nutrición clínica y Dietética Hospitalaria

Artículo Original

Nutr Clín Diet Hosp. 2025; 45(2):289-297
DOI: 10.12873/452yoon

Relationship between pulse pressure and Fibrosis-4 score in non-drinking Korean adults using the Korea National Health and Nutrition Examination Survey: A cross-sectional study

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Recibido: 9/abril/2025. Aceptado: 26/mayo/2025.

ABSTRACT

Background: This cross-sectional study was conducted to assess the association between fibrosis-4 score (FIB-4) and pulse pressure (PP) in Korean adults.

Materials and Methods: Data on 4,236 adults aged 20 or older were obtained from the 2020 Korean National Health and Nutrition Examination Survey.

Results: There were several key findings in the present study. First, after adjusting the relevant variables, compared with the quartile 1 (Q1) of FIB-4, the odds ratio (OR) of high PP (PP > 60 mmHg) was significantly higher in Q2 (OR, 3.469; 95% confidence interval [CI], 1.737–6.928), Q3 (OR, 7.256; 95% CI, 3.744–14.061), and Q4 (OR, 16.660; 95% CI, 8.671–32.007). Second, for predicting high PP, the receiver-operating characteristic (ROC) curve analysis for FIB-4 (sensitivity, 72.4; specificity, 71.6; area under the ROC curve [AUC], 0.787; 95% CI, 0.769–0.804; $p < 0.001$). In addition, FIB-4 was superior to other non-invasive hepatic fibrosis indices, such as the aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ratio ($z = 11.857$; $p < 0.001$) or AST/platelet ratio index (z = 10.024; $p < 0.001$) for predicting high PP.

Conclusions: FIB-4 was positively associated with PP and SBP in Korean adults but was inversely associated with DBP. In addition, FIB-4 was superior to other non-invasive hepatic fibrosis indices for predicting high PP.

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KEYWORDS

Epidemiology, Liver health, Population data, National surveys

INTRODUCTION

Pulse pressure (PP), which is the difference between systolic blood pressure (SBP) and diastolic blood pressure (DBP), is a predictor of left ventricular hypertrophy and hardening of the arteries[1]. High PP occurs with several diseases, such as aortic sclerosis, aortic regurgitation, arteriosclerosis by less compliant arteries, severe iron deficiency anemia by reduced blood viscosity, and hyperthyroidism by increased SBP, and can increase the risk of all-cause and cardiovascular disease mortality[2]. The European Society of Hypertension/European Society of Cardiology 2013 guidelines included high PP in the asymptomatic organ damage index because PP has been recognized as a risk factor for cardiovascular disease[3].

Non-alcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease, with a global prevalence of NAFLD accounting for approximately 29.8% of the adult population and growing rapidly[4]. Liver fibrosis is the most important predictor of prognosis in patients with NAFLD. In patients with NAFLD, hepatic stellate cells can be transformed into myofibroblasts due to chronic inflammation, which is called 'non-alcoholic steatohepatitis (NASH)[5]. In diagnosing the extent of liver fibrosis, an invasive liver biopsy is the most accurate, but as it is an invasive method, it cannot be performed as a screening test because there may be some risks during the procedure[6]. Liver stiffness measured by transient elastography or shear wave elastography is a useful method for assessing liver fibrosis non-invasively[7]. However, because these tests are economically burdensome to apply as screen-

ing tests for a large number of people, many researchers have studied simple and economical non-invasive liver fibrosis indices.

The fibrosis-4 score (FIB-4) is a simple indicator to evaluate liver fibrosis calculated by four clinical parameters: age, platelet count (PLT), aspartate aminotransferase (AST), and alanine aminotransferase (ALT)[8]. FIB-4 has better diagnostic accuracy for advanced fibrosis when compared to other non-invasive clinical scores, such as the AST/ALT ratio (AAR) or AST/platelet ratio index (APRI), and the predictive power of adverse outcomes due to the high fibrosis scores seen in patients with NAFLD[9]. Previous studies have been conducted worldwide on the relationship between the non-invasive liver fibrosis index and coronary artery diseases, such as atherosclerosis and left ventricular hypertrophy[10,11]. However, studies on the relationship between the non-invasive liver fibrosis index and PP, a predictor of atherosclerosis and left ventricular hypertrophy, are rare. Therefore, the present study aimed to investigate the association between FIB-4 and PP in Korean adults. The data were obtained from the 2020 Korean National Health and Nutrition Examination Survey (KNHANES VIII-2), which is representative of the Korean population.

