ORIGINAL ARTICLE

Severity of fatty liver is highly correlated with the risk of hypertension and diabetes: a cross-sectional and longitudinal cohort study

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Abstract

Background and aims Fatty liver disease (FLD) is associated with several metabolic derangements. We conducted a retrospective cross-sectional and longitudinal study to evaluate the role of FL severity in the risk of new-onset and co-existing hypertension (HTN) and diabetes mellitus (DM).

Methods The cross-sectional cohort consisted of 41,888 adults who received health checkups in a tertiary hospital of Taiwan from 1999 to 2013. Of them, 34,865 without HTN and/or DM at baseline and within 1 year after enrollment were included as a longitudinal cohort (mean, 6.45 years for HTN; 6.75 years for DM). FL severity based on the degree of hepatic steatosis was assessed by ultrasound sonography.

Results In cross-sectional cohort, 22,852 (54.6%) subjects had FL (18,203 [43.46%] mild FL and 4,649 [11.10%] moderate/severe FL); 13.5% (n = 5668) had HTN; and 3.4% (n = 1411) had DM. Moderate/severe FL and mild FL had significantly higher risks of existing HTN (adjusted odds ratio/95% confidence interval [CI] 1.59/1.43–1.77 and 1.22/1.13–1.32, respectively). In longitudinal cohort, 3,209 and 822 subjects developed new-onset HTN and DM, respectively (annual incidence, 14.3 and 3.5 per 1000 person-years; 10-year cumulative incidence, 14.35% and 3.89%, respectively). Moderate/severe and mild FL had significantly higher risks of new-onset HTN (adjusted hazard ratio [aHR]/CI 1.54/1.34–1.77 and 1.26/1.16–1.37, respectively) and DM (aHR/CI 5.88/4.44–7.81 and 3.22/2.56–4.07, respectively). Resolved FL during follow-up decreased the risk of HTN and/or DM.

Conclusions Patients with FL are at high risk of prevalent and incident HTN and/or DM. The risk increases with the severity of FL.

Keywords Hypertension · Diabetes · Non-alcoholic fatty liver disease · Metabolic syndrome · Risk factor · Ultrasound sonography · NAFLD · MAFLD · Metabolic dysfunction associated fatty liver disease · Good health and well-being · Hypertriglyceridemia · IFG · Impaired fasting sugar · Pre-hypertension · Incidence

Abbreviations

aHR	Adjusted hazard ratio
ALT	Alanine aminotransferase
aOR	Adjusted odds ratio
AST	Aspartate aminotransferase
BS	Blood sugar
cHR	Crude HR
CLR	Cumulative lifetime risk
DBP	Diastolic blood pressure
DM	Diabetes
FL	Fatty liver
FLD	Fatty liver disease
HDL-C	High-density lipoprotein cholesterol
HTN	Hypertension
IFG	Impaired fasting glucose
LDL-C	Low-density lipoprotein cholesterol
NAFLD	Non-alcoholic fatty liver disease
SBP	Systolic blood pressure
USG	Ultrasound sonography

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Introduction

Non-alcoholic fatty liver disease (NAFLD) is the most common form of chronic liver disease, which can lead to hepatocellular carcinoma and end-stage liver disease [1, 2]. Approximately 25% of people have NAFLD globally [3]. Despite the growing disease burden of NAFLD, there remains a significant gap in the awareness and knowledge of NAFLD among physicians and policy makers [4, 5].

NAFLD is considered to be a hepatic component of a multisystem disease stemming from insulin resistance and is highly associated with metabolic syndrome, including hypertension (HTN), type 2 diabetes mellitus (DM), and dyslipidemia [6–8]. NAFLD is associated with a significantly higher risk of developing incident HTN [9, 10] and incident DM [11, 12], which have been the major causes of death for NAFLD and metabolic syndrome [13]. However, little is known about the risk of NAFLD severity and risk of HTN and DM.

Recently, a new nomenclature of FLD, metabolic dysfunction-associated FLD (MAFLD), was proposed based on the co-existence of FL and metabolic abnormality, without excluding other etiologies such as chronic viral hepatitis [14, 15]. The spectrum of MAFLD may help identify individuals with metabolically complicated FL, who are at higher risk of cardiovascular disease [16].

In this study, we aimed to evaluate the role of FL severity and the risk of HTN and DM in Taiwan, a country hyperendemic for hepatitis B virus (HBV) and hepatitis C virus (HCV) infections [17, 18]. We adopted a cross-sectional and longitudinal cohort design to investigate the risk factors associated with co-existing (prevalent) and new-onset (incident) HTN and DM.

Materials and methods

Population

A total of 509,239 person-visits (225,308 subjects) to the Department of Preventive Medicine and Health Management Center, Kaohsiung Medical University Hospital (KMUH) for health checkups between 1999 and 2013, were screened for the current study. Information that identifies the research subjects were eliminated from the dataset before commencement.

Cross-sectional cohort

A total of 41,922 subjects (259,927 person-visits), who visited the department at least twice, were aged 18–65 years during the first visit, and had complete anthropometric measurement, blood test data available, and liver ultrasound sonography (USG), were initially enrolled in the study. Twenty-three subjects with suspected alcoholic-related liver disease (ratio of serum aspartate aminotransferase (AST) to alanine aminotransferase (ALT) level > 2 and AST level > 2 times the upper limit of normal or with heavy alcohol consumption (≥ 5 drinks on any day or ≥ 15 per week in men and ≥ 4 drinks on any day or ≥ 8 per week in female for > 5 years) [19, 20] and 11 subjects with a history of major organ transplantation were excluded. Consequently, the cross-sectional cohort was established with a total 41,888 subjects to evaluate the correlation between FL and the presence of existing HTN and DM at enrollment (Supplementary Fig. 1).

Longitudinal cohort

To evaluate the impact of FL on the incidence of new-onset HTN and/or DM, 6,529 subjects with HTN and/or DM at baseline and 445 subjects with HTN and/or DM diagnosed within 1 year after enrollment, and 49 subjects with an estimated glomerular filtration rate < 30 mL/min/1.73 m^2 were excluded. Finally, 34,865 subjects were included as the longitudinal cohort for statistical analyses (Supplementary Fig. 1).

Assessment of FL

Abdominal USG was performed by 8 well-trained and qualified hepatologists at KMUH, using Toshiba SSA-250, SSA-520A, and SSA-660A devices with 3.5 MHz convex transducers (Toshiba, Tokyo, Japan). The diagnosis of FL was based on brightness of the liver on USG compared with the kidney, vascular blurring of the hepatic vein trunk, and deep attenuation in the right hepatic lobe. The severity of FL was classified as: 1) no FL, a normal echo texture and absence of fatty changes; 2) mild FL, a mild increase in fine echoes in the liver parenchyma with blurring of diaphragm and intrahepatic vessels; and 3) moderate/severe FL, a marked increase in fine echoes in the parenchyma with poorly visible or invisible intrahepatic vessels, diaphragm, and posterior right lobe of the liver. USG is a reliable and accurate imaging technique to screen FL [21, 22].

