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Original Article

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Association between a Single-time Measurement of Fatty Liver Index and Occurrence of Sepsis among Individuals without Excessive Alcohol Consumption

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ABSTRACT

Background: Non-alcoholic fatty liver disease is increasing worldwide, and sepsis remains a major global health challenge owing to its high mortality. Given the lack of specific therapeutic agents for sepsis, identifying high-risk populations and implementing preventive measures are critical. This study aimed to investigate the association between a single-time fatty liver index (FLI) measurement and the long-term risk of sepsis.

Materials and Methods: The cohort included participants from the 2009 Korean National Health Screening Program with no excessive alcohol consumption or acute or chronic liver diseases. The FLI was calculated at baseline and categorized into three groups: low (<30), moderate (30–60), and high (>60). The subjects were followed-up for up to 10 years until sepsis diagnosis or death. Patients with sepsis identified during the washout and one-year lag periods were excluded.

Results: Of 3,222,171 participants, 64,226 (2.0%) developed sepsis during the follow-up period. The incidence rates per 1,000 person-years in the low-, moderate-, and high-FLI groups were 1.68, 2.52, and 2.58, respectively. In the multivariable Cox regression model, the high-FLI group had a significantly increased risk of sepsis, with an adjusted hazard ratio of 1.52 (95% confidence interval, 1.49–1.55) compared with the low-FLI group. Restricted cubic spline analysis showed a J-shaped nonlinear relationship between FLI and sepsis with increased sepsis risk above an FLI of 23.6.

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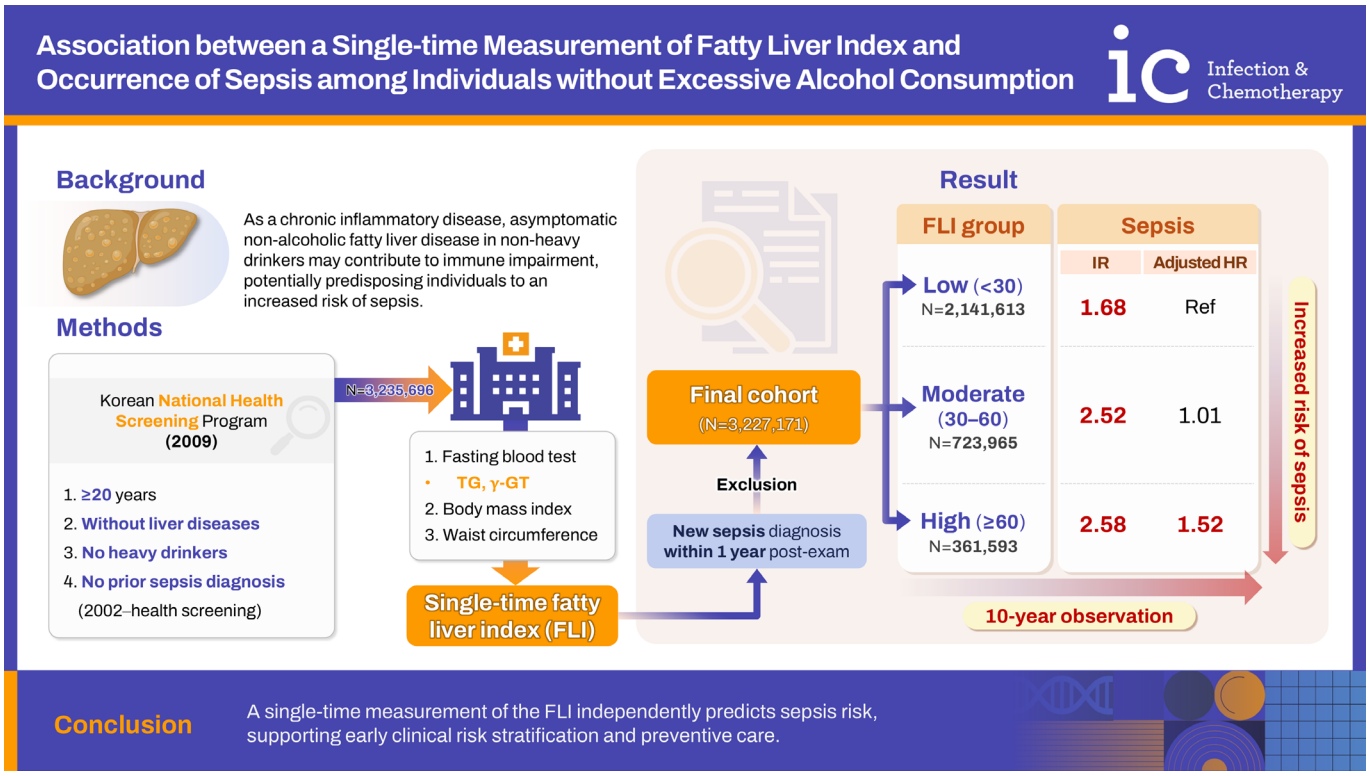
Conclusion: This large-scale, long-term observational study demonstrated a significant association between single-time FLI measurement and sepsis risk, highlighting the potential role of FLI in early risk stratification and the prevention of sepsis.

Keywords: Fatty liver index; Non-alcoholic fatty liver disease; Non-invasive test; Risk; Sepsis

GRAPHICAL ABSTRACT



INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) in individuals without excessive alcohol consumption represents a heterogeneous clinical spectrum of chronic hepatocellular steatosis in relation to various components of metabolic syndrome (MetS) [1, 2]. NAFLD encompasses two histological phenotypes of non-alcoholic fatty liver, lacking inflammation or exhibiting mild inflammation and non-alcoholic steatohepatitis, showing necrotizing damage in hepatocytes [1]. The ongoing accumulation of fat in NAFLD can gradually progress to fibrosis, compensated or decompensated liver cirrhosis (LC), hepatocellular carcinoma, and ultimately liver transplantation or mortality [2].

The prevalence of NAFLD is continuously growing alongside the rise in obesity, type 2 diabetes mellitus (T2DM), MetS, and aging. The pooled prevalence of NAFLD worldwide is considerably high, ranging from 30–35%, and shows a clear increasing trend in recent years [3]. Korea has a high prevalence (21–44%) and incidence (45–54/1,000 person-years) of NAFLD diagnosed by ultrasound in the general population [4, 5]. Unlike NAFLD in the Western countries, which has a significant relationship with overweight or insulin resistance, Asia has a higher proportion of lean NAFLD characterized by low body mass index (BMI) and metabolically obese state [3].