METHODS

Study participants

The KNHANES is a cross-sectional survey conducted nationwide by the Division of Korean National Health and Welfare. This study analyzed data from the KNHANES VIII-1 (2020) dataset, which provides the most recent homeostasis model assessment. KNHANES VIII-1 was administered from January 2020 to December 2020. In the KNHANES VIII-1 iteration, 7,359 individuals over 1 year of age were sampled. Among the 6,071 participants eligible for the current study, we limited the analyses to adults aged ≥ 20 years. We excluded 689 participants with data that were missing for important analytic variables, such as the homeostasis model assessment of SBP, DBP, PP, AST, ALT, PLT, and various blood chemistry tests. In addition, we excluded 1,146 participants with a history of cirrhosis, self-reporting alcohol intake of 3 or more drinks per day, and a diagnosis of hepatitis B virus or hepatitis C virus. A total of 4,236 participants were finally included in the statistical analysis. The KNHANES VIII-2 study was conducted according to the principles expressed in the declaration of Helsinki. Ethical permission was sought and granted (Institutional Review Board No, 2018-01-03-2C-A). All participants in the survey signed a written informed consent form. Further information can be found in "The KNHANES VIII-2 Sample", which is available on the KNHANES website. The data from KNHANES is available on request by email or by logging on to the "Korea National Health and Nutrition Examination Survey" website (https://knhanes.kdca.go.kr/knhanes/rawDataDwnld/rawDataDwnld.do).

General characteristics and blood chemistry

Research participants were classified by gender (men or women), smoking status (non-smoker or current smoker), and participation in regular exercise (yes or no). In the smoking category, participants who smoked more than one cigarette a day and those who never smoked were classified as current smokers and non-smokers, respectively. Regular exercise was indicated as "yes" for participants who had exercised on a regular basis regardless of whether this was indoors or outdoors. It was defined as 30 min at a time and 5 times/week in the case of moderate exercise, such as table tennis, swimming slowly, badminton, doubles tennis, volleyball, and carrying light objects; and for 20 min at a time and 3 times/week in the case of vigorous exercise, such as running, squash, singles tennis, climbing, cycling fast, swimming fast, skipping, football, basketball, and carrying heavy objects. Anthropometric measurements included waist circumference (WC), body mass index (BMI), SBP, and DBP measurements. Obesity was defined BMI ≥ 25.0 kg/m^2 [12]. Hypertension was defined SBP ≥ 140 mmHg or DBP ≥ 140 mmHg or hypertensive medication[12]. Blood chemistries included measurements of AST, ALT, total cholesterol (TC), triglycerides (TGs), high density lipoprotein cholesterol (HDL-C), and fasting blood glucose (FBG), platelet count, blood urea nitrogen (BUN), serum creatinine (Crea), and estimated glomerular filtration rate (eGFR). Type 2 diabetes mellitus (T2DM) was defined as FBG ≥ 126 mg/dL or diabetes medications[12]. GFR was estimated from the simplified equation developed using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation: GFR = 141 × min (Scr/κ, 1) $^{\alpha}$ × max (Scr/κ,1) $^{-1.209}$ × 0.993^{Age} × 1.018 [if female] × 1.159 [if black], where Scr indicates serum creatinine and κ is a correction factor, defined as follows: → 0.7 if women and → 0.9 if men [12]. Chronic kidney disease (CKD) was classified as eGFR < 60 ml/min/1.73 m^2 [12].

High PP, FIB-4, and noninvasive liver fibrosis indices

Blood pressure was measured from the right arm using a standard mercury sphygmomanometer (Baumanometer, WA Baum Co., New York, USA) after 5 minutes of rest in the sitting position. SBP and DBP were measured three times at 30-second intervals, and the second and third measurements were averaged to produce the final blood pressure used for analysis. PP was calculated as the difference between SBP and DBP. High PP was classified as > 60 mmHg [13]. Various previously published noninvasive indices, including FIB–4, AAR, and APRI were analyzed to predict liver fibrosis and cirrhosis. These indices were calculated using the following formulas[8]: FIB–4 score, age (years) x AST [U/L]/(PLT count [10^9/L] x (ALT [U/L])$^{1/2}$; AAR, AST (U/L)/ALT (U/L) ratio; APRI, (AST [U/L]/upper limit of normal) x 100/PLT count (10^9/L). FIB–4 score was classified as quartiles because the cut-offs for FIB–4 was not yet clear.