Follow-up FL examination

During each follow-up visit, the participants underwent USG examination. Follow-up FL status was defined as the severity of FL measured by USG at the time when participants developed new-onset HTN or DM. For participants who did not develop new-onset HTN or DM, the FL measured by

USG findings at the last visit were used as their follow-up FL status.

Definitions of pre-HTN, HTN, impaired fasting glucose, and DM

Pre-HTN is defined as a systolic blood pressure (SBP) of 120–139 mmHg and diastolic BP (DBP) of 80–89 mmHg. HTN is defined as persistent SBP $\geq$ 140 mmHg, DBP $\geq$ 90 mmHg, or the use of antihypertensive agents [23]. The year of new-onset HTN was defined as the first year in the series during which time the subjects met the definition of HTN or began using antihypertensive agents.

Impaired fasting glucose (IFG) is defined as a serum FG level of 100–125 mg/dL, and DM is defined as FG $\geq$ 126 mg/dL or the use of antihyperglycemic agents [24]. The year of new-onset DM was defined as the first year during which time the subjects met the definition of DM or began taking antihyperglycemic agents.

Laboratory data

FG, AST, ALT, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), total cholesterol and triglycerides, HBV surface antigen (HBsAg), HCV antibody (anti-HCV), and histories of antihypertensive and antihyperglycemic treatments were retrieved. Body mass index (BMI) cut-offs were suggested by the Health Promotion Administration in Taiwan (normal weight 18.5–23.9 kg/m^2, overweight 24–26.9 kg/m^2, and obese $\geq$ 27 kg/m^2).

Statistical analyses

Data were analyzed with JMP version 10 (SAS Inc., Cary, NC, USA). Cohort characteristics were described using numbers with percentage (%), and the results of continuous variables are expressed as the mean $\pm$ standard deviation. Pearson's chi-square test was used to analyze the dichromatic differences. Factors with $p < 0.1$ in univariate analyses were further evaluated in multiple logistic regression analyses [25]. Kaplan–Meier survival curves were used to determine the cumulative incidences and lifetime risk of new-onset HTN and DM. Adjusted hazard ratios (aHRs) for factors associated with new-onset HTN and DM were determined using the Cox proportional hazards model. All tests were two-tailed, and statistical significance was set at $p < 0.05$.

Results

Cross-sectional cohort

Of the 41,888 subjects in the cross-sectional cohort (Table 1, mean age: 40.4 years) 80.9% were male, 19.4% seropositive for HBsAg, and 2.7% seropositive for anti-HCV. A total of 22,852 (54.6%) subjects had FL, including 18,203 (43.46%) with mild FL and 4,649 (11.10%) with moderate/severe FL (Supplementary Table 1 and Supplementary Table 2). The prevalence rates of existing HTN and DM were 13.5% (n = 5668) and 3.4% (n = 1411), respectively.

Factors associated with existing HTN in the cross-sectional cohort

The prevalence of existing HTN in the cross-sectional cohort was 7.75% (1476/19036), 16.66% (3033/18203), and 24.93% (1159/4649) among subjects without FL, with mild FL, and with moderate/severe FL, respectively. In multivariate regression analyses, older age (56–65 years) and (46–55 years), obesity, and DM had leading adjusted odds ratio (aORs) of 7.11, 5.37, 3.51, and 2.13 respectively. Moderate/severe and mild FL were significantly associated with a higher risk of existing HTN (aOR/95% confidence intervals [CIs] 1.59/1.43–1.77 and 1.22/1.13–1.32, respectively). Male, hypercholesterolemia, hypertriglyceridemia, higher AST and ALT levels, smoking, and HBsAg seropositivity were also associated with existing HTN (Supplementary Table 1).

Factors associated with existing DM in the cross-sectional cohort

The prevalence of existing DM in the cross-sectional cohort was 1.46% (277/19,036), 4.21% (766/18,203), and 7.92% (368/4,649) among subjects without FL, with mild FL, and with moderate/severe FL, respectively. In multivariate regression analyses for risk of existing DM, older age (56–65 years) and (46–55 years), moderate/severe FL, and HTN had leading aORs of 16.48, 10.70, 2.63, and 2.36 respectively, followed by hypertriglyceridemia, AST and ALT levels, and obesity. Moderate/severe FL and mild FL were significantly associated with a higher risk of existing DM (aOR/CI: 2.63/2.17–3.19 and 1.72/1.48–2.01). High BMI, pre-HTN and HTN, hypertriglyceridemia, and higher AST and ALT levels were also significantly associated with existing DM (Supplementary Table 2).

Longitudinal cohort

Of 34,865 subjects in the longitudinal cohort (Table 1, mean age 39.4 years) 78.9% were male, 19.6% seropositive for HBsAg, and 2.5% seropositive for anti-HCV. We censored the

Table 1 Demographic data of cross-sectional and longitudinal cohorts

Variables[a]	Cross-sectional cohort n = 41,888	Longitudinal cohort[b] n = 34,865	p value
Age, years	40.4 ± 8.8	39.4 ± 8.7	**< 0.0001**
Sex, male, n (%)	33,871 (80.9)	27,514 (78.9)	**< 0.0001**
Body Height, cm	167.3 ± 7.3	167.4 ± 7.4	0.3324
Body weight, kg	68.2 ± 11.6	67.2 ± 11.4	**< 0.0001**
Body mass index, kg/m^2	24.3 ± 3.4	23.9 ± 3.2	**< 0.0001**
SBP, mmHg	124.6 ± 15.5	121.0 ± 12.3	**< 0.0001**
DBP, mmHg	79.5 ± 11.1	77.0 ± 9.1	**< 0.0001**
Smoker, n (%)	8701 (20.8)	7287 (20.9)	0.6623
Fasting blood sugar, mg/dL	96.2 ± 22.5	92.6 ± 10.9	**< 0.0001**
Total cholesterol[c], mg/dL	187.1 ± 33.1	185.5 ± 32.3	**< 0.0001**
Triglyceride[d], mg/dL	131.5 ± 98.2	122.7 ± 84.1	**< 0.0001**
HDL-C[e], mg/dL	54.3 ± 13.2	55.0 ± 13.3	**0.0001**
LDL-C[f], mg/dL	110.8 ± 31.3	109.9 ± 30.4	**0.0233**
HBsAg seropositivity, n (%)	8119 (19.4)	6826 (19.6)	0.4953
Anti-HCV seropositivity, n (%)	1117 (2.7)	878 (2.5)	0.1984
Fatty liver, n (%)	22,852 (54.6)	17,632 (50.6)	**< 0.0001**
AST, U/L	18.2 ± 11.9	17.7 ± 11.2	**< 0.0001**
ALT, U/L	20.5 ± 20.6	19.6 ± 20.0	**< 0.0001**
Hypertension, n (%)	5668 (13.5)	0 (0.0)	**< 0.0001**
Diabetes, n (%)	1411 (3.4)	0 (0.0)	**< 0.0001**