NAFLD increases the risk of developing various diseases affecting organs other than the liver, including chronic kidney disease, cardiovascular diseases, arrhythmias, stroke, dementia, and sarcopenia [6-9]. In addition, the low-grade long-term systemic inflammation, impaired clearance of microorganisms, dysregulation of

metabolism or immune mechanisms, and gut dysbiosis driven by NAFLD can result in vulnerability to invasion of pathogens and progression to infectious diseases [10, 11]. Sepsis has a fairly high mortality rate even in the modern era due to a lack of specific anti-sepsis drug and imprecise target for early resuscitation [12]. From a long-term public health perspective, determining whether mostly asymptomatic NAFLD is associated with the higher risk for sepsis may help prevent sepsis through the encouragement of vaccination and compliance with personal hygiene principles [13].

The standard methods for diagnosing NAFLD are biopsy and ultrasound with disadvantages of invasiveness and differences of results depending on the examiners, but simple assessments using usual clinical and laboratory parameters are required for easy detection with affordable cost in the large-scale population [14]. Several algorithms, including fatty liver index (FLI), NAFLD liver fat score, and hepatic steatosis index, have been proposed to evaluate the steatosis rather than fibrosis in NAFLD [14]. Among them, FLI, which is calculated based on serum triglyceride (TG), gamma glutamyl transferase (GGT), BMI, and waist circumference (WC), has been widely used and validated as an accurate and suitable non-invasive test (NIT) for epidemiologically screening NAFLD [15, 16]. This study aimed to verify the association between NAFLD diagnosed by FLI and the risk of sepsis in an Asian national cohort by utilizing health check-up data applicable to public health in clinical settings.

MATERIALS AND METHODS

1. Study population and data extraction

This longitudinal, retrospective cohort study used data from the Korean National Health Insurance Service (KNHIS). All populations in South Korea are mandatory enrolled in the KNHIS, and adults over the age of 20 years can voluntarily undergo the General Health Insurance Service-Health Screening (HEALS) program every two years without any extra cost [17]. The KNHIS-HEALS cohort database contains the following clinical information: (1) anthropometric measurements, including WC and BMI, (2) general examination, including blood pressure (BP), optometry, audiometry, urinalysis, and chest X-ray, (3) blood tests conducted after fasting from midnight prior to the HEALS, including glucose, total cholesterol, aspartate transaminase (AST), alanine transferase (ALT), TG and GGT, and (4) self-report questionnaires (**Supplementary Table 1**), including disease history, alcohol consumption, smoking, and physical activities [17].

From the 2009 HEALS program, we established a study population comprising adults aged 20 years or older, of whom 40% of all health screening participants were randomly sampled using a sex- and age-stratified random selection method for analysis. Individuals with preexisting liver diseases such as acute hepatitis A or chronic hepatitis B/C virus infection including carrier status, LC, or hepatocellular carcinoma, as well as those with heavy alcohol consumption, were excluded to construct a NAFLD cohort. To ensure temporal clarity in the relationship between NAFLD and sepsis, we further excluded individuals with a history of sepsis before or shortly after the baseline health examination. A one-year lag period following the health checkup was applied. Follow-up continued for up to ten years, during which participants were censored upon the first occurrence of sepsis or death.

2. Ethics statement

This study was approved by the Institutional Review Board of the Gangnam Severance Hospital, Yonsei University College of Medicine (Registration No. 3-2023-0267) with a waiver for informed consent. The permission to access the database was obtained from the KNHIS. The study was performed in accordance with the Declaration of Helsinki, ensuring that all participants' data were completely anonymized to uphold the principles of privacy protection.

3. FLI

We calculated the FLI with fasting laboratory data and measurements at HEALS according to the following formula: $e^x/(1+e^x)\times100$, $X=0.953\times\log_e TG$ (mg/dL)$+0.139\times$BMI (kg/m^2)$+0.718\times\log_e GGT$ (international unit [IU]/L)$+0.053\times$WC (cm)-15.745 [15]. Cohort participants were categorized into three groups based on FLI levels; high (≥60), moderate (30≤FLI<60), and low (<30).

4. Method for data extraction and definitions of clinical variables

The occurrence of the first sepsis during emergency department care and/or hospitalization was identified according to the ICD-10 codes that are consistent with the definition of sepsis syndrome (A02.1, A20.7, A22.7, A26.7, A32.7, A40, A41, A42.7, B37.7, R57.2, R65.0, and R65.1),

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except for sepsis in newborns (P36) and puerperal sepsis (O85) (**Supplementary Table 2**). To eliminate misdiagnoses of sepsis, cases with sepsis codes documented exclusively during outpatient visit were excluded.

Information on whether examinees had previously diagnosed T2DM, dyslipidemia, hypertension, or well-established comorbidities associated with increased sepsis risk before the HEALS was obtained using ICD-10 codes and prescription data in the KNHIS database. To enhance risk adjustment for sepsis, we incorporated a set of sepsis-related chronic conditions, including solid organ or hematopoietic stem cell transplantation status, hematologic malignancies, solid tumors, HIV infection, chronic heart disease, chronic lung disease, chronic kidney disease (CKD) including cases of end-stage renal disease undergoing dialysis, systemic connective tissue disorders, Crohn's disease, and ulcerative colitis (**Supplementary Table 3**). In addition, the inclusion of newly diagnosed cases after HEALS was strictly limited to instances in which both the relevant ICD-10 codes and corresponding medication claims were documented in the database within six months following the health screening. To ensure diagnostic accuracy, self-reported medical history and isolated laboratory findings from the HEALS was not used.

We defined heavy alcohol consumption as an average daily intake of over 30 g for men and over 20 g for women, based on the 7-day recall questionnaire [2]. Mild-to-moderate drinkers were defined as individuals who consumed less alcohol than those meeting this threshold. The BMI was divided into five categories by the World Health Organization Asia-Pacific region and the Korean Society for the Study of Obesity (<18.5 kg/m^2: underweight, 18.5–22.9 kg/m^2: normal, 23.0–24.9 kg/m^2: overweight, 25.0–29.9 kg/m^2: class I obesity, ≥30.0 kg/m^2: class II and III obesity), based on criteria that account for the unique characteristics of the Asian population, who exhibit an increased risk of T2DM and cardiovascular diseases at lower BMI thresholds compared to Western populations [18]. Participants on regular exercise were defined as mild-exercise for ≥5 days a week or vigorous exercise for ≥3 days a week on a self-reported questionnaire [19]. A WC of ≥90 or ≥85 cm was considered abdominal obesity in males and females, respectively (**Supplementary Table 4**) [18]. In the 2010 Population and Housing Census, participants with the smallest household income among the four quartiles of the entire population were assigned to the lowest 25th percentile group (Q1).