Statistical analysis

The data were statistically analyzed using SPSS (version 18.0, IBM, USA). The distributions of participant characteristics were converted into percentages, and the successive data were presented as averages with standard deviations. The distribution and average difference in clinical characteristics according to the normal PP and high PP groups were calculated using chi-square and a t-test (Table 1). The distribution and average difference in clinical characteristics according to the quartiles of FIB-4 were calculated using chi-square and an analysis of variance (ANOVA) test (Table 2). A multiple linear regression analysis model was constructed for FIB-4 (Table 3). When a logistic regression was per-

Table 1. Clinical characteristics of research subjects

					(n = 4,236)
Variables	**Category**	**Overall (n = 4,236)**	**Normal PP (n = 3,689)**	**High PP (n = 547)**	**p-value**
Age (years)		52.61 ± 17.63	49.77 ± 16.83	71.77 ± 8.64	< 0.001
Gender	Men	1,624 (38.8)	1,459 (39.6)	165 (30.2)	< 0.001
Smoking	Current smoker	522 (12.3)	494 (13.4)	28 (5.1)	< 0.001
Exercising	Regular exerciser	3,634 (85.8)	3,205 (86.9)	429 (78.7)	< 0.001
SBP (mmHg)		118.95 ± 16.65	115.28 ± 13.67	143.70 ± 13.54	< 0.001
DBP (mmHg)		74.87 ± 9.75	75.15 ± 9.52	72.94 ± 10.99	< 0.001
Hypertension		1,350 (31.9)	902 (24.5)	448 (81.9)	< 0.001
PP (mmHg)		44.08 ± 13.79	40.13 ± 9.14	70.76 ± 9.64	< 0.001
BMI (kg/m^2)		24.17 ± 3.78	24.15 ± 3.87	24.35 ± 3.09	0.253
WC (cm)		84.25 ± 10.71	83.83 ± 10.91	87.09 ± 8.68	< 0.001
Obesity		1,573 (37.1)	1,358 (36.8)	215 (39.3)	0.140
TC (mg/dL)		188.68 ± 38.88	189.96 ± 38.49	180.07 ± 40.42	< 0.001
TGs (mg/dL)		124.68 ± 94.43	124.67 ± 97.23	124.71 ± 72.88	0.993
HDL-C (mg/dL)		50.95 ± 12.19	51.25 ± 12.31	48.92 ± 11.15	< 0.001
FBG (mg/dL)		101.50 ± 23.77	100.32 ± 22.21	109.49 ± 31.24	< 0.001
T2DM		360 (8.5)	274 (7.4)	86 (15.7)	< 0.001
BUN (mg/dL)		15.32 ± 5.09	14.81 ± 4.61	18.72 ± 6.64	< 0.001
Crea (mg/dL)		0.80 ± 0.25	0.79 ± 0.22	0.85 ± 0.40	< 0.001
eGFR (ml/min/1.73 m^2)		91.25 ± 19.51	92.90 ± 18.76	80.09 ± 20.71	< 0.001
CKD		177 (4.2)	100 (2.7)	77 (14.1)	< 0.001
PLT (10^6/μL)		254.45 ± 61.30	92.90 ± 18.76	80.09 ± 20.71	< 0.001
AST (U/L)		24.49 ± 15.54	24.29 ± 15.73	25.81 ± 14.12	0.033
ALT (U/L)		23.13 ± 19.28	23.35 ± 19.71	21.69 ± 15.99	0.060
AAR		1.26 ± 0.51	1.25 ± 0.51	1.34 ± 0.46	< 0.001
APRI		0.35 ± 0.30	0.34 ± 0.26	0.41 ± 0.49	< 0.001
FIB-4		1.23 ± 0.89	1.13 ± 0.71	1.92 ± 1.46	< 0.001

SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; BMI, body mass index; WC, waist circumference; TC, total cholesterol; TGs, triglycerides; HDL-C, HDL-cholesterol; FBG, fasting blood glucose; T2DM, type 2 diabetes mellitus; BUN, blood urea nitrogen; Crea, serum creatinine; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; PLT, platelet; AST, aspartate aminotransferase; ALT, alanine aminotransferase; AAR, AST/ALT ratio; APRI, AST/platelet ratio index; FIB-4, fibrosis-4.