Statistical significance with a p < 0.05 was indicated in bold

SBP systolic blood pressure, *DBP* diastolic blood pressure, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *HBsAg* hepatitis B surface antigen, *anti-HCV* hepatitis C antibody

[a]Data are shown as the number (%) or means ± standard deviations unless otherwise indicated

[b]Subjects who had no history of hypertension and/or diabetes at enrollment were enrolled as the longitudinal cohort

[c]Missing data n = 36

[d]Missing data n = 66

[e]Data were based on 11,583 and 9985 subjects, respectively, in cross-sectional and longitudinal cohorts, respectively

[f]Data were based on 11,566 and 9978 subjects, respectively, in cross-sectional and longitudinal cohorts, respectively

date according to the events analyzed, such as the time of HTN or DM development if the participants developed new-onset of HTN or DM. On an average, participants underwent the health check-up process 6 times before reaching to their endpoints or last visit. In the assessment of HTN development, the mean follow-up period was 6.45 (±4.18) years (range, 1–14 years). The mean follow-up period was 6.75 (±4.31) years (range, 1–14 years) in the assessment of DM development.

Incidence and risk of new-onset HTN in the longitudinal cohort

A total of 3,208 subjects developed new-onset HTN during 224,810 person-years follow-up (annual incidence, 14.3/1,000 person-years). The 3-, 5-, 7- and 10-year cumulative incidences of HTN were 2.56%, 5.57%, 8.92%, and

14.35%, respectively. The cumulative lifetime risk of HTN at 40, 50, 60, and 65 years old was 1.35%, 8.71%, 24.41%, and 32.93%, respectively (Fig. 1, Supplementary Table 3).

Risk of new-onset HTN and severity of FL

Among the 17,233 subjects without FL, 1,037 (6.02%) developed HTN during 109,981 person-years follow-up (annual incidence, 9.4/1000 person-years). For the 14,427 subjects with mild FL, 1,834 (12.71%) developed HTN during 100,695 person-years follow-up (annual incidence, 18.2/1000 person-years). Of the 4,649 subjects with moderate/severe FL, 337 (10.51%) developed HTN during 14,134 person-years follow-up (annual incidence, 23.8/1000 person-years).

In Kaplan–Meier analysis, the 3-, 5-, 7- and 10-year cumulative incidences of HTN were 1.57%, 3.51%,

Fig. 1 Cumulative lifetime risk of new-onset hypertension and diabetes
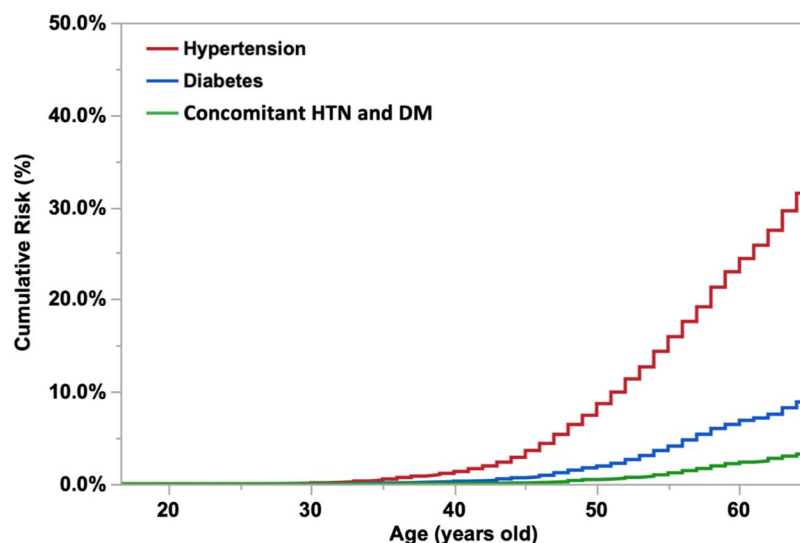
No. at risk

Hypertension	34708	32822	23965	14290	2587
Diabetes	34705	32841	24092	14891	2954
Concomitant HTN and DM	34699	32836	24113	15010	3037

5.79% and 9.49%, respectively, in subjects without FL, compared to 3.21%, 6.96%, 11.08%, and 17.89%, respectively, in subjects with mild FL (crude HR [cHR]/CI 1.89/1.75–2.04), and 4.96%, 10.71%, 16.97% and 26.16%, respectively, in subjects with moderate/severe FL (cHR/CI 2.97/2.62–3.36). The cumulative lifetime risk of HTN at 40, 50, 60, and 65 years old was 0.73%, 5.93%, 18.65%, and 25.88%, respectively, in subjects without FL, compared to 1.59%, 10.46%, 28.57%, and 37.23%, respectively, in subjects with mild FL (cHR/CI: 1.74/1.61–1.88), and 3.54%, 14.66%, 32.18%, and 45.92%, respectively, in subjects with moderate/severe FL (cHR/CI: 2.37/2.10–2.69; Fig. 2, Supplementary Table 4 and Supplementary Table 5).

Factors associated with new-onset HTN

In Cox proportional regression analyses, pre-HTN at baseline had the highest risk of developing HTN (aHR/CI 4.23/3.75–4.75) followed by older age (56–65 years; aHR/CI 2.31/1.75–3.07) (46–55 years; aHR/CI 2.22/1.99–2.50) and obesity (aHR/CI: 1.93/1.74–2.14). Subjects with mild FL and moderate/severe FL remained at significantly higher risk of new-onset HTN (aHR/CI: 1.26/1.16–1.37 and 1.54/1.34–1.77, respectively), compared to those without FL. Male sex, smoking, anti-HCV seropositivity, IFG, and higher level of TG were also significantly associated with new-onset HTN (Table 2).

Risk of new-onset HTN and change in severity of FL during follow-up (Table 3)

Among 17,233 subjects without FL at baseline, 3604 (20.91%) developed mild FL and 758 (4.39%) developed moderate/severe FL at censored date or last visit. The annual incidence of new-onset HTN was 8.2/1000 person-years for subjects with persistent no FL, 12.2/1000 person-years for subjects progressing to mild FL and 15.5/1000 person-years for those progressing to moderate/severe FL. Cox proportional regression analyses showed that the risk of new-onset HTN was significantly higher in those developing mild FL (aHR/CI 1.54/1.33–1.78) and moderate/severe FL (aHR/CI: 1.76/1.41–2.19) compared to those who remained no FL.

Among 14,427 subjects with mild FL at baseline, 4,528 (31.39%) regressed to no FL and 3,577 (24.79%) progressed to moderate/severe FL at censored date or last visit. The annual incidence of HTN was 10.7/1000 person-years for FL regressed subjects, 23.3/1000 person-years for persistent mild FL subjects, and 20.5/1000 person-years for FL progressed subjects. Cox proportional regression analysis showed that FL regressed individuals had a significantly lower risk of new-onset HTN (aHR/CI: 0.46/0.40–0.52 and aHR/CI: 0.59/0.52–0.68, respectively), compared to those who remained with mild FL and those who progressed to moderate/severe FL.

