Fatty liver index and development of cardiovascular disease in Koreans without pre-existing cardiovascular disease: a large population-based study

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Abstract

Background Despite the known association between non-alcoholic fatty liver disease (NAFLD) and cardiovascular disease (CVD), it remains uncertain whether NAFLD predicts future CVD events, especially CVD mortality. We evaluated the relationship between fatty liver index (FLI), a validated marker of NAFLD, and risk of major adverse cardiac events (MACE) in a large population-based study.

Methods We identified 3,011,588 subjects without a history of CVD who underwent health examinations from 2009 to 2011 in the Korean National Health Insurance System cohort. The primary endpoint was a composite of cardiovascular deaths, non-fatal myocardial infarction (MI), and ischemic stroke. Cox proportional hazards regression analysis was performed to assess the independent association between FLI and the primary endpoint.

Results During the median follow-up of 6 years, there were 46,010 cases of MACE (7,148 cases of cardiovascular death, 16,574 non-fatal MI, and 22,228 ischemic stroke). There was a linear association between higher FLI values and higher incidence of the primary endpoint. In the multivariable models adjusted for factors including body weight and cholesterol levels, the hazard ratio (95% CIs) for the primary endpoint comparing the highest vs. lowest quartiles of FLI was 1.99 (1.91–2.07). The corresponding odds ratios (95% CIs) for cardiovascular death, non-fatal MI, and ischemic stroke were 1.98 (1.9-2.06), 2.16 (2.01-2.31), and 2.01 (1.90-2.13), respectively. The results were similar when we stratified analysis by age, sex, dyslipidemia medication, obesity, diabetes, and hypertension.

Conclusions Our findings indicate that FLI, a surrogate marker of NAFLD, has prognostic value for detecting individuals at higher risk of cardiovascular events.

Background

Non-alcoholic fatty liver disease (NAFLD) is characterized by the accumulation of fat in the liver due to causes other than alcohol or drug use, which is known to cause liver diseases. NAFLD is currently the most common cause of chronic liver disease globally; its prevalence in the adult population is reported to be 20–30%, which increases up to 70–90% in obese or diabetic patients[1] [2]. NAFLD was previously considered an intra-hepatic phenotype of metabolic syndrome; however, it has since been revealed that NAFLD itself is an independent risk factor for various chronic diseases such as cardiovascular disease (CVD)[3], hypertension[4], diabetes[5, 6], and chronic kidney disease[7]. In addition, as CVD is the most common cause of death in NAFLD patients, studies on the relationship between NAFLD and CVD and its mechanism have been actively conducted [8].

Because NAFLD has a variable prognosis, it is clinically important to identify subjects with NAFLD, and the gold standard for diagnosing NAFLD is liver biopsy. However, liver biopsy is not only practically difficult but also unnecessary to be performed in all patients with NAFLD because of the risk of complications due to its invasive nature, sampling error, and high cost[9]. Therefore, some non-invasive, non-imaging approaches have been applied and studied in the general population for diagnosing fatty

liver, including the fatty liver index (FLI), SteatoTest, and NAFLD liver fat score[10]. FLI is a surrogate marker of hepatic steatosis that has been extensively validated in a large group of subjects[11]. Currently, FLI is being used in epidemiological studies and screening for the general population as an alternative to ultrasonography.

Regarding the known close association between NAFLD and CVD, several longitudinal studies have shown that steatosis, assessed by the FLI, predates the occurrence of early carotid atherosclerosis and its progression[12]. Pais et al. demonstrated that the FLI effectively predicts intermediate/high Framingham scores[13]. Despite the known usefulness of the FLI as a surrogate marker of NAFLD, there has been no study on the occurrence of CVD using large datasets consisting of more than 1 million people. Furthermore, it remains uncertain whether NAFLD is directly associated with the occurrence of cardiovascular (CV) death. To extensively investigate an independent contribution of hepatic steatosis to CVD, including CV deaths, we conducted a large population cohort study using the Korea National Health Insurance Service (NHIS) data.