Table 2. Clinical characteristics according to the quartiles of FIB-4

n (%), Mean ± SD, (n = 4,236)						
Variables	**FIB-4**				**p-value**	**Post hoc analysis (Duncan)**
	Quartile 1 [a] (≤ 0.667) (n = 1.059)	**Quartile 2 [b] (0.668–1.071) (n = 1.059)**	**Quartile 3 [c] (1.072–1.577) (n = 1.058)**	**Quartile 4 [d] (≥ 1.578) (n = 1.060)**		
FIB-4	0.48 ± 0.12	0.86 ± 0.12	1.31 ± 0.15	2.29 ± 1.13	< 0.001	a<b<c<d
AAR	1.11 ± 0.47	1.16 ± 0.44	1.26 ± 0.44	1.51 ± 0.57	< 0.001	a<b<c<d
APRI	0.24 ± 0.10	0.28 ± 0.14	0.35 ± 0.16	0.53 ± 0.51	< 0.001	a<b<c<d
Age (years)	31.41 ± 9.62	48.73 ± 11.54	60.76 ± 10.57	69.54 ± 9.38	< 0.001	a<b<c<d
Gender (Men)	486 (45.9)	407 (38.4)	352 (33.3)	379 (35.8)	< 0.001	
Current smoker	175 (16.5)	164 (15.5)	107 (10.1)	76 (7.2)	< 0.001	
Regular exerciser	923 (87.2)	910 (85.9)	924 (87.3)	877 (82.7)	0.008	
Hypertension	112 (10.6)	261 (24.6)	560 (43.5)	517 (48.8)	< 0.001	
Obesity	422 (39.8)	387 (36.5)	414 (39.1)	350 (33.0)	0.005	
T2DM	38 (3.6)	101 (9.5)	121 (11.4)	100 (9.4)	< 0.001	
CKD	5 (0.5)	17 (1.6)	52 (4.9)	103 (9.7)	< 0.001	
High PP	10 (0.9)	57 (5.4)	163 (15.4)	317 (29.9)	< 0.001	

Hypertension, SBP ≥ 140 mmHg or DBP ≥ 90 mmHg or medication; T2DM, FBG ≥ 126 mg/dL or medication. Obesity was defined as BMI ≥ 25 kg/m^2; CKD, eGFR < 30 ml/min/1.73 m^2; High PP, PP > 60 mmHg.

Table 3. Multiple linear regression analysis for the independent factors determining FIB-4 score

(n = 4,236)						
Variables	**FIB-4**			**FIB-4**		
	β	**95% CI**	**p-value**	***β***	**95% CI**	**p-value**
Men	0.005	-0.045 to 0.064	0.729	0.015	-0.027 to 0.080	0.333
Current smoker	-0.053	-0.221 to -0.064	< 0.001	-0.052	-0.219 to -0.061	0.001
Regular exerciser	-0.019	-0.119 to 0.022	0.176	-0.022	-0.127 to 0.014	0.113
Obesity	-0.051	-0.147 to -0.041	0.001	-0.066	-0.173 to -0.070	< 0.001
T2DM	0.021	-0.022 to 0.157	0.137	0.023	-0.016 to 0.164	0.106
CKD	0.079	0.225 to 0.477	< 0.001	0.083	0.240 to 0.492	< 0.001
SBP (mmHg)	0.438	0.022 to 0.025	< 0.001		–	
DBP (mmHg)	-0.319	-0.032 to -0.026	< 0.001		–	
PP (mmHg)		–		0.364	0.022 to 0.025	< 0.001

Table 4. Comparisons of high PP according to quartiles of FIB-4

(n = 4,236)					
Category		**High PP**			
		Model 1	**Model 2**	**Model 3**	**Model 4**
FIB-4	Q1	1	1	1	1
	Q2	5.858 (2.972–11.544)	5.727 (2.905–11.290)	5.790 (2.939–11.410)	3.469 (1.737–6.928)
	Q3	18.687 (9.802–35.625)	18.022 (9.449–34.372)	18.241 (9.564–34.791)	7.256 (3.744–14.061)
	Q4	44.199 (23.383–83.547)	43.126 (22.810–81.538)	41.609 (22.001–78.698)	16.660 (8.671–32.007)

High PP, PP > 60 mmHg.
Model 1 [OR (95% CI)], Non-adjusted; Model 2 [OR (95% CI)], adjusted for gender; Model 3 [OR (95% CI)], Model 2 further adjusted for smoking, drinking, and regular exercising; Model 4 [OR (95% CI)], Model 3 further adjusted for obesity, T2DM, CKD, and hypertension.