Among 4649 subjects with moderate/severe FL at baseline, 266 (5.72%) had no FL at end-of-follow-up and 841 (18.09%) regressed to mild FL at censored date or last visit.

Fig. 2 Cumulative lifetime risk of new-onset hypertension by the severity of fatty liver
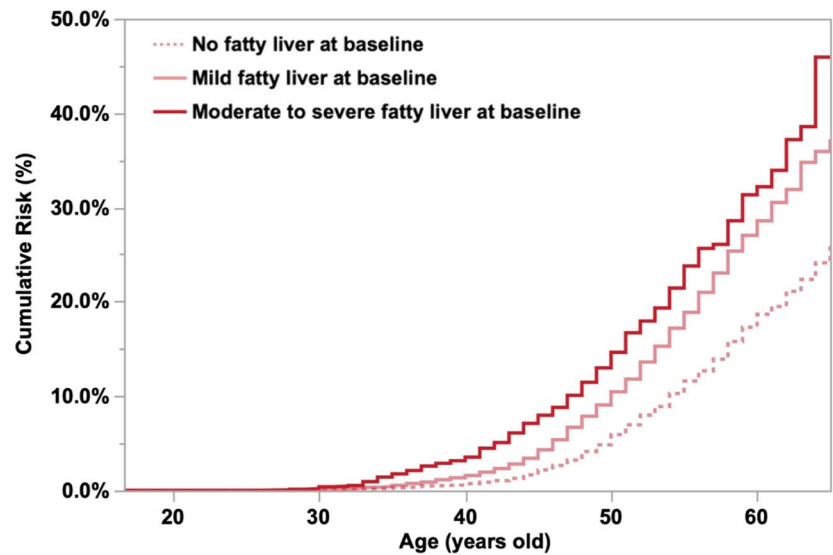
No. at risk					
No fatty liver	17150	15878	11106	6590	1210
Mild fatty liver	14365	13923	11113	6858	1217
Moderate / Severe fatty liver	3193	3021	1746	842	160

The annual incidence of HTN was 17.7/1,000 person-years for FL resolved subjects, 24.1/1,000 person-years for subjects with regression to mild FL, and 24.8/1000 person-years for those with persistent moderate/severe FL. Cox proportional regression analysis showed that FL resolved individuals had a significantly lower risk of new-onset HTN (aHR/CI 0.66/0.44–1.00) compared to those who remained with moderate/severe FL.

Incidence and risk of new-onset DM in the longitudinal cohort

A total of 822 subjects developed new-onset DM during 235,499 person-years follow-up (annual incidence, 3.5/1000 person-years). The 3-, 5-, 7- and 10-year cumulative incidences of DM were 0.62%, 1.39%, 2.36%, and 3.89%, respectively. The cumulative lifetime risk of DM at 40, 50, 60, and 65 years old was 0.30%, 1.94%, 6.90%, and 10.57%, respectively (Fig. 1, Supplementary Table 3).

Risk of new-onset DM and severity of FL

Among the 17,233 subjects without FL, 93 (0.54%) developed DM during 114,081 person-years follow-up (annual incidence, 0.8/1000 person-years). For the 18,203 subjects with mild FL, 560 (4.21%) developed DM during 106,582 person-years follow-up (annual incidence, 5.3/1000 person-years). Of the 4649 subjects with moderate/severe FL, 169 (7.92%) developed DM during 14,836

person-years follow-up (annual incidence, 11.4/1000 person-years).

In Kaplan–Meier analysis, the 3-, 5-, 7- and 10-year cumulative incidences of DM were 0.12%, 0.34%, 0.57%, and 0.85%, respectively, in subjects without FL, compared to 0.93%, 2.02%, 3.41%, and 5.73%, respectively, in subjects with mild FL (cHR/CI 6.26/5.03–7.80), and 1.99%, 4.54%, 8.64%, and 15.38%, respectively, in subjects with moderate/severe FL (cHR/CI 16.18/12.55–20.87). The cumulative lifetime risk of DM at 40, 50, 60, and 65 years old was 0.08%, 0.47%, 1.85%, and 2.54%, respectively, in subjects without FL, compared to 0.37%, 2.78%, 9.71%, and 14.03%, respectively, in subjects with mild FL (cHR/CI 5.83/4.68–7.27), and 1.19%, 5.78%, 20.75%, and 40.20%, respectively, in subjects with moderate/severe FL (cHR/CI 13.58/10.53–17.51; Fig. 3, Supplementary Tables 6 and 7).

Factors associated with new-onset DM

In Cox proportional regression analyses, moderate/severe FL (aHR/CI 5.88/4.44–7.81) had the highest risk of developing new-onset DM followed by IFG (aHR/CI 4.54/3.92–5.25), older age (56–65 years, aHR/CI 3.84/2.36–6.24), and mild FL (aHR/CI 3.22/2.56–4.07). Male sex, obesity, smoking, anti-HCV seropositivity, pre-HTN, IFG, and higher levels of TG and ALT were also significantly associated with the risk of new-onset DM (Table 4).

Table 2 Factors associated with new-onset of HTN in a longitudinal cohort

Factors	New-onset HTN		Cox proportional regression			
	Total, n	Yes, n (%)	Univariate HRs (95% CI)	p value	Multivariate aHRs (95% CI)	p value
Number	34,865	3208 (9.20)				
Age						
≤ 35 years old	12367	419 (3.39)	1		1	
36–45 years old	13,868	1718 (12.39)	2.03 (1.82–2.26)	< 0.0001	1.88 (1.69–2.10)	< 0.0001
46–55 years old	7551	1015 (13.44)	2.41 (2.15–2.71)	< 0.0001	2.22 (1.99–2.50)	< 0.0001
56–65 years old	1079	56 (5.19)	2.49 (1.88–3.29)	< 0.0001	2.31 (1.75–3.07)	< 0.0001
Sex						
Female	7351	209 (2.84)	1		1	
Male	27,514	2999 (10.90)	2.54 (2.21–2.92)	< 0.0001	1.37 (1.18–1.59)	< 0.0001
Body mass index						
< 24 kg/m^2	18,422	992 (5.38)	1		1	
24–27 kg/m^2	11,176	1344 (12.03)	2.05 (1.89–2.23)	< 0.0001	1.41 (1.29–1.54)	< 0.0001
≥ 27 kg/m^2	5267	872 (16.56)	3.32 (3.03–3.63)	< 0.0001	1.93 (1.74–2.14)	< 0.0001
Smoking						
Never	27,578	2258 (8.19)	1		1	
Yes/ever	7287	950 (13.04)	1.32 (1.22–1.42)	< 0.0001	1.25 (1.15–1.35)	< 0.0001
Fatty liver						
None	17,233	1037 (6.02)	1		1	
Mild	14,427	1834 (12.71)	1.89 (1.75–2.04)	< 0.0001	1.26 (1.16–1.37)	< 0.0001
Moderate/severe	3205	337 (10.51)	2.97 (2.62–3.36)	< 0.0001	1.54 (1.34–1.77)	< 0.0001
HBsAg seropositivity						
No	28,039	2501 (8.92)	1			
Yes	6826	707 (10.36)	1.03 (0.95–1.12)	0.4549	–	–
Anti-HCV seropositivity						
No	33,987	3088 (9.09)	1		1	
Yes	878	120 (13.67)	1.28 (1.07–1.54)	0.0081	1.29 (1.07–1.55)	0.0066
BP at baseline						
Normal	13,010	315 (2.42)	1		1	
Prehypertension	21,855	2893 (13.24)	5.25 (4.67–5.90)	< 0.0001	4.23 (3.75–4.75)	< 0.0001
BS at baseline						
Normoglycemia	26,400	2232 (8.45)	1		1	
IFG	8465	976 (11.53)	1.35 (1.35–1.46)	< 0.0001	1.12 (1.04–1.21)	0.0032
Total cholesterol[a]						
< 200 mg/dL	24,046	2081 (8.65)	1		1	
≥ 200 mg/dL	10,785	1123 (10.41)	1.28 (1.19–1.38)	< 0.0001	1.00 (0.93–1.07)	0.9505
Triglyceride[b]						
< 150 mg/dL	26,379	1950 (7.39)	1		1	
≥ 150 mg/dL	8436	1252 (14.84)	1.87 (1.74–2.00)	< 0.0001	1.20 (1.10–1.29)	< 0.0001
AST						
< 40 U/L	34,031	3136 (9.22)	1		1	
≥ 40 U/L	834	72 (8.63)	1.33 (1.05–1.67)	0.0182	0.94 (0.72–1.23)	0.6394
ALT						
< 40 U/L	32,227	2964 (9.20)	1		1	
≥ 40 U/L	2638	244 (9.25)	1.57 (1.37–1.79)	< 0.0001	1.11 (0.95–1.29)	0.1766