5. Statistical analysis

Continuous variables were expressed as the mean ± standard deviation or geometric mean (95% confidence interval [CI]), and one-way analysis of variance or Kruskal-Wallis test were used for comparisons among the three FLI groups. Categorical variables are presented as numbers (percentages), and were compared using the chi-square test. The incidence rate (IR) was recorded as the number of events per 1,000 person-years (PY).

We obtained the adjusted hazard ratios (aHRs) with 95% CI from multivariable Cox proportional hazard analysis to reveal the difference in the IR of sepsis according to FLI categories, after adjusting for age and sex (model 1); age, sex, income status, smoking, alcohol consumption, regular exercise, hypertension, dyslipidemia, and BMI (model 2); and the variables included in model 2 plus well-established major risk factors for sepsis, such as chronic comorbidities and immunocompromised conditions (Refer to **Supplementary Tables 3** and **4** for details) (model 3). In each model, the aHRs were calculated using the group with the lowest FLI (<30) as a reference. In addition, a restricted cubic spline (RCS) curve using the multivariable Cox regression model 3, which represents the relationships between continuous FLI values and aHRs of sepsis, was constructed to identify the FLI point with the lowest risk of sepsis.

All statistical analyzes were performed with the SAS software (version 9.4, SAS Institute Inc., Cary, NC, USA) and a two-tailed *P*-value ≤0.05 was considered statistically significant. The incidence probability of sepsis according to follow-up duration and the RCS curve were visualized using the SAS software and R-language (version 4.3.1, R Foundation for Statistical Computing, Vienna, Austria), respectively.

RESULTS

1. Baseline clinical characteristics of populations by FLI groups at the time of check-up

Of the individuals aged ≥20 years who participated in the HEALS program in 2009, we randomly selected 40% (N=4,234,415) for analysis. After excluding those with viral hepatitis, liver cirrhosis, hepatocellular carcinoma, heavy alcohol consumption, and missing data, a total of 3,240,956 participants were identified as the NAFLD

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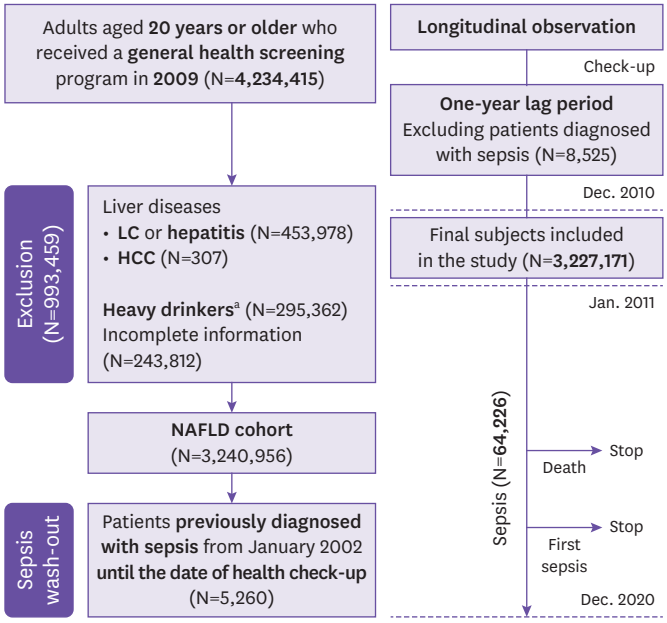

Figure 1. Schematic flow chart of the study subject's selection and follow-up process.
[a]Heavy alcohol consumption was defined as an average alcohol intake of ≥30 g/d and 20 g/d for men and women, respectively.
LC, liver cirrhosis; HCC, hepatocellular carcinoma; NAFLD, non-alcoholic fatty liver disease.

cohort. We further excluded individuals with prior sepsis (N=5,260) or sepsis occurring within one year after the health checkup (N=8,525), resulting in a final analytic cohort of 3,227,171 participants. These individuals were followed from January 2011 to December 2020 until the first occurrence of sepsis or death (**Fig. 1**).

The final study participants (N=3,227,171) in our cohort were classified as having low (N=2,141,613, 66.4%), moderate (N=723,965, 22.4%), or high (N=361,593, 11.2%) FLI. The most common age range was 40–65 years in all groups (53.6–59.5%), and the individuals in the low FLI group were the youngest (45.9±14.3 years) (*P*<0.001). Although the sex ratio of entire participants was similar, the proportion of male sex (40.3%, 68.8%, and 80.8% in the low, moderate, and high FLI group, respectively, *P*<0.001), BMI (22.2±2.4, 25.5±2.3, and 28.0±3.1 kg/m^2, *P*<0.001) and obesity with a BMI of 25.0 kg/m^2 or more (12.8%, 59.1%, and 86.4%, *P*<0.001), including the abdominal obesity (4.8%, 35.1%, and 68.6%, *P*<0.001), continued to increase from the low FLI to the high FLI group. Conversely, the percentages of never smokers (71.0%, 51.0%, and 39.6%, *P*<0.001) and never drinkers (60.1%, 50.0%, and 39.1%, *P*<0.001) continued to decrease from the low FLI to the high FLI group. Participants with T2DM, hypertension, or dyslipidemia were more frequent in the high FLI group than in the low and moderate FLI groups (all *P*<0.001).

The differences between the FLI groups in one-time measurements (systolic and diastolic BP) or laboratory values (glucose, total cholesterol, and TG) in HEALS exhibited a pattern similar to that of strictly defined comorbid diseases, according to ICD-10 codes and medications. The geometric mean values of AST (21.1, 24.9, and 30.2 IU/L, *P*<0.001), ALT (17.2, 26.1, and 37.2 IU/L, *P*<0.001), and GGT (18.4, 35.2, and 62.6 IU/L, *P*<0.001), which are most closely related to liver damage, also showed the same tendency, increasing from the low FLI to the high FLI group.