Herein, we studied the prospective association of FLI with the risk of incident non-fatal MI, ischemic stroke, and CV death, as well as the predictive value of FLI to identify individuals who will develop incident CVD events in analyses stratified by age, sex, statin use, and presence or absence of obesity, diabetes, and hypertension. We hypothesized that FLI would be a predictor of progression to incident CVD in a large population-based cohort study.

Methods

Study participants

In our cohort study, we used data from the NHIS, which is a government policy that has been implemented since 2000 and covers approximately 98% of the Korean population. All clinics, hospitals, and pharmacies in Korea are required to participate in the NHIS, and they are reimbursed for their services through the NHIS after filing claims electronically. Those who are over 40 years of age and enrolled in the NHIS receive regular health screenings at least once every 2 years. In this study, the target population was adult men and women over 40 years of age who underwent two or more health screenings from 2009 to 2011. The study exclusion criteria were 1) those diagnosed with cardiovascular disease (myocardial infarction (MI) or ischemic stroke) from 2002 to 2009, 2) those for whom we could not calculate the FLI owing to missing values, 3) heavy drinkers (≥ 2 days per week, and more than seven units of alcohol for men and five units for women per day), 4) those who used drugs known to cause fatty liver, and 5) those diagnosed with hepatitis B or C virus. A total of 3,014,643 subjects were included in the study. The flow chart of subject selection is depicted in Additional file 1. This study was approved by the Institutional Review Board of Yonsei University Wonju College of Medicine, Republic of Korea (No. CR318352). Anonymous and de-identified information was used for analysis; therefore, informed consent was not obtained.

Measurements

Healthcare institutions are designated for screening according to the Framework Act on Health Examinations and must meet the standards for manpower, facilities, and equipment[14]. To minimize errors in measurements, the average values of all laboratory test data from 2009 to 2011 were used. Values outside the extreme outlier were treated as missing values. Height, body weight, and waist circumference were measured, and body mass index (BMI) was calculated as the subject's weight in kilograms divided by the square of the subject's height in meters. Blood samples for serum glucose and cholesterol level measurements were obtained after an overnight fast.

Definition of CV events

We enrolled the population at risk between 2009 and 2011 and evaluated the primary endpoints in the follow-up period from 2014 to 2017. To minimize the influence of possible "reverse causation"

(illnesses causing low FLI), we excluded subjects with CV events occurring within 3 years after measurements at baseline. The primary endpoint was CV events, which is a composite of newly developed CV deaths, MI, and ischemic stroke during the follow-up period. The diagnosis was based on the International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10) codes. MI was determined based on either the recording of ICD-10 code I21 or I22 during hospitalization of ≥ 4 days or the recording of these codes at least twice. Ischemic stroke was described as the recording of the ICD-10 code I63 or I64 during hospitalization of ≥ 4 days with claims for brain magnetic resonance imaging or brain computerized tomography[15]. Follow-up evaluation for CV death was based on nationwide death certificate data from the Korea National Statistical Office. Subjects were considered to have completed the study on the date of their CV events or at the end of follow-up, whichever came first.

Calculation of FLI

The formula for FLI according to a previously published report by Bedogni et al. is as follows [11]: $FLI = [e^{0.953 \times \log_e(\text{triglycerides}) + 0.139 \times BMI + 0.718 \times \log_e(\gamma\text{-glutamyltransferase}) + 0.053 \times \text{waist circumference} - 15.745}] / [1 + e^{0.953 \times \log_e(\text{triglycerides}) + 0.139 \times BMI + 0.718 \times \log_e(\gamma\text{-glutamyltransferase}) + 0.053 \times \text{waist circumference} - 15.745}] \times 100$, with triglycerides measured in mmol/l, γ -glutamyltransferase in U/l, and waist circumference in cm. The score ranges from 0 to 100. The values used in the FLI formula were calculated as the mean value of the data measured during the health screenings from 2009 to 2011. Glucocorticoid, tamoxifen, and tetracycline are known to cause fatty liver; hence, we excluded subjects who had any history of prescription of these drugs