Table 5. Comparisons of the receiver-operating characteristic curve analyses for the FIB-4, AAR, and APRI associated with the prevalence of high PP

(n = 4,236)							
Paired Criterion Variables		**AUC 1**	**AUC 2**	**Difference [AUC1 – AUC2]**	**Difference Std Error**	**z Value**	**p-value**
Criterion 1	**Criterion 2**						
FIB-4	AAR	0.787 (0.769–0.804)	0.573 (0.548–0.597)	0.214 (0.172–0.256)	0.019	11.857	< 0.001
FIB-4	APRI	0.787 (0.769–0.804)	0.606 (0.581–0.631)	0.181 (0.138–0.223)	0.018	10.024	< 0.001

formed for the OR of high PP, the 4 models constructed were: 1) non-adjusted; 2) adjusted for gender; 3) further adjusted for smoking and regular exercise; and 4) further adjusted for obesity, T2DM, CKD, and hypertension (Table 4). Receiver operating characteristic (ROC) curve difference analysis for FIB-4, AAR, and APRI was performed using the MedCalc (version 23.2.1, https://www.medcalc.org/download/). ROC curve analysis was performed for the FIB-4, AAR, and APRI related to the prevalence of high PP (Table 5 and Figure 1). The significance level for all statistical data was set at $p < 0.05$.

RESULTS

Clinical characteristics of participants in the normal PP and high PP groups

The clinical characteristics of participants in the normal PP and high PP groups are shown in Table 1. The prevalence rate of high PP was 547 (14.8%). The mean ± standard deviation (M ± SD) of PP, AAR, APRI, and FIB-4 was 44.08 ± 13.79 mmHg, 1.26 ± 0.51, 0.35 ± 0.30, and 1.23 ± 0.89, respectively. Hypertension, obesity, T2DM, CKD, age, SBP, AAR, APRI, and FIB-4 in the high PP were higher than those in the normal PP group (all, $p < 0.001$), but DBP and HDL-C were lower than those in the normal PP group (all, $p < 0.001$).

Clinical characteristics of participants according to the quartiles of FIB-4

The clinical characteristics of participants according to the quartiles of FIB-4 are shown in Table 2. Age, AAR, APRI, hypertension, CKD, and high PP were positively associated with the quartiles of FIB-4 (all, $p < 0.001$), but current smoker was inversely associated with the quartiles of FIB-4 ($p < 0.001$).

Multiple linear regression analysis for independent factors determining PP

The multiple linear regression analysis for independent factors determining PP is presented in Table 3. FIB-4 was positively associated with SBP (β, 0.438; 95% confidence interval [CI], 0.022 to 0.025; $p < 0.001$) and PP (β, 0.364; 95% CI, 0.022 to 0.025; $p < 0.001$). However, FIB-4 was inversely associated with DBP (β, -0.315; 95% CI, -0.032 to -0.026; $p < 0.001$).