Table 1. Comparison of basic characteristics and measurement values at the time of the general health screening examination or comorbid diseases of participants divided into three groups according to fatty liver index

Characteristics	Total participants (N=3,227,171)	FLI			*P*-value
		Low (<30) (N=2,141,613)	Moderate (30–60) (N=723,965)	High (≥60) (N=361,593)	
Age, years	47.1±14.1	45.9±14.3	50.3±13.5	47.6±12.8	<0.001
Age groups, years					<0.001
<40	1,016,940 (31.5)	736,750 (34.4)	171,237 (23.7)	108,953 (30.1)	
40–64	1,788,647 (55.4)	1,147,835 (53.6)	430,373 (59.5)	210,439 (58.2)	
≥65	421,584 (13.1)	257,028 (12.0)	122,355 (16.9)	42,201 (11.7)	
Sex, male	1,653,673 (51.2)	863,105 (40.3)	498,283 (68.8)	292,285 (80.8)	<0.001
BMI, kg/m^2	23.6±3.2	22.2±2.4	25.5±2.3	28.0±3.1	<0.001
BMI groups[a], kg/m^2					<0.001
<18.5	126,426 (3.9)	125,564 (5.9)	731 (0.1)	131 (0.04)	
18.5–22.9	1,296,340 (40.2)	1,205,796 (56.3)	80,646 (11.1)	9,898 (2.7)	
23.0–24.9	789,677 (24.5)	535,718 (25.0)	214,679 (29.7)	39,280 (10.9)	
25.0–29.9	905,649 (28.1)	271,882 (12.7)	403,697 (55.8)	230,070 (63.6)	
≥30.0	109,079 (3.4)	2,653 (0.1)	24,212 (3.3)	82,214 (22.7)	
Waist circumference, cm	79.8±9.1	75.5±7.0	86.0±5.4	92.3±6.9	<0.001

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Table 1. (Continued) Comparison of basic characteristics and measurement values at the time of the general health screening examination or comorbid diseases of participants divided into three groups according to fatty liver index

Characteristics	Total participants (N=3,227,171)	FLI			*P*-value
		Low (<30) (N=2,141,613)	Moderate (30–60) (N=723,965)	High (≥60) (N=361,593)	
Abdominal obesity[b]	604,057 (18.7)	101,949 (4.8)	254,223 (35.1)	247,885 (68.6)	<0.001
Smoking					<0.001
Never	2,033,679 (63.0)	1,521,130 (71.0)	369,317 (51.0)	143,232 (39.6)	
Former	429,934 (13.3)	221,997 (10.4)	135,852 (18.8)	72,085 (19.9)	
Current	763,558 (23.7)	398,486 (18.6)	218,796 (30.2)	146,276 (40.5)	
Alcohol drinking[c]					<0.001
Never	1,789,487 (55.5)	1,286,228 (60.1)	362,020 (50.0)	141,239 (39.1)	
Mild-to-moderate	1,437,684 (44.6)	855,385 (39.9)	361,945 (50.0)	220,354 (60.9)	
Regular exercise[d]	567,894 (17.6)	372,269 (17.4)	134,742 (18.6)	60,883 (16.8)	<0.001
Income, lowest quartile	644,231 (20.0)	456,750 (21.3)	126,243 (17.4)	61,238 (16.9)	<0.001
Co-morbidities					
T2DM	256,560 (8.0)	103,897 (4.9)	87,938 (12.2)	64,725 (17.9)	<0.001
Hypertension	779,720 (24.2)	369,620 (17.3)	253,321 (35.0)	156,779 (43.4)	<0.001
SBP, mmHg	122.0±15.0	119.1±14.4	126.6±14.4	130.0±14.71	<0.001
DBP, mmHg	76.0±10.0	74.1±9.6	78.8±9.6	81.5±10.1	<0.001
Dyslipidemia	545,040 (16.9)	254,384 (11.9)	175,627 (24.3)	115,029 (31.8)	<0.001
CKD	224,695 (7.0)	134,846 (6.3)	60,948 (8.4)	28,901 (8.0)	<0.001
ESRD on dialysis	2,226 (0.1)	1,444 (0.1)	556 (0.1)	226 (0.1)	0.010
SOT or HSCT recipients	654 (0.02)	445 (0.02)	162 (0.02)	47 (0.01)	0.003
Hematologic malignancies	1,591 (0.05)	1,043 (0.05)	395 (0.05)	153 (0.04)	0.018
Solid cancers	44,475 (1.4)	31,354 (1.5)	9,622 (1.3)	3,499 (1.0)	<0.001
HIV infection	231 (0.01)	119 (0.01)	72 (0.01)	4 (0)	<0.001
Chronic heart diseases	206,337 (6.4)	108,561 (5.1)	65,241 (9.0)	32,535 (8.9)	<0.001
Chronic lung diseases	305,261 (9.5)	193,829 (9.1)	76,257 (10.5)	35,175 (9.6)	<0.001
Autoimmune diseases	71,979 (2.2)	48,438 (2.3)	16,835 (2.3)	6,706 (1.8)	<0.001
IBD	4,971 (0.2)	3,458 (0.2)	1,093 (0.2)	420 (0.1)	<0.001
Fasting blood tests					
Glucose, mg/dL	96.7±23.0	93.4±18.7	101.0±26.3	107.1±32.9	<0.001
Total C, mg/dL	195.2±36.7	189.3±34.6	203.9±36.9	212.5±39.3	<0.001
HDL-C, mg/dL	56.1±27.7	58.5±26.0	52.1±30.7	49.5±29.12	<0.001
LDL-C, mg/dL	114.4±38.3	112.6±36.2	120.0±40.4	114.1±44.9	<0.001
AST, IU/L	22.8 (22.8–22.8)	21.1 (21.1–21.1)	24.8 (24.9–24.9)	30.2 (30.2–30.3)	<0.001
ALT, IU/L	20.6 (20.6–20.6)	17.2 (17.2–17.2)	26.1 (26.1–26.1)	37.2 (37.2–37.3)	<0.001
GGT, IU/L	24.4 (24.4–24.5)	18.4 (18.4–18.4)	35.2 (35.2–35.3)	62.6 (62.5–62.8)	<0.001
Triglyceride, mg/dL	110.1 (110.0–110.1)	86.7 (86.7–86.8)	154.9 (154.7–155.1)	227.9 (227.5–228.2)	<0.001
eGFR, mL/min/1.73m^2	87.5±45.4	88.5±44.4	85.1±45.9	85.9±50.1	<0.001
Sepsis	64,226 (2.0)	36,518 (1.7)	18,353 (2.5)	9,355 (2.6)	<0.001

All data are presented as mean ± standard deviation, geometric mean (95% CI), or number (percent).
[a]The obesity criteria by the WHO Asia-Pacific region obesity and the Korean Society for the Study of Obesity, reflecting research findings targeting Asians (<18.5 kg/m^2: underweight, 18.5–22.9 kg/m^2: normal, 23.0–24.9 kg/m^2: overweight, 25.0–29.9 kg/m^2: class I obesity, ≥30.0 kg/m^2: class II and III obesity).
[b]Abdominal obesity was defined as a WC of ≥90 cm in males or ≥85 cm in females.
[c]Alcohol consumption was classified according to the average daily drinking habit: (1) never, 0 g/day; (2) mild-to-moderate, <30 g/day.
[d]Defined as mild-term exercise for ≥5 days a week or vigorous exercise for ≥3 days in a week on the last 7-day self-report questionnaire.
FLI, fatty liver index; BMI, body mass index; T2DM, type 2 diabetes mellitus; SBP, systolic blood pressure; DBP, diastolic blood pressure; CKD, chronic kidney disease; ESRD, end-stage kidney disease; SOT, solid organ transplant; HSCT, hematopoietic stem cell transplant; HIV, human immunodeficiency virus; IBD, inflammatory bowel diseases; Total C, total cholesterol; HDL-C, high density lipoprotein-cholesterol; LDL-C, low density lipoprotein-cholesterol; AST, aspartate transaminase; IU, international unit; ALT, alanine aminotransferase; GGT, gamma-glutamyl transferase; eGFR, estimated glomerular filtration rate; CI, confidence interval; WHO, World Health Organization; WC, waist circumference.