Statistical analysis

Statistical analysis was performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA) and R 3.1.0 (R Foundation for Statistical Computing, Vienna, Austria). For each group, the mean and standard deviation were presented for the continuous variables and the frequency and percentages were presented for the categorical variables. Participants were classified into four groups according to the FLI quartiles. To compare each group, we performed two-sample t-test, one-way analysis of variance (ANOVA), and chi-

square test, as appropriate. The incidence rate of primary outcomes was calculated by dividing the number of incident cases by the total follow-up duration (person-years). Hazard ratios (HR) and 95% confidence intervals (95% CIs) for CV death, MI, and stroke were analyzed using the multivariate Cox proportional hazards model for quartile or decile groups of FLI. The multivariable-adjusted proportional hazards models were as follows: Model 1 was adjusted for age and sex; Model 2 was further adjusted for current smoking, regular exercise, and income; and Model 3 was further adjusted for body weight, total cholesterol, presence of diabetes mellitus and hypertension, and medication for dyslipidemia. The potential effect modification by age, sex, obesity, diabetes mellitus, hypertension, and use of lipid-lowering agents was evaluated through stratified analysis and interaction testing using a likelihood ratio test. In subgroup analyses, HR (95% CI) of the highest quartile (Q4) was compared with that of the lower three quartiles (Q1–3) as a reference. Results with a p-value < 0.05 were defined as having statistical significance. The risk was expressed as 95% CIs.

Results

Baseline characteristics

A total of 3,011,588 subjects were analyzed in this study. Participants were classified according to the quartiles of FLI, and the baseline characteristics are presented in Table 1. The cutoffs for the quartile groups were 8.49, 18.67, and 38.08, and the numbers of subjects in Q1, Q2, Q3, and Q4 were 753,155, 753,007, 752,868, and 752,528, respectively. In total, 1,290,580 (42.9%) subjects were male, and the proportion of males increased with increasing FLI quartiles: Q1 (18.2%, n=137,010), Q2 (35.3%, n=265,501), Q3 (50.5%, n=380,022), and Q4 (67.5%, n=507,975). At baseline, the mean age was 51.86 ± 8.20 years. The mean age and BMI were higher in the higher FLI groups; however, the mean age of Q4 was slightly lower than that of Q3. As expected, systolic/diastolic blood pressure, fasting glucose, and cholesterol levels were elevated in higher FLI groups. The proportion of subjects who performed regular exercise showed no significant difference between the FLI quartile groups. For smoking status, the proportion of current smokers was higher in Q4 than in Q2 and Q3; however, this proportion was also high in Q1. The higher the FLI, the greater was the proportion of subjects with hypertension, diabetes, or dyslipidemia.

FLI and primary endpoints

During the median follow-up of 6 years, there were 46,010 cases of adverse CV events (7,148 cases of CV death, 16,574 cases of non-fatal MI, and 22,228 cases of ischemic stroke) (Table 2). An incrementally higher risk of CV event was observed with higher FLI quartiles when compared with Q1 in all models. After adjustment for age, sex, current smoking, regular exercise, income, body weight, total cholesterol, hypertension, diabetes, and medication for dyslipidemia, the relationship between FLI and adverse CV events still remained significant [HR (95% CI): Q2, 1.31 (1.27-1.36); Q3, 1.61 (1.55-1.66); Q4, 1.99 (1.91-2.07)]. To determine the linear trends of the risk, we investigated the HRs of primary endpoints according to FLI decile groups, with the first decile serving as the reference category. The multivariable-adjusted HRs

of primary endpoints increased continuously and linearly, and statistical significance was observed from the 2nd decile (D2) of FLI group (Fig. 1). When this association was stratified by the type of CV event, higher FLI quartiles had a significantly increased risk of non-fatal MI, non-fatal ischemic stroke, and CV deaths. Analysis according to decile groups also demonstrated that a linearly increasing risk of all types of CV outcomes was observed in higher FLI decile groups when compared with the lowest decile group (Additional file 2). The risk of MI and stroke significantly increased from the 2nd decile (D2) of FLI group, and the risk of CV mortality significantly increased from the 5th decile (D5) of FLI group.