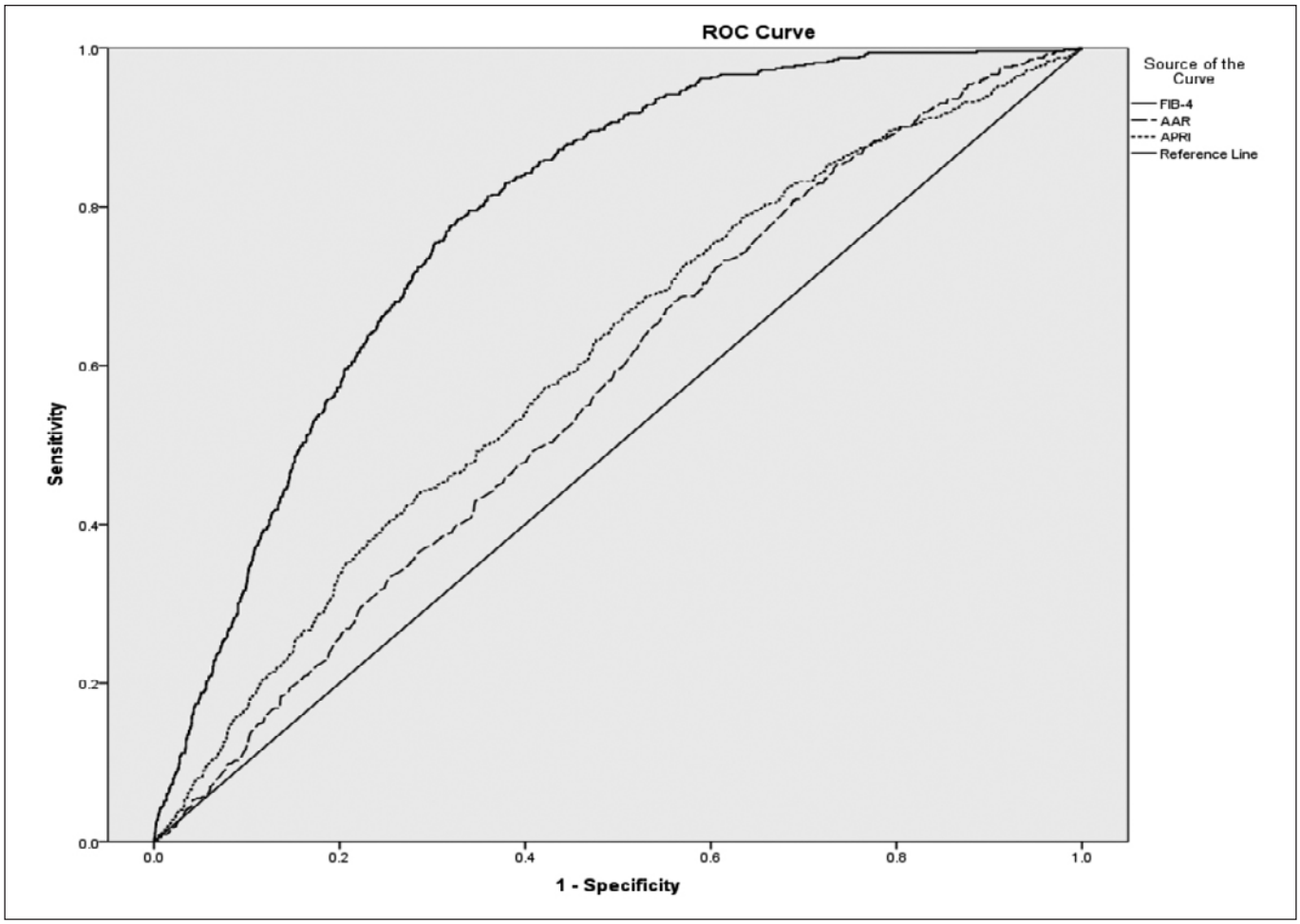

Figure 1. Receiver-operating characteristic curve analysis for the FIB-4, AAR, and APRI associated with the prevalence of high PP.

Comparisons of PP level and high PP according to the quartiles of FIB-4

Comparisons of PP level and high PP according to the quartiles of FIB-4 are presented in Table 4 and Supplementary Table 1. After adjusting for related variables (gender, smoking, **regular exercise**, obesity, T2DM, CKD, and hypertension), PP was positively associated with the quartiles of FIB-4 ($p < 0.001$) (Supplementary Table 1). After adjusting for related variables, compared with the quartile 1 (Q1) of FIB-4, the odds ratio (OR) of high PP (PP > 60 mmHg) was significantly higher in Q2 (OR, 3.469; 95% CI, 1.737–6.928), Q3 (OR, 7.256; 95% CI, 3.744–14.061), and Q4 (OR, 16.660; 95% CI, 8.671–32.007) (Table 4).

Receiver-operating characteristic curve analysis for FIB-4, AAR, and APRI associated with the prevalence of high PP

Results of the receiver-operating characteristic (ROC) curve analysis for FIB-4, AAR, and APRI associated with the prevalence of high PP are presented in Table 5 and Figure 1 and Supplementary Table 2. For predicting high PP, the ROC curve analysis for FIB-4 (area under the receiver-operating characteristic curve [AUC], 0.787; 95% CI, 0.769–0.804; $p < 0.001$), AAR (AUC, 0.573; 95% CI, 0.548–0.597; $p < 0.001$), and APRI (AUC, 0.606; 95% CI, 0.581–0.631; $p < 0.001$) (Supplementary Table 2). In addition, FIB-4 was superior to AAR ($z = 11.857$; $p < 0.001$) or APRI ($z = 10.024$; $p < 0.001$) for predicting high PP (Table 5 and Figure 1).

DISCUSSION

Using data from the KNHANES VIII-2, this study investigated the association between FIB-4 and PP in Korean adults. FIB-4 was positively associated with PP and SBP but inversely associated with DBP. In addition, FIB-4 was superior to AAR or APRI for predicting high PP.