IFG impaired fasting glucose, *HRs* hazard ratios, *aHRs* adjusted hazard ratios, *CI* confidence interval, *BP* blood pressure, *BS* blood sugar, *DM* diabetes mellitus, *HTN* hypertension, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *HBsAg* hepatitis B surface antigen; anti-*HCV* hepatitis C antibody

[a]Missing data n = 36

[b]Missing data n = 66

Table 3 New-onset HTN in longitudinal cohorts by the change in FL status

Follow-up FL status[a]	New-onset HTN			Cox proportional regression	
	Total, n	Yes, n (%)	Annual Incidence (Per 1000 person-years)	Adjusted[bcd] HRs (95% CI)	p value
No fatty liver at baseline					
No	12,871	667 (5.18)	8.2	1	
Mild	3604	276 (7.66)	12.2	1.54 (1.33–1.78)	<0.0001
Moderate/severe	758	94 (12.40)	15.5	1.76 (1.41–2.19)	<0.0001
Mild fatty liver at baseline					
No	4528	368 (8.13)	10.7	1	
Mild	6322	893 (14.13)	23.3	2.19 (1.94–2.48)	<0.0001
Moderate/Severe	3577	573 (16.02)	20.5	1.69 (1.48–1.93)	<0.0001
Moderate/severe fatty liver at baseline					
No	266	26 (9.77)	17.7	1	
Mild	841	90 (10.70)	24.1	1.55 (1.00–2.40)	0.0513
Moderate/severe	2098	221 (10.53)	24.8	1.51 (1.00–2.28)	0.0484
Total	34,865	3208 (9.20)	14.3		

HRs hazard ratios, *CI* confidence interval, *BP* blood pressure, *BS* blood sugar, *HTN* hypertension, *TC* Total cholesterol, *TG* Triglyceride

[a]Follow-up FL status was defined as the severity of FL measured by USG at the time when participants developed new-onset HTN. For participants who did not develop new-onset HTN, the USG findings during the last visit will be used as their follow-up FL status
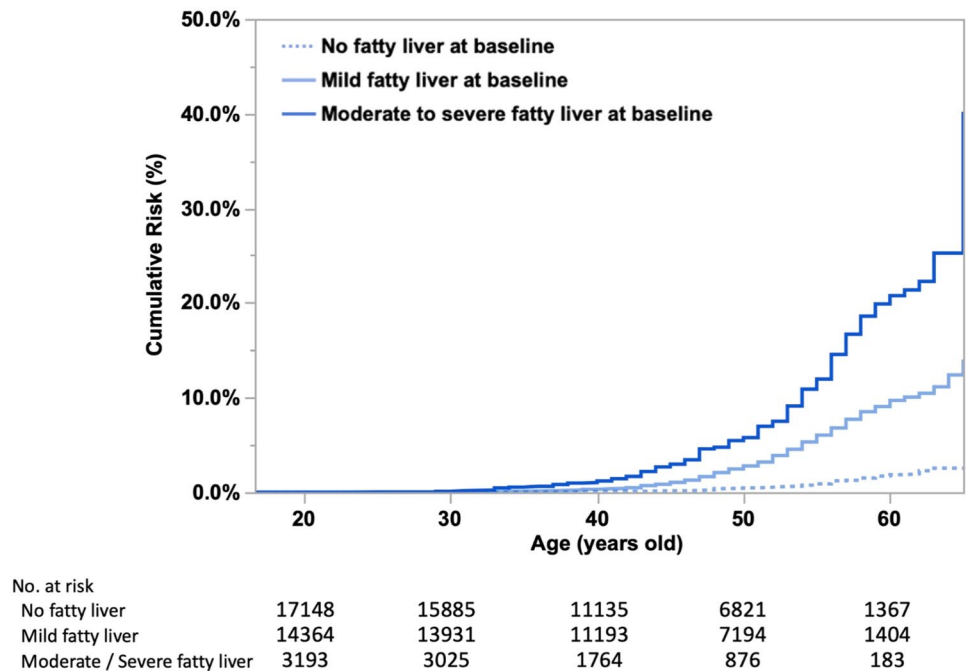
[b]Adjusted for age; sex; BMI; smoking; baseline BP; baseline BS; and TC, TG levels (No fatty liver at baseline)

[c]Adjusted for age; sex; BMI; smoking; baseline BP; baseline BS; and TC, TG levels (Mild fatty liver at baseline)

[d]Adjusted for age; sex; BMI; baseline BP; and TG levels (Moderate/Severe fatty liver at baseline)

Fig. 3 Cumulative lifetime risk of new-onset diabetes by the severity of fatty liver

No. at risk					
No fatty liver	17148	15885	11135	6821	1367
Mild fatty liver	14364	13931	11193	7194	1404
Moderate / Severe fatty liver	3193	3025	1764	876	183

Risk of new-onset DM and change in severity of FL during follow-up (Table 5)

Among the 17,233 subjects without FL at baseline, 3572 (20.72%) developed mild FL and 792 (4.60%) developed moderate/severe FL at censored date or last visit. The annual incidence of new-onset DM was 0.34/1000 person-years for subjects with persistent no FL, 0.98/1,000 person-years for subjects progressing to mild FL and 1.77/1000 person-years for those progressing to moderate/severe FL. Cox proportional regression analyses showed that subjects developing mild FL and moderate/severe FL had significantly higher risks of new-onset DM (aHR/CI 2.22/1.41–3.48 and 2.81/1.51–5.21, respectively), compared to those who remained without FL.