During the 10-year follow-up period, sepsis was diagnosed in 1.99% (N=64,226) of the study participants. In the low-, moderate-, and high FLI groups, 36,518 (1.7%), 18,353 (2.5%), and 9,355 (2.6%) cases of sepsis occurred, respectively (**Table 1**).

2. Differences in the risk of sepsis by FLI category

The IR of sepsis was the highest at 2.58/1,000 PY in the high FLI group and the lowest in the low FLI group (1.68/1,000 PY). The unadjusted hazard ratio of sepsis based on the low FLI group was 1.50 (95% CI, 1.47–1.53)

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Table 2. Comparisons of incidence rate of sepsis according to fatty liver index subgroups

FLI group	Subjects (No)	Sepsis (No)	F/U duration (Years)	IR[a]	HR (95% CI)			
					Univariable	Multivariable		
					Unadjusted	Model 1[b]	Model 2[c]	Model 3[d]
Low	2,141,613	36,518	21,690,214	1.68	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
Moderate	723,965	18,353	7,277,295	2.52	1.50 (1.47–1.53)	1.11 (1.09–1.13)	1.02 (1.00–1.04)	1.01 (0.99–1.02)
High	361,593	9,355	3,628,321	2.58	1.54 (1.51–1.58)	1.44 (1.41–1.48)	1.23 (1.19–1.25)	1.52 (1.49–1.55)

[a]Per 1,000 person-years.
[b]Adjusted for age and sex.
[c]Adjusted for age, sex, income, smoking, alcohol consumption, regular exercise, hypertension, dyslipidemia, and BMI.
[d]Adjusted for well-established major risk factors for sepsis, including chronic comorbidities (*e.g.*, T2DM, CKD, chronic lung/heart diseases) and immunocompromised conditions, in addition to the variables included in model 2. All *P*-values within the model were ≤0.001.
FLI, fatty liver index; F/U, follow-up; IR, incidence rate; HR, hazard ratio; CI, confidence interval; BMI, body mass index; T2DM, type 2 diabetes mellitus.CKD, chronic kidney disease.

and 1.54 (1.51–1.58) in the moderate and high FLI group, respectively. In multivariable model 3, which was adjusted for various metabolic syndrome–related variables associated with FLI and established risk factors for sepsis, the risk of developing sepsis was not statistically significant in the moderate FLI group (aHR, 1.01; 95% CI, 0.99–1.02), whereas it remained significantly elevated in the high FLI group (aHR, 1.52; 95% CI, 1.49–1.55), corresponding to a 52% higher risk compared with the low FLI group (**Table 2**).

The 10-year cumulative incidence curves for first sepsis demonstrated that patients with low FLI consistently had the lowest risk in both the unadjusted model (**Fig. 2A**) and model 3 (**Fig. 2B**) (all *P*<0.001). In the unadjusted model, both moderate and high FLI groups had higher incidence than the low FLI group, whereas after adjustment, only the high FLI group remained at significantly increased risk. Differences in incidence became apparent as early as 1–2 years after baseline and progressively widened over time (**Fig. 2A and 2B**).