Several studies have reported the association between liver fibrosis and coronary artery disease. In a cohort, Ostovaneh et al. revealed that liver fibrosis was associated with a history of

Supplementary Table 1. Comparisons of PP according to quartiles of FIB-4

					(n = 4,236)
Category		**PP (mmHg)**			
		Model 1	**Model 2**	**Model 3**	**Model 4**
FIB-4	Q1	36.70 ± 0.38 (35.96–37.43)	36.70 ± 0.38 (35.96–37.44)	36.79 ± 0.38 (36.05–37.52)	39.64 ± 0.35 (38.96–40.32)
	Q2	39.67 ± 0.38 (38.94–40.41)	39.67 ± 0.38 (38.94–40.41)	39.74 ± 0.38 (39.01–40.48)	40.69 ± 0.34 (40.03–41.34)
	Q3	46.80 ± 0.38 (46.06–47.53)	46.79 ± 0.38 (46.06–47.53)	46.80 ± 0.38 (46.07–47.54)	45.29 ± 0.34 (44.63–45.95)
	Q4	53.15 ± 0.38 (52.42–53.89)	53.15 ± 0.38 (52.42–53.89)	52.99 ± 0.38 (52.25–53.73)	50.70 ± 0.34 (50.03–51.37)
	p-value	< 0.001	< 0.001	< 0.001	< 0.001

High PP, PP > 60 mmHg.
Model 1 [M ± SE (95% CI)], Non-adjusted; Model 2 [M ± SE (95% CI)], adjusted for gender; Model 3 [M ± SE (95% CI)], Model 2 further adjusted for smoking, drinking, and regular exercising; Model 4 [M ± SE (95% CI)], Model 3 further adjusted for obesity, T2DM, CKD, and hypertension.

Supplementary Table 2. Receiver-operating characteristic curve analysis for the FIB-4, AAR, and APRI associated with the prevalence of high PP

					(n = 4,236)
Variables	**AUC (95% CI)**	**Cutoff value**	**Sensitivity (%)**	**Specificity (%)**	**p-value**
FIB-4	0.787 (0.769–0.804)	1.37	72.4	71.6	< 0.001
AAR	0.573 (0.548–0.597)	1.22	54.8	53.7	< 0.001
APRI	0.606 (0.581–0.631)	0.31	57.6	57.4	< 0.001

Hypertension, SBP ≥ 140 mmHg or DBP ≥ 90 mmHg or medication; T2DM, FBG ≥ 126 mg/dL or medication. Obesity was defined as BMI ≥ 25 kg/m^2; CKD, eGFR < 30 ml/min/1.73 m^2.; High PP, PP > 60 mmHg.

atrial fibrillation, heart failure, and coronary heart disease, and this association was mediated by atherosclerosis[14]. Dogan et al. reported a positive correlation between the NAFLD fibrosis score and the Framingham risk score ($r = 0.373$, $p < 0.001$) [15]. In addition, they argued that the assessment of liver fibrosis could be useful for the risk stratification of coronary heart disease and left ventricular diastolic dysfunction and that its severity depends on the stage of cirrhosis.

The pathophysiology underlying the association of liver fibrosis and atherosclerosis is still unclear, but there are several potential mechanisms linking them. For cardiovascular damage to occur in patients with NAFLD, pro-atherosclerotic, pro-inflammatory, and pro-thrombotic changes in the vascular environment are essential[16]. In patients with NAFLD or NASH, hepatic dysfunction can inhibit endothelial-derived nitric oxide by increasing asymmetric dimethylarginine, leading to cardiovascular damage[17]. Excessive fat accumulation in the liver causes mitochondrial reactive oxygen species (ROS) production and endoplasmic reticulum stress, which can develop into NASH[18]. Oxidative stress can promote atherosclerosis by inducing macrophage infiltration and oxidizing low-density-lipoprotein cholesterol to thicken the blood vessel walls[19]. ROS can be involved in plaque development in coronary arteries by oxidizing unsaturated fatty acids in the lipid membrane[20].