Among 14,427 subjects with mild FL at baseline, 4,572 (31.70%) resolved FL and 3,745 (25.96%) deteriorated to moderate/severe FL at censored date or last visit. The annual incidence of DM was 1.42/1000 person-years for FL regressed subjects, 3.83/1000 person-years for persistent mild FL subjects, and 6.97/1000 person-years for FL progressed subjects. Cox proportional regression analysis showed that subjects who resolved FL had a significantly lower risk of new-onset DM (aHR/CI: 0.36/0.27–0.47 and 0.32/0.24–0.42, respectively) compared to those who remained mild FL and those who progressed to moderate/severe FL.

Among 4,649 subjects with moderate/severe FL at baseline, 256 (5.51%) resolved FL, while 837 (18.00%) regressed to mild FL at censored date or last visit. Cox regression analysis showed that subjects who resolved FL had a significantly lower risk of new-onset DM compared to those who regressed to mild FL and those who remained with moderate/severe FL (aHR/CI: 0.22/0.08–0.63 and 0.20/0.08–0.55, respectively).

Incidence of new onset of concomitant HTN and DM in the longitudinal cohort

A total of 252 subjects developed new-onset concomitant HTN and DM during 238,058 person-years follow-up (annual incidence, 1.1/1000 person-years). The 3-, 5-, 7- and 10-year cumulative incidences of concomitant HTN and DM were 0.05%, 0.23%, 0.55%, and 1.20%, respectively. The cumulative lifetime risk of concomitant HTN and DM at 40, 50, 60, and 70 years old was 0.06%, 0.52%, 2.31%, and 4.42%, respectively (Fig. 1, Supplementary Table 3).

Risk of new-onset concomitant HTN and DM and severity of FL

Among the 17,233 subjects without FL, 21 (0.12%) developed both HTN and DM during 114,400 person-years follow-up (annual incidence, 0.2/1,000 person-years). For the 14,427 subjects with mild FL, 163 (1.13%) developed DM during 108,416 person-years follow-up (annual incidence, 1.5/1,000 person-years). Of the 3,205 subjects with moderate/severe FL, 68 (2.12%) developed both HTN and DM during 15,242 person-years follow-up (annual incidence, 4.5/1,000 person-years).

Table 4 Factors associated with new-onset of DM in a longitudinal cohort

Factors	New-onset DM		Cox proportional regression			
	Total, n	Yes, n (%)	Univariate HRs (95% CI)	p value	Multivariate aHRs (95% CI)	p value
Number	34,865	822 (2.36)				
Age						
≤35 years old	12,367	82 (0.66)	1		1	
36–45 years old	13,868	420 (3.03)	2.51 (1.98–3.18)	<0.0001	2.34 (1.84–2.97)	<0.0001
46–55 years old	7551	299 (3.96)	3.54 (2.77–4.52)	<0.0001	3.21 (2.50–4.13)	<0.0001
56–65 years old	1079	21 (1.95)	4.69 (2.90–7.58)	<0.0001	3.84 (2.36–6.24)	<0.0001
Sex						
Female	7351	53 (0.72)	1		1	
Male	27,514	769 (2.79)	2.52 (1.90–3.33)	<0.0001	1.36 (1.02–1.81)	0.0389
Body mass index						
<24 kg/m²	18,422	172 (0.93)	1		1	
24–27 kg/m²	11,176	274 (2.45)	2.33 (1.93–2.82)	<0.0001	1.17 (0.96–1.43)	0.1159
≥27 kg/m²	5267	376 (7.14)	7.84 (6.55–9.39)	<0.0001	2.72 (2.22–3.32)	<0.0001
Smoking						
Never	27,578	537 (1.95)	1		1	
Yes/ever	7287	285 (3.91)	1.65 (1.43–1.90)	<0.0001	1.40 (1.21–1.63)	<0.0001
Fatty liver						
None	17,233	93 (0.54)	1		1	
Mild	14,427	560 (3.88)	6.26 (5.03–7.80)	<0.0001	3.22 (2.56–4.07)	<0.0001
Moderate/severe	3205	169 (5.27)	16.18 (12.55–20.87)	<0.0001	5.88 (4.44–7.81)	<0.0001
HBsAg seropositivity						
No	28,039	646 (2.30)	1			
Yes	6826	176 (2.58)	1.00 (0.84–1.18)	0.9688	–	–
Anti-HCV seropositivity						
No	33,987	784 (2.31)	1		1	
Yes	878	38 (4.33)	1.57 (1.13–2.17)	0.0066	1.69 (1.22–2.36)	0.0018
BP at baseline						
<120/80 mmHg	13,010	160 (1.23)	1		1	
Pre-HTN	21,855	662 (3.03)	2.19 (1.84–2.60)	<0.0001	1.34 (1.13–1.60)	0.0011
BS at baseline						
Normoglycemia	26,400	282 (1.07)	1		1	
IFG	8465	540 (6.38)	6.01 (5.20–6.94)	<0.0001	4.54 (3.92–5.25)	<0.0001
Total cholesterol[a]						
<200 mg/dL	24,046	491 (2.04)	1		1	

Table 4 (continued)

Factors	New-onset DM		Cox proportional regression			
	Total, n	Yes, n (%)	Univariate HRs (95% CI)	p value	Multivariate aHRs (95% CI)	p value
≥200 mg/dL	10,785	331 (3.07)	1.59 (1.38–1.83)	<0.0001	0.97 (0.84–1.12)	0.6475
Triglyceride[b]						
<150 mg/dL	26,379	367 (1.39)	1		1	
≥150 mg/dL	8436	455 (5.39)	3.50 (3.05–4.02)	<0.0001	1.63 (1.41–1.89)	<0.0001
AST						
<40 U/L	40,642	2597 (6.39)	1		1	
≥40 U/L	1246	199 (15.97)	2.13 (1.47–3.08)	<0.0001	0.96 (0.63–1.46)	0.8325
ALT						
<40 U/L	38,237	2318 (6.06)	1		1	
≥40 U/L	3651	478 (13.09)	2.68 (2.17–3.29)	<0.0001	1.30 (1.02–1.66)	0.0353

IFG impaired fasting glucose, *HRs* hazard ratios, *aHRs* adjusted hazard ratios; *CI* confidence interval, *BP* blood pressure, *BS* blood sugar, *DM* diabetes mellitus, *HTN* hypertension, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *HBsAg* hepatitis B surface antigen, *anti-HCV* hepatitis C antibody

[a]Missing data n=36

[b]Missing data n=66

In Kaplan–Meier analysis, the 3-, 5-, 7-, and 10-year cumulative incidences of both HTN and DM were 0.01%, 0.02%, 0.08%, and 0.18%, respectively, in subjects without FL, compared to 0.07%, 0.33%, 0.73%, and 3.16%%, respectively, in subjects with mild FL (cHR/CI 7.66/4.86–12.07), and 0.17%, 0.96%, 3.16%, and 11.758%, respectively, in subjects with moderate/severe FL (cHR/CI 33.41/20.46–54.56). The cumulative lifetime risk of both HTN and DM at 40, 50, 60, and 70 years old was 0.01%, 0.10%, 0.46%, and 0.69%, respectively, in subjects without FL, compared to 0.08%, 0.74%, 3.12%, and 6.91%, respectively, in subjects with mild FL (cHR/CI 7.39/4.69–11.64), and 0.29%, 1.74%, 9.36%, and 14,36%, respectively, in subjects with moderate/severe FL (cHR/CI 23.71/14.54–38.69; Fig. 4, Supplementary Tables 8 and 9).