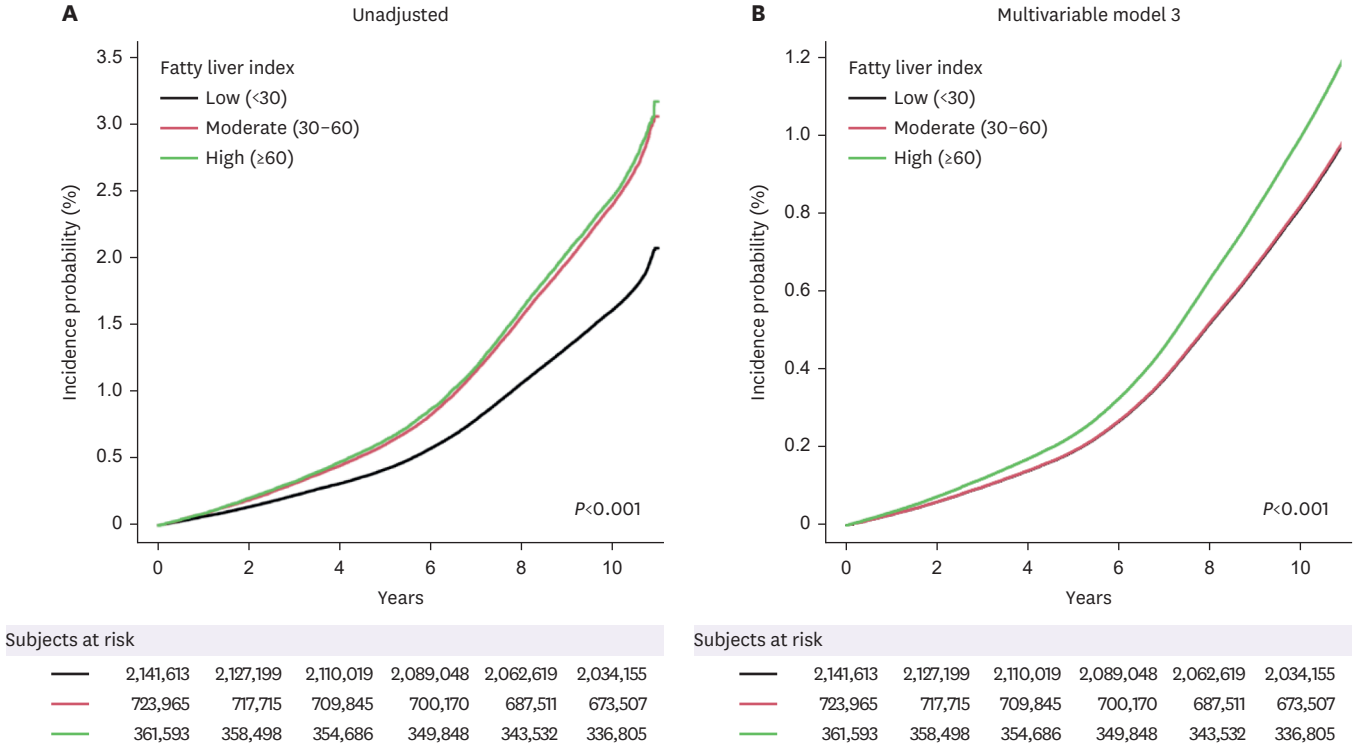

Figure 2. Changes in the incidence probability for first onset of sepsis according to fatty liver index during the 10-year follow-up period.
Multivariable model 3 was adjusted for well-established major risk factors for sepsis, including chronic comorbidities and immunocompromised conditions, in addition to the variables included in model 2 (age, sex, income, smoking, alcohol consumption, regular exercise, hypertension, dyslipidemia, and BMI).
BMI, body mass index.

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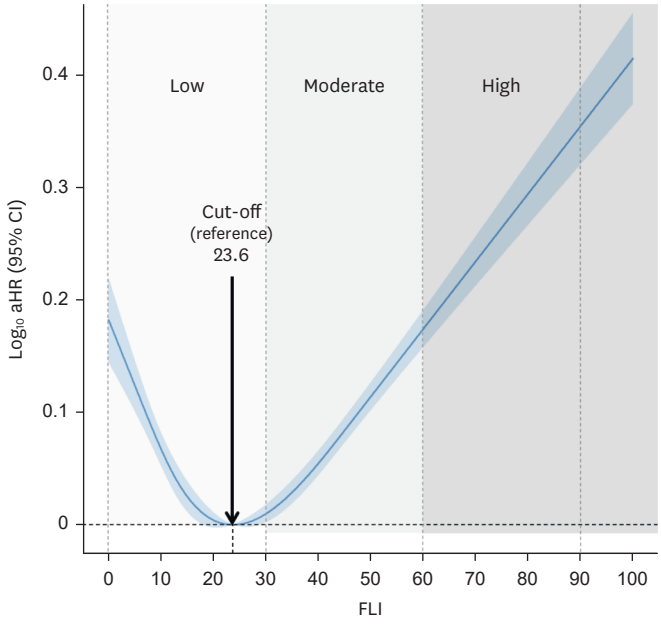

Figure 3. Continuous relationship between one-time fatty liver indices and adjusted risks for the first onset of sepsis using the restricted cubic spline curve in the multivariable Cox regression analysis.
This graph shows all aHRs transformed such that the $\log_{10}$ aHR becomes zero in patients with a cut-off FLI value, which indicates the lowest risk of developing sepsis. The solid blue line and light blue shadow represent aHR and 95% CI, respectively. The aHRs in the RCS curve were obtained using the multivariable Cox proportional regression model 3.
aHR, adjusted hazard ratio; CI, confidence interval; FLI, fatty liver index; RCS, restricted cubic spline.

3. Risk of sepsis according to each factor that constitutes the FLI

The risk of developing sepsis was significantly reduced in patients with overweight (aHR, 0.86; 95% CI, 0.84–0.87) and class I obesity (aHR, 0.89; 95% CI, 0.88–0.91) based on normal BMI in the multivariable model 3. However, underweight (aHR, 1.51; 95% CI, 1.45–1.57) and class II/III obesity (aHR, 1.18; 95% CI, 1.14–1.23) were independently associated with the significantly higher risk of sepsis compared to normal BMI. Patients with abdominal obesity (aHR, 1.08; 95% CI, 1.07–1.10), high TG (≥150 mg/dL, aHR, 1.02; 95% CI, 1.01–1.04) and GGT values (highest quartile group, *i.e.*, the ≥48 and ≥24 IU/L in men and women, respectively, aHR, 1.23; 95% CI, 1.21–1.26) had a significantly higher risk of sepsis than patients without these characteristics in the multivariable model 3 (**Table 3**).

4. Risk of sepsis among baseline demographic variables and metabolic syndrome-related characteristics

Subgroup analyses of variables included in multivariable Cox regression analysis revealed that high FLI was consistently associated with an increased risk of sepsis across all subgroups. Notably, in individuals aged <40 years and in men, the moderate FLI group had a significantly lower risk compared with the low FLI group, whereas in all other subgroups, both moderate and high FLI groups exhibited higher risks than the low FLI group. The IR of sepsis was highest in the high FLI group among individuals aged ≥65 years (11.5 per 1,000 PY), while the aHR, relative to the low FLI group, was greatest in the high FLI subgroup with underweight (aHR 2.12; 95% CI, 1.64–2.76). The variables with statistically insignificant interaction *P*-value within the subgroup were regular exercise and hypertension, indicating that the aHRs for sepsis within the same FLI group were similar regardless of these subgroup characteristics (*e.g.*, with or without regular exercise).

According to the age groups, the risk of sepsis in the same FLI group was higher the 40–64 years age (moderate FLI: aHR, 1.08; 95% CI, 1.05–1.11 and high FLI: aHR, 1.40; 95% CI, 1.35–1.45) compared to those aged 65 years or older. The female participants had the highest risk in the moderate (aHR, 1.06; 95% CI, 1.04–1.09) and high (aHR, 1.40; 95% CI, 1.35–1.46) FLI group than the male participants (aHR, 0.95; 95% CI, 0.93–0.98 and aHR, 1.11; 95% CI, 1.04–1.09, respectively) (**Supplementary Table 5**).

5. Association between one-time FLI value and occurrence of sepsis

The RCS curve confirmed that the 23.6 of FLI value had the lowest aHR for sepsis and a positive relationship between FLI and the risk of sepsis in the range of 23.6 or higher. However, in categories below the cut-off value, the aHR for sepsis increased as the FLI decreased. Ultimately, the relationship between the FLI and sepsis produced a J shape (**Fig. 3**).