Currently, there are few studies on the direct relationship between FIB-4 and PP, but there are studies that indirectly reveal their relationship. PP is known as a predictor of atherosclerosis and left ventricular hypertrophy, and there are several studies on the relationship between FIB-4 and atherosclerosis or left ventricular hypertrophy. Among studies conducted in Asians, Watanabe et al. reported that the FIB-4 index was positively associated with the intima-media thickness ($\beta = 0.241$, $p = 0.004$), carotid artery calcification ($\beta = 0.139$, $p = 0.001$), and aortic artery calcification ($\beta = 0.265$, $p < 0.001$) in Japanese adults with T2DM[21]. In addition, they suggested that the FIB-4 index is an important predictor of arterial damage and future risk of coronary heart disease. Among studies conducted in Europeans,

Sesti et al. revealed that in the ROC analysis for predicting left ventricular hypertrophy, FIB-4 (AUC, 0.642; 95% CI, 0.592–0.690; p = 0.006) and APRI (AUC, 0.504; 95% CI, 0.453–0.555; p < 0.0001) were significant[22]. They argued that hepatic fibrosis, as determined by non-invasive fibrosis markers, was independently associated with cardiovascular organ damage. In our results, high PP was positively associated with the quartiles of FIB-4 (Table 4). In addition, FIB-4 was superior to AAR or APRI for predicting high PP (Table 5 and Figure 1). According to Paul's study, FIB-4 showed a specificity of 98.2% to confirm the presence of significant fibrosis, and the specificity for fibrosis was higher than other non-invasive fibrosis indices, such as APRI (72%), the NAFLD fibrosis score (93%), the fibrosis index score (81%), the FibroTest (90%), and the Forns index (66%)[23].

In the presented study, we cannot clearly elucidate the mechanism for the relationship between PP and FIB-4. However, there are potential mechanisms for their relationship. Similar to our results, Long et al. revealed that advanced fibrosis was not associated with SBP (OR, 3.42; 95% CI, -1.12 to 7.96; p = 0.14) but was inversely associated with DBP (OR, -3.42; 95% CI, -6.29 to -0.55; p = 0.02) and positively associated with PP (OR, 6.85; 95% CI, 3.14 to 10.55; p = 0.0003) [24]. As mentioned above, PP is calculated as SBP minus DBP. From the arithmetic perspective, PP increases in the following cases; first, when SBP increases and DBP does not increase; second, when SBP does not increase and DBP decreases; third, when SBP increases and DBP decreases. In our results, FIB-4 was positively associated with SBP but was inversely associated with DBP (Table 3), and this is the third case where PP increases with increasing FIB-4. An increase in SBP can induce left ventricular overload, leading to increased myocardial wall stress[25]. Low coronary flow reserve in patients with left ventricular hypertrophy is associated with an increase in SBP[26]. Yilmaz et al. reported that liver fibrosis scores are an independent predictor of decreased coronary flow reserve (β = -0.60; t = -2.44, p = 0.021) [27].

FIB-4, a non-invasive liver fibrosis index, is closely related to NAFLD, NASH, cirrhosis, end-stage liver disease diagnosis, and hepatocellular carcinoma[28]. If liver fibrosis progresses, there is an increase in the risk of atherosclerosis, left ventricular hypertrophy, and all-cause and cardiovascular mortality[29]. Therefore, a study argued that clinicians should fully evaluate the risk factors associated with cardiovascular disease and fibrosis for a better approach and treatment plan aimed at preventing hepatic, cardiovascular, and metabolic complications in patients with an accidental diagnosis of fatty liver[30].

The presented study has several limitations. Non-invasive indices for liver fibrosis include FIB-4, AAR, and APRI, as well as the NAFLD fibrosis score, fibrosis index score, FibroTest, and Forns index. In order to calculate these indices, the levels of serum albumin, haptoglobin, α2-macroglobulin, apolipoprotein, total bilirubin, and gamma-glutamyl transferase are required, but these values were not investigated in the KNHANES VIII-2 data. Therefore, the prediction of high PP between FIB-4 and other liver fibrosis indices (NAFLD fibrosis score, fibrosis index score, FibroTest, and Forns index) could not be compared. Future studies require a comparison of high PP predictions between FIB-4 and other liver fibrosis indices (NAFLD fibrosis score, fibrosis index score, FibroTest, Forns index). Additionally, because this is a cross-sectional study, it is difficult to clearly identify the direct causal relationship between FIB-4 and PP. Therefore, it is thought that clearer results can be obtained if a cohort study can be performed on the relationship between FIB-4 and PP.

CONCLUSION

The presented study investigated the association between FIB-4 and PP in Korean adults using data from KNHANES VIII-2 (2020). FIB-4 was positively associated with PP. FIB-4 was positively associated with SBP but was inversely associated with DBP. In addition, FIB-4 was superior to AAR or APRI for predicting high PP.

FUNDING RESOURCES

This paper was financially supported by Wonkwang Health Science University.

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