Factors associated with new-onset concomitant HTN and DM

In Cox proportional regression analyses, moderate/severe FL (aHR/CI 9.10/5.33–15.54) had the highest risk of developing both HTN and DM, followed by pre-HTN (aHR/CI: 4.18/2.54–6.86), mild FL (aHR/CI 3.42/2.13–5.50), IFG (aHR/CI 3.40/2.63–4.40), and obesity (BMI ≥ 27 kg/m^2, aHR/CI 3.09/2.07–4.63). Age, obesity, smoking, anti-HCV seropositivity, and higher levels of TG, AST, and ALT were also significantly associated with the risk of new-onset DM and HTN (Table 6).

Discussion

In the current large-scale study, we demonstrated that patients with FL were at a high risk of HTN and DM in both cross-sectional and longitudinal settings, and the risk increased with the FL severity. The prevalence of HTN and DM among subjects without FL, with mild FL, and with moderate/severe FL was 7.75% and 1.46%, 16.66% and 4.21%, and 24.93% and 7.92%, respectively. The annual incidences of incident HTN and DM among subjects without FL, with mild FL, and with moderate/severe FL were 9.4 and 0.8, 18.2 and 5.3, and 23.8 and 11.4 per 1000 person-years, respectively, with a 10-year cumulative incidence rate of 9.49% and 0.85%, 17.89% and 5.73%, 26.16% and 15.38%, respectively.

Consistent with previous studies [12, 26–28], we further demonstrated that mild FL and moderate/severe FL were correlated with a 1.22- and 1.59-fold risk of co-existing HTN, respectively, in the general population and a 1.26- and 1.54-fold risk of developing new-onset HTN, respectively, among those without baseline HTN. Similarly, we also found

Table 5 New-onset DM in longitudinal cohorts by the change in FL status

Follow-up FL status[a]	New-onset DM			Cox proportional regression	
	Total, n	Yes, n (%)	Annual Incidence (Per 1000 person-years)	Adjusted[bcd] HRs (95% CI)	p value
No fatty liver at baseline					
No	12,869	44 (0.34)	0.5	1	
Mild	3572	35 (0.98)	1.5	2.22 (1.41–3.48)	0.0006
Moderate/Severe	792	14 (1.77)	2.1	2.81 (1.51–5.21)	0.0011
Mild fatty liver at baseline					
No	4572	65 (1.42)	1.8	1	
Mild	6109	234 (3.83)	5.9	2.80 (2.12–3.68)	< 0.0001
Moderate/Severe	3745	261 (6.97)	8.4	3.11 (2.35–4.11)	< 0.0001
Moderate/Severe fatty liver at baseline					
No	256	4 (1.56)	2.7	1	
Mild	837	42 (5.02)	10.7	4.45 (1.59–12.44)	0.0044
Moderate/Severe	2112	123 (5.82)	13.0	4.89 (1.80–13.28)	0.0018
Total	34,865	822 (2.36)	3.5		

HRs hazard ratios, *CI* confidence interval, *BP* blood pressure, *BS* blood sugar, *DM* diabetes mellitus, *TC* Total cholesterol, *TG* Triglyceride

[a]Follow-up FL status was defined as the severity of FL measured by USG at the time when participants developed new-onset DM. For participants who did not develop new-onset DM, the USG findings during the last visit will be used as their follow-up FL status

[b]Adjusted for age; sex; BMI; smoking; baseline BP; baseline BS; and TC, TG levels (No fatty liver at baseline)

[c]Adjusted for age; sex; BMI; smoking; baseline BP; baseline BS; and TC, TG levels (Mild fatty liver at baseline)

[d]Adjusted for age; BMI; baseline BS; and TG levels (Moderate/Severe fatty liver at baseline)

Fig. 4 Cumulative lifetime risk of new-onset concomitant hypertension and diabetes by the severity of fatty liver
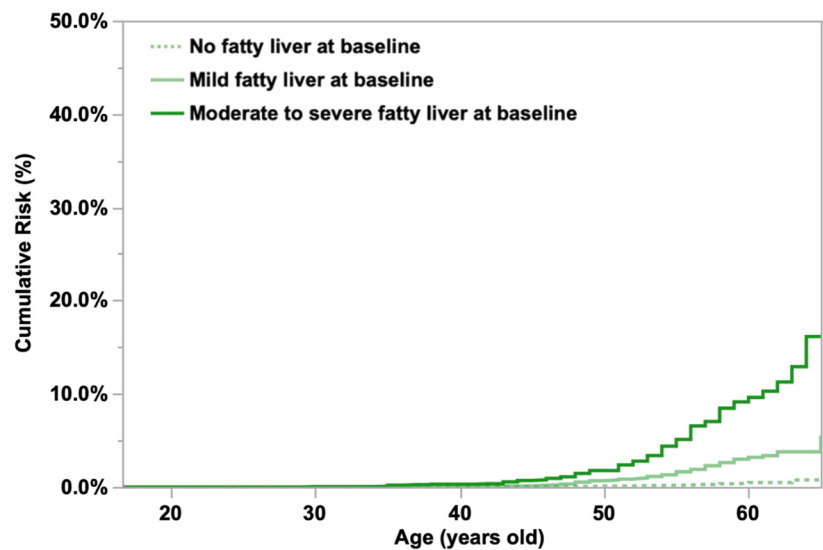
that mild FL and moderate/severe FL were associated with a 1.72- and 2.63-fold risk of co-existing DM, respectively, in the general population and a 3.22- and 5.88-fold risk of developing new-onset DM, respectively.