DISCUSSION

This long-term observational study involving millions of individuals verified significant relationship between single FLI measurements and sepsis. The additional key findings of our analyses are as follows: (1) the participants with ≥60 of FLI, generally indicating

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Table 3. Association between each component included in obtaining the fatty liver index value and risk for sepsis

Variables	Subjects (No.)	Sepsis (No.)	F/U duration (years)	IR[a]	HR (95% CI)			
					Univariable	Multivariable		
					Unadjusted	Model 1[b]	Model 2[c]	Model 3[d]
BMI (kg/m^2)								
<18.5[e]	126,426	2,730	1,254,537	2.18	1.24 (1.20–1.29)	1.48 (1.42–1.54)	1.51 (1.45–1.57)	1.51 (1.45–1.57)
18.5–22.9[e]	1,296,340	23,079	13,092,937	1.76	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
23.0–24.9[e]	789,677	15,397	7,989,816	1.93	1.09 (1.07–1.11)	0.88 (0.86–0.90)	0.85 (0.84–0.87)	0.86 (0.84–0.87)
25.0–29.9[e]	905,649	20,158	9,157,136	2.20	1.25 (1.22–1.27)	0.97 (0.95–0.99)	0.89 (0.88–0.91)	0.89 (0.88–0.91)
≥30.0[e]	109,079	2,862	1,101,403	2.60	1.48 (1.42–1.53)	1.40 (1.35–1.46)	1.18 (1.13–1.23)	1.18 (1.14–1.23)
Abdominal obesity[f]								
No	2,623,114	44,306	26,560,497	1.67	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
Yes	604,057	19,920	6,035,332	3.30	1.98 (1.95–2.02)	1.19 (1.17–1.21)	1.11 (1.09–1.18)	1.08 (1.07–1.10)
TG (mg/dL)								
<150	2,311,912	41,831	23,389,266	1.79	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
≥150	915,259	22,395	9,206,563	2.43	1.36 (1.34–1.38)	1.12 (1.10–1.14)	1.05 (1.03–1.06)	1.02 (1.01–1.04)
GGT (IU/L)[g]								
Low (Q1–Q3)	2,426,778	43,839	24,560,859	1.78	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
High (Q4)	800,393	20,387	8,034,970	2.54	1.43 (1.40–1.45)	1.33 (1.31–1.35)	1.26 (1.27–1.56)	1.23 (1.21–1.26)

[a]Per 1,000 person-years.
[b]Adjusted for age and sex.
[c]Adjusted for age, sex, income, smoking, alcohol consumption, regular exercise, hypertension, dyslipidemia, and BMI.
[d]Adjusted for well-established major risk factors for sepsis, including chronic comorbidities (*e.g.*, T2DM, CKD, chronic lung/heart diseases) and immunocompromised conditions, in addition to the variables included in model 2.
[e]The obesity criteria by the WHO Asia-Pacific region obesity and the Korean Society for the Study of Obesity, reflecting research findings targeting Asians (<18.5 kg/m^2: underweight, 18.5–22.9 kg/m^2: normal, 23.0–24.9 kg/m^2: overweight or pre-obese, 25.0–29.9 kg/m^2: class I obesity, ≥30.0 kg/m^2: class II and III obesity).
[f]Abdominal obesity was defined as a WC of ≥90 cm in males or ≥85 cm in females.
[g]Quartiles of GGT results were obtained in our cohort, and the cutoff value for the highest quartile (Q4) was ≥48 IU/L in males or ≥24 IU/L in females.
All *P*-values within the model were ≤0.001.
F/U, follow-up; IR, incidence rate; HR, hazard ratio; CI, confidence interval; BMI, body mass index; TG, triglyceride; GGT, gamma-glutamyl transferase; Q, quartile; IU, international unit; T2DM, type 2 diabetes mellitus; CKD, chronic kidney disease; WHO, World Health Organization; WC, waist circumference.

NAFLD, had a 1.5 times higher risk of sepsis compared to those with <30 of FLI, which can rule out NAFLD [20]; (2) the FLI with the lowest risk for sepsis was 23.6, and the developing sepsis conversely increased when the FLI was lower than above cut-off value; (3) as time elapsed after the FLI measurement, a greater difference in the incidence of sepsis emerged between the group with ≥60 and <30 of FLI; and (4) comparing <30 of FLI as the reference, the risk of sepsis was highest in female with a FLI of 60 or higher.

These results suggest that the one-time FLI values obtained from the four easily measurable factors may predict the risk of developing sepsis. Indicators that can estimate diseases development in large populations can be widely applied in practice when the NIT process are inexpensive and simple. In this respect, information on the FLI might be an effective public health education that could inform the risk of sepsis [21]. Awareness of the increased risk for sepsis may lead to efforts to avoid infections, including proper vaccination, hand washing, strengthening sanitary toilets and good respiratory hygiene [12, 21]. Our previous data showed that the risk of sepsis was also associated with cigarette smoking and low aerobic physical activities, which are commonly known unhealthy lifestyle habits [19, 22]. Because sepsis is complexly linked to many clinical factors and can have causal relationships with various immunopathological processes, improving just one risk indicator as FLI would not substantially reduce the risk [12, 23]. However, lifestyle modifications and medical treatments decreasing the FLI to <60 and reducing severity of NAFLD could simultaneously change other risk factors or behaviors for sepsis (*e.g.*, severe obesity, T2DM, MetS, smoking and lack of exercise, etc.) [12, 19, 22], and ultimately, might contribute to lowering the development of sepsis. As the incidence of sepsis shows a progressively widening gap between individuals with high and low FLI values over time after the identification of high FLI, early education and intervention would be more helpful in reducing the occurrence of sepsis.

Previous research has examined the association between NAFLD and the development or severity/mortality

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of various acute infections [21, 24-26]. The recurrent bacterial infections were significantly frequent in patients with ultrasound-based NAFLD (N=247) than age- and sex-matched controls group without NAFLD during a 3-year follow-up (22% *vs.* 8%, *P*<0.001) [24]. The hospitalized coronavirus disease 2019 patients (N=553) with abdominal imaging-based NAFLD received mechanical ventilation more frequently and stayed in the intensive care unit for a longer period of time, compared to those without NAFLD [25]. Recent two Swedish population-based cohort studies revealed that the patients with ICD codes-based or biopsy-proven NAFLD (N=14,869 or 12,133, respectively) had about twice as high risk of severe infections (aHR for 424 and 1,012 sepsis, 2.4 and 2.2, respectively) and infection-related mortality [21, 26]. However, there have been no studies on the association between continuous FLI values and the incidence of sepsis or between NAFLD and the risk of sepsis in large sepsis cohort of tens of thousands and populations of several millions. Our adjusted risk of sepsis in patients with high FLI was similar to that in the two Swedish cohorts [21, 26].

