The Relationship between 10-Year Cardiovascular Risk Calculated Using the Pooled Cohort Equation and the Severity of Non-Alcoholic Fatty Liver Disease

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Background: We investigated the association between the severity of non-alcoholic fatty liver disease (NAFLD) and the estimated 10-year risk of cardiovascular disease (CVD) calculated by Pooled Cohort Equation (PCE) and Framingham risk score (FRS).

Methods: A total of 15,913 participants (mean age, 46.3 years) in a health screening program were selected for analysis. The presence and severity of fatty liver was assessed by abdominal ultrasonogram. Subjects who drank alcohol more than three times a week were excluded from the study.

Results: Among the participants, 57.6% had no NAFLD, 35.4% had grade I, 6.5% had grade II, and 0.5% had grade III NAFLD. Mean estimated 10-year CVD risk was 2.59%, 3.93%, 4.68%, and 5.23% calculated using the PCE (P for trend <0.01) and 4.55%, 6.39%, 7.33%, and 7.13% calculated using FRS, according to NAFLD severity from none to severe (P for trend <0.01). The odds ratio for ≥7.5% estimated CVD risk calculated using the PCE showed a higher correlation with increasing severity of NAFLD even after adjustment for conventional CVD risk factors (1.52, 2.56, 3.35 vs. the no NAFLD group as a reference, P<0.01) compared with calculated risk using FRS (1.65, 1.62, 1.72 vs. no NAFLD group as a reference, P<0.01).

Conclusion: In our study of apparently healthy Korean adults, increasing severity of NAFLD showed a higher correlation with estimated 10-year CVD risk when calculated using the PCE than when calculated using FRS.

Keywords: Non-alcoholic fatty liver disease; Pooled Cohort Equation; Framingham risk score

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) falls on a pathologic spectrum ranging from simple steatosis and non-alcoholic steatohepatitis, progressing to end-stage liver disease with liver cirrhosis and hepatocellular carcinoma [1]. NAFLD is recognized as the most common cause of liver disease worldwide, with a prevalence of 15% to 35% in various populations [2-7]; an increasing incidence of NAFLD has been observed.

Recent studies demonstrate that 10-year cardiovascular risk...
factors may correlate with the severity of NAFLD [8,9]. In 2010, Chiang et al. [8] observed that the severity of NAFLD had a significant positive correlation with Framingham risk score (FRS). However, in 2013, the American College of Cardiology (ACC)/American Heart Association (AHA) Task Force released a new report on the treatment of blood cholesterol, suggesting the four groups with benefit of statin treatment and removing the specific target levels for blood cholesterol for the reduction of cardiovascular disease (CVD) from the guideline [10]. This guideline recommended a new risk assessment tool to assess 10-year atherosclerotic cardiovascular disease (ASCVD) risk, named the Pooled Cohort Equation (PCE), which uses age, sex, race, total cholesterol, high density lipoprotein cholesterol (HDL-C), systolic blood pressure, treatment for high hypertension, diabetes and smoking as risk factors. This is different from assessment with FRS, which uses age, sex, total cholesterol, HDL-C, blood pressure, and smoking as risk factors [11]. Although the FRS has been validated in many populations, its accuracy is somewhat limited among Asian populations [12,13]. There is no report validating or applying the PCE to assess CVD risk with severity of NAFLD.

Therefore, we investigated the association between NAFLD severity and 10-year cardiovascular risk and compared cardiovascular risk estimated by the PCE with that estimated by FRS in a healthy Korean population.

**METHODS**

**Study design and population**

This was a cross-sectional study of a subset of participants in a medical health checkup program in the Health Promotion Center of Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Korea. The purpose of the medical health checkup program is to promote the health of employees through regular health checkups and to enhance early detection of existing diseases. Most of the participants are employees and family members of various industrial companies from around the country. The cost of medical examinations is largely paid for by their employers, and a considerable proportion of the participants undergo examinations annually or biannually.

The initial study population included 19,920 subjects who participated in the medical checkup program from January 2011 to December 2012, and in whom fatty liver grades were available. We excluded participants who drank three or more times a week and those with medical illnesses that could affect liver function, such as chronic liver disease, liver cirrhosis, and malignancy. In addition, we excluded the subjects with history of ischemic stroke, ischemic heart disease or taking aspirin due to other atherosclerotic diseases. These strict exclusion criteria resulted in a final study population of 15,913 participants.

