest risk score of 65 points is 50.50%. For example, if a patient is in the 40s (12 points), male (6 points), smoker (3 points), non-alcoholic (0 points), and has normal values in all clinical factors, the total score for the patient is 21 points. The points system gives a 10-year estimate of risk of 2.43%, employing the Cox model directly gives 2.33%. Another example is that if a patient is in the 50s (22 points), female (0 points), BMI 24 (2 points), total cholesterol >240 (4 points), the total score for the patient is 28 points. The points system gives a 10-year estimate of risk of 4.10%, employing the Cox model directly gives 4.22%.

Table 3.3 A point system for 10-year IHD risk factor

Variables	Category	Point
Sex	Men	6
	Women	0
Age group	30-39	0
	40-49	12
	50-59	22
	60-69	27
	70-79	32
	80-	34
Smoking	Non-smoker or Ex-smoker	0
	Smoker	3
Alcohol	Yes	-2
	No	0
Body mass index, kg/m ²	<23	0
	23-24.9	2
	25-29.9	4
	30-34.9	7
	≥35	8
Blood pressure, mmHg	Normal	0
	Prehypertension I	1
	Prehypertension II	3
	Hypertension I	5
	Hypertension II	4
Fasting blood sugar, mg/dL	Normal	0
	Impaired fasting glucose	1
	Diabetes	6
Total Cholesterol, mg/dL	<200	0
	200-239	1
	>240	4

4. Discussion

In this study, we have developed a prediction model for 10-year risk of IHD related to risk factors using NHIS-NSC. We followed 106,167 subjects who are not deceased or had not been hospitalized for malignant neoplasm, cerebrovascular disease, and IHD, until 2013. The total number of study subjects was 106,167 and total person-years followed were 1,071,584 (mean follow-up period: 10.09 years).

Looking at risk factors for IHD, men were 1.58 times riskier than women. The risk of developing IHD was elevated with increasing age as compared with those in their 30s. Hazard

Table 3.4 Estimate of 10-year risk of IHD

Total point	10-year risk	Total point	10-year risk	Total point	10-year risk
-2	0.0042	23	0.0282	48	0.1751
-1	0.0046	24	0.0304	49	0.1876
0	0.0049	25	0.0328	50	0.2008
1	0.0053	26	0.0353	51	0.2149
2	0.0058	27	0.0381	52	0.2298
3	0.0062	28	0.0410	53	0.2456
4	0.0067	29	0.0442	54	0.2622
5	0.0072	30	0.0476	55	0.2798
6	0.0078	31	0.0513	56	0.2982
7	0.0084	32	0.0553	57	0.3176
8	0.0091	33	0.0595	58	0.3380
9	0.0098	34	0.0641	59	0.3593
10	0.0106	35	0.0690	60	0.3815
11	0.0114	36	0.0742	61	0.4046
12	0.0123	37	0.0799	62	0.4285
13	0.0133	38	0.0859	63	0.4533
14	0.0143	39	0.0924	64	0.4788
15	0.0154	40	0.0993	65	0.5050
16	0.0167	41	0.1068		
17	0.0180	42	0.1147		
18	0.0194	43	0.1232		
19	0.0209	44	0.1323		
20	0.0225	45	0.1420		
21	0.0243	46	0.1523		
22	0.0262	47	0.1634		

Ratio (HR) was 1.29 for smoker compared to non-smoker or ex-smoker. Drinking decreased the risk with HR of 0.83. The risk levels increased with BMI, blood pressure, fasting blood sugar, and total cholesterol as compared with those in their respective reference categories.

This Cox proportional hazards regression model only assesses the relative risk compare to reference categories. We calculated 10-year absolute risk of IHD using Framingham risk score function. The Framingham model has been used for a considerable time and as a leading model in the disease risk model. Sullivan proposed a point system to make this disease risk model easier to access and use clinically. Since the point system facilitates the results already calculated, there is no need for a user to calculate the risk by using the formula, which makes the model readily available. Furthermore, it has a high correlation with the Framingham risk, which proves the validity of the result (Sullivan, 2004). In this study, risk factors of IHD were scored using Sullivan's point system to estimate the risk for 10 years (Table 3.3, Table 3.4). These results show that self-prediction of IHD risk can be useful in clinic settings or for individuals who have their own health status information.

Study subjects included in the study were people who had their general medical examination done. In South Korean health care system, those who receive medical examination are mostly currently employed population, which may limit the generalizability. Further subgroup analysis based on occupation or geographic distribution will be required in the future

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