Subgroup analysis

Because subjects with higher FLI values had a higher risk of CVD when compared to those with lower FLI values, we further conducted analysis stratified by age, sex, obesity, diabetes mellitus, hypertension, and use of lipid-lowering agents (Fig 2 and Additional file 3). The highest FLI quartile group (Q4 group) remained predictive of newly developed non-fatal MI, stroke, and CV death in all subgroups when compared with the Q1–3 groups. This finding indicates that significant associations between higher FLI and future CV events exist in all subgroups. Higher adjusted HRs of CV events were observed among those with younger age (age <55 years), male subjects, and those with obesity, diabetes, and hypertension. The lipid-lowering agent subgroup did not show any significant differences in the association between FLI and risk of CV events, except MI.

Discussion

In this large-scale, nationwide, longitudinal cohort study, we investigated the relationship between FLI, a validated surrogate marker of NAFLD, and future CV events in subjects without a history of CVD. We found that FLI was an independent predictor of CV events, even after adjusting for possible confounding factors including body weight and cholesterol levels, during a median follow-up period of 6 years. There was a linear association between the increase in FLI values and primary outcome measures. When this association was stratified by outcome, a higher FLI level was significantly associated with an increased risk of non-fatal MI, non-fatal ischemic stroke, and CV death. We also demonstrated a greater impact of FLI on subjects with other co-morbidities such as hypertension and diabetes. To our knowledge, the current study is the largest to date to evaluate the relationship between a clinical marker of NAFLD and future CV events in the general population.

NAFLD is recognized as a risk factor for CVD. A recent meta-analysis demonstrated that the presence of NAFLD was significantly associated with a 64% increased risk of a composite endpoint of CVD [16]. In addition, a cross-sectional study of 3,270 subjects who were referred for coronary angiography reported that high FLI levels were independently associated with increased all-cause, CV, and non-CV mortality, as well as cancers [17]. To determine the effect of NAFLD on CVD in the general population, we used FLI. The proportion of patients with newly developed CV events in our study gradually increased across FLI quartiles and FLI deciles, suggesting a quantitative relationship, with the amount of hepatic steatosis playing a major role in the development of CVD. Regarding the fact that FLI < 30 is suggested to rule out

NAFLD, we identified that even the normal range of FLI (7.02-29) was associated with a higher risk of incident CVD. When this association was stratified by the presence or absence of various CV risk factors (e.g., old age, obesity, diabetes, hypertension, and use of anti-dyslipidemia agents), the relationship between higher FLI levels and future risk of CVD remained. Considering the fact that the NHIS database includes the entire South Korean population, our finding provides robust evidence of the association between FLI and risk of CVD events in the general population. This finding suggests that FLI would be a useful screening tool as a predictor of CVD incidence.

Despite the known close relationship between NAFLD and CVD, whether NAFLD independently increases the risk of CV death remains controversial. Several studies demonstrated unequivocally increased incidence of CV deaths in patients with NAFLD[18, 19]. Nevertheless, some meta-analyses failed to confirm this association[16, 20]. Moreover, Hwang et al. reported that the association between NAFLD and mortality caused by CVD was observed only in women and not in men[21]. In addition, in a 15-year follow-up study of 2,075 middle-aged Caucasian, FLI was not independently associated with CVD mortality, while it was a significant predictor of increased risk of liver-related mortality [22]. However, these previous studies were conducted in specific cohorts with relatively small numbers of patients. Consequently, the findings of these studies have limited generalizability to a general population. Conversely, the current study was a large-scale population-based study. We demonstrated that FLI is associated with mortality caused by CVD independent of traditional CV risk factors such as body weight, cholesterol levels, hypertension, diabetes, and medication for dyslipidemia. We also observed that the association between higher FLI values and CV death is significant in both sexes. It would be important to determine whether NAFLD also affects future CV deaths, and our study contributes supportive and confirmative data regarding this emerging issue.

Previously, NAFLD was regarded as a hepatic manifestation of metabolic syndrome, which is a traditional CVD risk factor. The specific contribution of NAFLD to increased CVD risk, especially in clinical studies, is difficult to assess separately from the combination of risk factors that are shared between NAFLD and CVD[23]. However, there has been increasing evidence suggesting NAFLD itself to be an independent risk factor of CVD. Apart from genetic factors, various hepatokines related to the liver-gut axis and systemic insulin resistance can also induce endothelial cell deterioration due to inflammatory reactions and oxidative stress, structural changes in blood vessels, and changes in blood coagulation factors[24]. Although these mechanisms plausibly link NAFLD to the development and progression of CVD, no study to date has proven a cause-and-effect relationship between these two entities, and further research is required to gain mechanistic insights into the pathophysiology linking NAFLD to the development and progression of these extrahepatic chronic diseases.