All participants provided written informed consent for the use of their health screening data for this study. The design, protocol and the consent procedure of this study were reviewed and approved by Institutional Review Board of Kangbuk Samsung Hospital in accordance with the Helsinki Declaration of 1975.

**Laboratory measurements**

Height and weight were measured twice and then averaged. Body mass index (BMI) was calculated by dividing the weight (kg) by the square of the height (m). Blood pressure was measured using a standardized sphygmomanometer after 5 minutes of rest. A smoker was defined as a participant who had smoked at least five complete packs of cigarettes in his or her lifetime. All participants were examined after an overnight fast. The hexokinase method was used to test fasting glucose concentrations (Hitachi Modular D2400, Roche, Tokyo, Japan). Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels were measured by a photometric UV test (Hitachi Modular D2400). An enzymatic calorimetric test was used to measure total cholesterol and triglyceride concentrations. A selective inhibition method was used to measure the level of HDL-C, and a homogeneous enzymatic calorimetric test was used to measure the level of low density lipoprotein cholesterol (LDL-C).

The presence of diabetes mellitus was determined according to a self-administered questionnaire and the diagnostic criteria of the American Diabetes Association [14]. Whether a participant was taking antihypertensive medication was assessed via self-administered questionnaire. The presence or absence of metabolic syndrome was defined according to the criteria from the International Diabetes Federation and AHA/National Heart, Lung and Blood Institute [15].

**Assessment of the severity of NAFLD**

The diagnosis of fatty liver was based on abdominal ultrasonography results with a 3.5-MHz transducer (Logic Q700 MR, GE, Milwaukee, WI, USA). Three experienced radiologists who were blinded to both study aims and laboratory values performed ultrasonography. Images were captured in a standard fashion, with participants in the supine position with their right arm raised above their head. All ultrasonographic images were stored on the image server and were also taken with instant film for later inspection by radiologists and physicians. Grade I fatty
liver was defined as when echogenicity was increased, grade II as when the echogenic liver obscured the echogenic walls of the portal vein branches, and grade III fatty infiltration as when the echogenic liver obscured the diaphragmatic outline [16,17].

**Ten-Year CVD risk calculation**

Individual estimation of participants’ 10-year CVD risk was performed with the use of two calculations, the PCE, which was recommended by the new guidelines, and FRS.

### Statistical analysis

All data were presented as the mean±SD, and were analyzed using SPSS version 18.0 (SPSS Inc., Chicago, IL, USA). Participants were divided into four groups according to NAFLD grade: grade 0, grade I, grade II, and grade III. Comparisons of the parameters between participants with NAFLD grade were performed using Student t tests and chi-square tests. Bivariate correlation analyses between 10-year CVD risk and the other variables were performed using Pearson’s correlation analysis. One-way analysis of variance (ANOVA) tests were used to compare the means of the PCE and FRS according to severity of NAFLD. Univariate logistic regression analyses were performed to examine the association of ≥7.5% 10-year CVD risk levels with severity of NAFLD and multivariate-adjusted odds ratios (ORs) and their 95% confidence intervals (CIs) were assessed with adjustment for conventional CVD risk factors such as age, sex, BMI, hypertension, diabetes mellitus, dyslipidemia, metabolic syndrome, and smoking. Significance was defined as P<0.05.

### RESULTS

#### Baseline characteristics

Mean age of the total participants was 46 years and 92.3% were men. In total, 6,752 subjects (42.4%) had NAFLD, 1,228 subjects (7.7%) had diabetes, 1,247 subjects (7.8%) had hypertension, and 2,796 subjects (17.6%) had metabolic syndrome. Mean serum AST level was 23.0 IU/L, and mean ALT level was 26.3 IU/L (Table 1).