Table 6 Factors associated with new-onset concomitant HTN and DM in a longitudinal cohort

Factors	New-onset HTN and DM		Cox proportional regression			
	Total, n	Yes, n (%)	Univariate HRs (95% CI)	p value	Multivariate aHRs (95% CI)	p value
Number	34,865	252 (0.72)				
Age						
≤35 years old	12,367	23 (0.19)	1		1	
36–45 years old	13,868	134 (0.97)	2.26 (1.45–3.53)	0.0003	2.21 (1.41–3.47)	0.0006
46–55 years old	7551	92 (1.22)	3.14 (1.98–4.96)	<0.0001	3.10 (1.94–4.95)	<0.0001
56–65 years old	1079	3 (0.28)	3.27 (0.98–10.90)	0.0544	2.95 (0.87–9.95)	0.0816
Sex						
Female	7351	10 (0.14)	1		1	
Male	27,514	242 (0.88)	3.45 (1.83–6.51)	<0.0001	1.36 (0.71–2.61)	0.3610
Body mass index						
<24 kg/m^2	18,422	36 (0.20)	1		1	
24–27 kg/m^2	11,176	87 (0.78)	3.36 (2.28–4.96)	<0.0001	1.46 (0.98–2.19)	0.0631
≥27 kg/m^2	5267	129 (2.45)	12.29 (8.49–17.78)	<0.0001	3.09 (2.07–4.63)	<0.0001
Smoking						
Never	27,578	156 (0.57)	1		1	
Yes/ever	7287	96 (1.32)	1.78 (1.38–2.29)	<0.0001	1.42 (1.09–1.85)	0.0084
Fatty liver						
None	17,233	21 (0.12)	1		1	
Mild	14,427	163 (1.13)	7.66 (4.86–12.07)	<0.0001	3.42 (2.13–5.50)	<0.0001
Moderate/severe	3205	68 (2.12)	33.41 (20.46–54.56)	<0.0001	9.10 (5.33–15.54)	<0.0001
HBsAg seropositivity						
No	28,039	194 (0.69)	1			
Yes	6826	58 (0.85)	1.06 (0.79–1.42)	0.6873	–	–
Anti-HCV seropositivity						
No	33,987	235 (0.69)	1		1	
Yes	878	17 (1.94)	2.22 (1.35–3.63)	0.0015	2.57 (1.55–4.25)	0.0002
BP at baseline						
<120/80 mmHg	13,010	17 (0.13)	1		1	
Prehypertension	21,855	235 (1.08)	7.01 (4.29–11.47)	<0.0001	4.18 (2.54–6.86)	<0.0001
BS at baseline						
Normoglycemia	26,400	103 (0.39)	1		1	
IFG	8465	149 (1.76)	4.57 (3.55–5.88)	<0.0001	3.40 (2.63–4.40)	<0.0001
Total cholesterol[a]						
<200 mg/dL	24,046	146 (0.61)	1		1	

Table 6 (continued)

Factors	New-onset HTN and DM		Cox proportional regression				
	Total, n	Yes, n (%)	Univariate HRs (95% CI)	p value	Multivariate aHRs (95% CI)	p value
≥ 200 mg/dL	10,785	106 (0.98)	1.70 (1.33–2.19)	< 0.0001	1.00 (0.78–1.30)	0.9727
Triglyceride[b]						
< 150 mg/dL	26,379	84 (0.32)	1		1	
≥ 150 mg/dL	8436	168 (1.99)	5.37 (4.13–6.97)	< 0.0001	2.29 (1.73–3.02)	< 0.0001
AST						
< 40 U/L	34,031	238 (0.70)	1		1	
≥ 40 U/L	834	14 (1.68)	3.76 (2.19–6.45)	< 0.0001	1.77 (0.93–3.39)	0.0839
ALT						
< 40 U/L	32,227	218 (0.68)	1		1	
≥ 40 U/L	2638	34 (1.29)	3.30 (2.30–4.74)	< 0.0001	1.12 (0.72–1.74)	0.6125

IFG impaired fasting glucose, *HRs* hazard ratios, *aHRs* adjusted hazard ratios, *CI* confidence interval, *BP* blood pressure, *BS* blood sugar, *DM* diabetes mellitus, *HTN* hypertension, *ALT* alanine aminotransferase, *HBsAg* hepatitis B surface antigen, *anti-HCV* hepatitis C antibody

[a]Missing data n = 36

[b]Missing data n = 66

Studies have shown that the combination of HTN and DM increases the risk of stroke and microvascular and macrovascular complications [29–31]. Notably, in our study, mild FL and moderate/severe FL were associated with a 3.42- and 9.1-fold risk of developing new-onset concomitant DM and HTN, even among younger subjects. Our findings show that moderate/severe FL is the leading risk factor for developing concurrent DM and HTN, and patients should be monitored carefully for the development of these conditions. Therefore, screening of FL allows the early identification of risk of HTN and DM, which could help with the application of early intervention with lifestyle modification and weight reduction to avoid the progression of FL and prevent HTN and DM development [32].

Uncontrolled HTN is found in more than half of FL patients with HTN [28]. Cardiovascular disease is the leading cause of mortality in FL patients [13]. Therefore, screening for HTN in patients with FL and implementing appropriate interventions to control BP as well as cardiovascular risk would benefit the overall health outcomes.

We also observed that pre-HTN, older age, obesity, male sex, smoking, and hypertriglyceridemia were significantly associated with a higher risk of new-onset HTN, as observed in a nationwide survey in Japan [33]. Similarly, IFG, older age, obesity, hypertriglyceridemia, smoking, and male sex were also the leading factors of developing DM. These results suggest that early lifestyle modification such as quitting smoking, weight reduction, and control of pre-HTN and/or IFS play important roles in preventing HTN and/or DM.

Notably, we observed a significant impact of resolved and progressed FL during follow-up in the risk of HTN and DM. It demonstrated that the development or progression of FL are significantly associated with increased risks of developing HTN and DM. Conversely, FL regression or resolved are associated with reduced risks of developing HTN and DM. These findings suggest the importance of monitoring and managing fatty liver as a potential risk factor for HTN and DM. Life style modification, exercise and diet control, which have been associated with improvement of FL [34], might have benefits in risk reduction for HTN and DM among subjects with significant FL.

Moreover, we observed a strong interaction between HTN and DM. Patients with IFG have a higher risk of developing HTN as previously reported [35], and patients with pre-HTN have a higher risk of developing DM. A possible pathophysiology is that insulin resistance affects the body's ability to regulate BP, causing an increase in peripheral vascular resistance and volume of circulatory fluid, which further activates the sympathetic nervous system, leading to the development of HTN in patients with DM [36].

This study had some limitations. First, no data on mortality was available. We were unable to evaluate the risk of mortality among subjects who developed HTN and/or DM. Second, the severity of FL was assessed by USG instead of a pathologic method or other new technologies, such as controlled attenuation parameter or magnetic resonance imaging [37]. However, abdominal USG is a widely used, well-established, and lower-cost imaging technique with high sensitivity and specificity. Although liver biopsy is the gold standard for the diagnosis of FL, it has limitations such as costliness, sampling error, and invasiveness [38]. Third, because no pharmaceutical agents approved for FL in the study period, all patients with FL were advised to execute life style modification, exercise and diet control. However, we were unable to obtain the data regarding the adherence of the advice among the participants.

In conclusion, FL is a significant risk factor for both prevalent and incidental HTN and DM; the risk increases with the severity of FL. Subjects with moderate/severe FL are at high risk of developing concomitant HTN and DM. Regression of or resolved FL reduced the risks of HTN and DM. Thus, early intervention for FL with lifestyle modification and regular surveillance for HTN and DM should be mandatory for FL patients.

Declarations

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