The major strength of the current study was the large sample size, consisting of more than 3,000,000 subjects, and longitudinal data. However, several limitations of this study should also be addressed. The mortality rate was assessed over a short follow-up period of 6 years, which may be a limitation. A further limitation of our study is the use of FLI as a surrogate measure for NAFLD instead of the histological assessment for NAFLD. Furthermore, because FLI comprises known CV risk factors (BMI, triglyceride,

waist circumference), these variables account for the associations seen in the current study. However, to overcome this limitation, we conducted analysis stratified by the presence or absence of these CV risk factors. Second, because the NHIS database relies on physicians' assignment of a diagnostic code for CVD, there is a possibility of misdiagnosis of CVD, which may lead to under or overestimation of disease prevalence. Third, we did not collect data on medications or interventions, including weight reduction, that may have affected liver fat accumulation during the follow-up period. In addition, other unreported confounders, including socioeconomic status and genetic factors, may have affected the association between NAFLD and mortality in our study participants. Lastly, as our study subjects were mostly Korean, the results might not be generalizable to other ethnic groups.

Conclusions

In conclusion, in our nationwide population-based cohort study, we observed that FLI, a surrogate marker of NAFLD, is an independent predictor of the development of MI, ischemic stroke, and CV mortality. A linear relationship was noted between FLI and adverse outcome measures. All relationships were independent of multiple cardio-metabolic risk factors across a wide range of patient populations. Our findings suggest that FLI is an important predictor for major adverse cardiovascular outcomes, including CV deaths, in the general population. Further prospective studies are warranted to evaluate if a quantitative relationship between NAFLD and CV events exists, in order to determine whether early treatment of hepatic steatosis can prevent the occurrence of CVD.

Abbreviations

Non-alcoholic fatty liver disease (NAFLD), cardiovascular disease (CVD), fatty liver index (FLI), major adverse cardiac events (MACE), myocardial infarction (MI), National Health Insurance Service (NHIS), body mass index (BMI), one-way analysis of variance (ANOVA), hazard ratios (HR), 95% confidence interval (95% CI).

Declarations

Ethics approval and consent to participate: This study was approved by the Institutional Review Board of Yonsei University, Republic of Korea (No. CR318352). Anonymous and de-identified information was used for analysis; therefore, informed consent was not obtained.

Consent for publication: Not applicable.

Availability of data and materials: The datasets generated and analyzed during the current study are not publicly available due to rule of Korea National health insurance system.

Competing interests: The authors declare that they have no competing interests.

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Potential conflicts of interest related to project funding

The study sponsor was not involved in the design of the study; the collection, analysis, and interpretation of data; writing the report; or the decision to submit the report for publication

Authors' contributions:

J.H.H. and J.Y.K. conceived the study concept and design. J.H.K, J.S.M., J.H.L., and D.Y.K. acquired data and performed statistical analyses. J.H.H., and S.J.B. wrote the first draft, and conducted the literature search. J.H.H., K.C.S., and J.Y.K.. analyzed and interpreted data. All authors contributed to critical revision of the manuscript and read and approved the final submitted version of the manuscript. J.H.H. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Tables

Due to technical limitations, the tables are only available as a download in the supplemental files section.

Figures

Figure 1

Incidence rates, hazard ratios, and 95% confidence intervals of primary endpoint (cardiovascular disease mortality, myocardial infarction, and stroke) by deciles of FLI. FLI, fatty liver index; HR, hazard ratios; CI, confidence intervals; CVD *adjusted for age, sex, current smoking, regular exercise, income, body weight, total cholesterol, hypertension, diabetes, and medication for dyslipidemia

Figure 2

Hazard ratios and 95% confidence intervals of primary endpoint in the highest quartile (Q4) vs. lower three quartiles of fatty liver index in subgroups. *adjusted for age, sex, current smoking, regular exercise, income, body weight, total cholesterol, hypertension, diabetes, and medication for dyslipidemia

Supplementary Files

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