#### Table 1. Baseline Characteristics of the Participants

| Characteristic | Total | NAFLD grade | P value | P for trend |
|----------------|-------|-------------|---------|-------------|
|                |       | 0           | I       | II          | III         |         |         |
| No. (%)        | 15,913| 9,161 (57.6)| 5,639 (35.4)| 1,035 (6.5)| 78 (0.5)   | -       | -       |
| Age, yr        | 46.3±6.3| 46.4±6.43| 46.3±6.14| 44.8±5.09| 45.9±5.59| <0.01  | 0.151  |
| Male sex, %    | 12,301 (92.3) | 6,248 (68.2) | 4,785 (84.9) | 946 (91.4) | 72 (92.3) | <0.01  | <0.01  |
| BMI, kg/m²     | 24.3±3.0| 23.1±2.5| 25.5±2.5| 27.8±3.2| 140.7±32.6| <0.01  | <0.01  |
| WC, cm         | 85.0±8.3| 81.6±7.3| 86.6±6.6| 94.3±8.4| 96.1±8.6| <0.01  | <0.01  |
| SBP, mm Hg     | 113.5±12.7| 111.3±12.4| 115.7±12.3| 119.9±12.4| 117.7±13.1| <0.01  | <0.01  |
| FBS, mg/dL     | 99.9±17.6| 97.0±13.3| 102.9±20.4| 108.9±25.1| 111.3±33.8| <0.01  | <0.01  |
| AST, IU/L      | 23.0±13.0| 20.9±11.4| 24.5±13.4| 32.1±17.5| 33.1±15.6| <0.01  | <0.01  |
| ALT, IU/L      | 26.3±21.7| 20.4±15.9| 31.6±24.3| 48.9±27.1| 48.3±28.1| <0.01  | <0.01  |
| TC, mg/dL      | 204.3±33.2| 200.3±31.9| 208.9±34.1| 213.5±34.4| 215.2±38.0| <0.01  | <0.01  |
| TG, mg/dL      | 136.4±83.6| 111.0±60.2| 165.0±91.5| 202.7±115.0| 207.6±148.1| <0.01  | <0.01  |
| HDL-C, mg/dL   | 53.4±13.1| 57.3±13.4| 48.6±10.9| 45.0±9.4| 45.5±9.3| <0.01  | <0.01  |
| LDL-C, mg/dL   | 131.4±30.6| 121.1±29.4| 136.9±31.3| 139.2±31.2| 140.7±32.6| <0.01  | <0.01  |
| DM, %          | 1,228 (7.7)| 374 (4.1)| 619 (11.0)| 214 (20.7)| 21 (26.9)| <0.01  | <0.01  |
| HTN, %         | 1,247 (7.8)| 540 (5.9)| 559 (9.9)| 138 (13.3)| 10 (12.8)| <0.01  | <0.01  |
| Smoker, %      | 3,808 (23.9)| 1,886 (20.4)| 1,587 (28.1)| 330 (31.9)| 23 (29.5)| <0.01  | <0.01  |
| Mets, %        | 2,796 (17.6)| 698 (7.6)| 1,532 (27.2)| 527 (50.9)| 39 (50.0)| <0.01  | <0.01  |
| Medication for dyspemia, % | 801 (5.0)| 345 (3.8)| 367 (6.5)| 83 (8.0)| 6 (7.7)| <0.01  | <0.01  |

Values are expressed as mean±SD or number (%).

NAFLD, non-alcoholic fatty liver disease; BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; FBS, fasting blood sugar; AST, aspartate aminotransferase; ALT, alanine aminotransferase; TC, total cholesterol; TG, triglyceride; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; DM, diabetes mellitus; HTN, hypertension; Mets, metabolic syndrome.
Relationship between 10-year CVD risk and NAFLD severity
A one-way ANOVA test was performed between 10-year CVD risk and NAFLD severity to assess the relationship (Fig. 1). The severity of NAFLD was significantly positively correlated with 10-year CVD risk. In general, mean 10-year CVD risk estimated using the PCE according to NAFLD grade was numerically lower than those calculated using the FRS. The mean 10-year CVD risk estimated by the PCE was 2.59%, 3.93%, 4.68%, and 5.23% for NAFLD grades 0 to III (Fig. 1A). In contrast, mean 10-year CVD risk estimated by the FRS was 4.55%, 6.39%, 7.33%, and 7.13% for NAFLD grade 0 to III, although there were no significant differences between a few individual groups in post hoc analyses (Fig. 1B).

Correlation of 10-year CVD risk with various parameters
In correlation analyses, 10-year CVD risks calculated by the two risk scores showed significantly positive correlation with age, systolic blood pressure, fasting blood sugar, liver enzymes, total cholesterol, triglyceride, LDL-C, BMI, and WC, and showed negative correlation with HDL-C (Table 2).

Risk for ≥7.5% estimated CVD risk
Univariate logistic regression analyses were performed with ≥7.5% estimated CVD risk as the dependent variable. Compared with NAFLD grade 0, the unadjusted OR for ≥7.5% estimated CVD risk was significantly higher in more severe NAFLD and increased steadily with increasing NAFLD severity. The adjusted OR for conventional 10-year CVD risk followed the same pattern, with a significantly increasing OR for ≥7.5% estimated CVD risk with more severe NAFLD severity. In particular, increased severity of NAFLD showed numerically increasing OR for PCE compared with FRS. Adjusted ORs for 10-year CVD risk estimated using the PCE were 1.52 (95% CI, 1.24 to 1.86), 2.56 (95% CI, 1.83 to 3.59), and 3.35 (95% CI, 1.52 to 7.29; P<0.001) for NAFLD grades I to III, respectively, and those calculated using the FRS were 1.65 (95% CI, 1.45 to

Table 2. Correlation of PCE and FRS with Various Parameters

| Variable    | PCE risk r value | PCE risk P value | FRS risk r value | FRS risk P value |
|-------------|------------------|------------------|------------------|------------------|
| Age         | 0.537            | <0.01            | 0.383            | <0.01            |
| SBP         | 0.308            | <0.01            | 0.330            | <0.01            |
| FBS         | 0.319            | <0.01            | 0.310            | <0.01            |
| AST         | 0.115            | <0.01            | 0.137            | <0.01            |
| ALT         | 0.140            | <0.01            | 0.196            | <0.01            |
| TC          | 0.167            | <0.01            | 0.257            | <0.01            |
| TG          | 0.317            | <0.01            | 0.323            | <0.01            |
| HDL-C       | -0.307           | <0.01            | -0.440           | <0.01            |
| LDL-C       | 0.181            | <0.01            | 0.337            | <0.01            |
| BMI         | 0.217            | <0.01            | 0.281            | <0.01            |
| WC          | 0.279            | <0.01            | 0.349            | <0.01            |
| PCE         | 1                | -                | 0.826            | <0.01            |
| FRS         | 0.826            | <0.01            | 1                | -                |

PCE, Pooled Cohort Equation; FRS, Framingham risk score; SBP, systolic blood pressure; FBS, fasting blood sugar; AST, aspartate aminotransferase; ALT, alanine aminotransferase; TC, total cholesterol; TG, triglyceride; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; BMI, body mass index; WC, waist circumference.

Fig. 1. Comparison of 10-year cardiovascular disease risk estimated by (A) Pooled Cohort Equation and (B) Framingham risk score according to the severity of non-alcoholic fatty liver disease. ANOVA, analysis of variance. a Same superscript letters denote no significant differences in post hoc analyses.
4.02 (2.33–6.92)
2.41 (2.21–2.63)
3.3 (2.85–3.82)
1.00 (ref)
1.89 (1.63–2.20)
1.65 (1.45–1.86)
-
2.66 (1.60–4.41)
1.91 (1.72–2.13)
< 1.62 (1.30–2.02)
1.00 (ref)
3.24 (2.71–3.88)
2.02 (1.80–2.27)
1.00 (ref)
<
4.36 (2.74–6.93)
3.35 (1.52–7.39)
<
1.72 (0.93–3.17)
1.52 (1.24–1.86)
Model 2
3.71 (2.92–4.71)
1.00 (ref)
<
-
2.46 (2.06–2.94)
<
Model 1
1.00 (ref)
FRS
Model 2
1.00 (ref)
2.56 (1.83–3.59)
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trast, our study population included only healthy Koreans, and the PCE includes race as a risk factor when evaluating for 10-year CVD risk. In addition, NAFLD is known to be associated with insulin resistance and metabolic syndrome [24,25]. Based on these results, the association between NAFLD and 10-year CVD risk is influenced by the presence or absence of diabetes. These differences among risk factors may have contributed to our observation that the severity of NAFLD is significantly correlated with increasing 10-year CVD when estimated using the PCE.

Our study has several limitations. NAFLD was defined as fatty liver without chronic liver disease, such as liver cirrhosis or hepatocellular carcinoma. However, our study population was not evaluated for viral markers, such as the hepatitis B virus or hepatitis C virus. In addition, because our study population included active participants in the medical checkup program, the number of participants with NAFLD grade III was relatively small (n = 78).

In conclusion, more severe NAFLD is associated with greater 10-year CVD risk as estimated using the PCE. Increased NAFLD severity showed a numerically increasing adjusted OR for 10-year CVD as estimated using the PCE compared with that calculated using the FRS. These findings suggest that NAFLD severity was an independent factor for ≥7.5% estimated CVD risk and that the PCE calculation may be appropriate when assessing 10-year CVD risk among individuals with NAFLD.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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