Since elevated FLI is closely related to various metabolic abnormalities including insulin resistance, obesity, and vitamin D deficiency, NAFLD can result in impaired phagocytosis, neutrophil chemotaxis, intracellular killing against microbes, collectively increasing the risk of sepsis [11, 27]. However, our results, which adjusted for metabolic abnormalities, suggest that NAFLD may directly induce sepsis without having any relation to the MetS, originating from multiple interrelated immunometabolic alterations [11]. Lipid accumulation in hepatic tissue in the NAFLD triggers oxidative stress responses in hepatocytes, subsequently activating pro-inflammatory signaling pathways interrelated to release of damage-associated molecular patterns and activation of Kupffer cells [11, 28]. In particular, Kupffer cells play an important role in the clearance of endotoxins and phagocytosis of bacteria [28]. But, chronically activated Kupffer cells in the NAFLD undergo functional changes with persistent production of inflammatory cytokines and chemokines, leading to the impairment of their immunoregulatory capacity and promoting dysregulated innate or adaptive immune system [28, 29]. Concurrently, gut dysbiosis and increased intestinal permeability can facilitate translocation of gut-derived bacteria and endotoxins via the portal circulation, further aggravating bacterial overgrowth of intestine and systemic immune dysregulation [10, 11, 30]. In addition, chronic exposure to endotoxins (*i.e.*, lipopolysaccharides) through toll-like receptor signaling may desensitize innate immune responses and disrupt the balance of pattern recognition receptors [11, 28, 30].

Our findings, which demonstrate that the risk of sepsis increases even at an FLI≤20, are consistent with previous observations that underweight (BMI<18.5 kg/m^2) individuals with cachexia and malnutrition may be more vulnerable to infections [31]. This suggests that metabolically unfavorable conditions associated with a low FLI may contribute to impaired host defense mechanisms. However, further research is warranted to elucidate the risk of sepsis in individuals with lean NAFLD, characterized by low BMI and high FLI. A recent study reported that the cut-off value of the FLI, which indicates the presence of NAFLD, was approximately 50% lower in women (32 of FLI) than in men (60 of FLI) [32]. In our subgroup analysis, we observed that the risk of sepsis was particularly elevated in women with an FLI≥60. This finding may be attributable to the possibility that, at the same FLI level, the severity of NAFLD is greater in women. However, since all our multivariable Cox regression models included sex as an adjusted covariate, this observation is unlikely to have affected the overall conclusion regarding the association between the FLI and sepsis risk.

This study has some limitations. First, we used the old term of the NAFLD, and did not introduce the revised diagnosis of metabolic dysfunction-associated steatotic liver disease (MASLD), which considers five cardiometabolic criteria under the same amount of alcohol consumption as our cohort [33]. In addition, it might be unclear whether the FLI value could be an adequate NIT for the reclassification of steatotic liver diseases (SLD) including MASLD or metabolic and alcohol-associated liver disease [33]. However, the FLI has long been one of the most extensively studied and widely utilized NIT for assessing hepatic steatosis similar to abdominal ultrasound [15, 16, 20], and recent studies have also used the FLI to define MASLD [34, 35]. Therefore, we believe that the changes in the spectrum of SLD are unlikely to substantially affect our conclusion that an increasing degree of FLI is associated with a higher risk of sepsis. Second, the definition of sepsis syndrome evolved during the observation period of our study [12], and sepsis cases were retrospectively identified in the large administrative claims database (KNHIS) using an operational definition based on explicit ICD-10 diagnosis

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codes. Therefore, the accuracy of sepsis diagnosis in our study may have been affected by both overestimation and underestimation [36, 37]. Given the severity of sepsis, overestimation due to misclassification by healthcare providers (*e.g.*, coding sepsis in non-septic patients) is likely uncommon, whereas underestimation, particularly in hospital-acquired cases, is more plausible [37]. Although this represents an inherent limitation of population-based cohort studies, the large sample size (≥3 million participants) and the substantial number of sepsis cases (≥60,000) included in all regression analyses likely minimized the impact of potential bias on our findings [19, 22].

The implicit coding strategy for sepsis, which defines cases by the co-occurrence of infection and acute organ dysfunction codes, is widely used in claims-based research because of its high sensitivity and ability to capture a broad spectrum of patients [36, 37]. However, implicit coding also has important drawbacks that must be acknowledged. First, its reliance on organ dysfunction codes makes it vulnerable to misclassification, as chronic organ dysfunction unrelated to infection may be incorrectly classified as sepsis [36, 37]. Second, implicit algorithms cannot reliably differentiate infection-related organ failure from other causes such as postoperative complications or non-infectious critical illness, thereby inflating the number of false-positive cases [37]. Third, organ dysfunction codes themselves may be inconsistently applied across hospitals and time periods, introducing heterogeneity into case definitions [37, 38]. These limitations are particularly relevant in KNHIS claims data, where the lack of laboratory results and microbiology records further hampers case validation. Consequently, epidemiological estimates based on implicit coding may overestimate sepsis incidence [36, 38]. Nonetheless, several studies using the KNHIS claims database as well as other national hospital discharge databases have demonstrated that defining sepsis solely by explicit codes is also a valid and robust approach in large administrative cohorts, underscoring that explicit coding remains an acceptable method for sepsis case identification in this research context [37-40].

The major strengths of our study include the assessment of hepatic steatosis using the NIT based on directly measured parameters from general health screening data in a large-scale population, rather than relying on diagnostic codes. This approach allowed for the estimation of hepatic fat accumulation on a continuous scale using the FLI, a feature not possible with ultrasonography, while also providing substantial statistical power owing to the inclusion of millions of individuals. To our knowledge, this is the first large-scale cohort study to investigate the association between hepatic steatosis and the risk of developing sepsis, a highly severe and complex infectious condition. Considering the current lack of effective therapeutic agents that can markedly reduce sepsis-related mortality, identifying high-risk individuals through readily accessible and clinically applicable NIT may represent a valuable strategy for early risk stratification and targeted prevention.

In conclusion, this study demonstrated that the risk of sepsis increased with high FLI values, exhibiting a J-shaped non-linear association. The highest risk was observed in individuals with FLI ≥60 compared to those in the low FLI (<30) group. These findings suggest that sepsis, traditionally viewed as an acute inflammatory condition, is influenced by chronic metabolic disturbances and immunological exhaustion.

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SUPPLEMENTARY MATERIALS

Supplementary Table 1
Self-report questionnaires from the biennial voluntary general health screening program by the Korean National Health Insurance Service

Supplementary Table 2
List of diagnosis codes used to extract patients with sepsis

Supplementary Table 3
Well-established risk factors for sepsis and definitions of covariates used for risk adjustment

Supplementary Table 4
Definitions and categorization of clinical variables

Supplementary Table 5
Relationship between fatty liver index and risk of sepsis according to baseline demographic variables and metabolic syndrome–related characteristics included in multivariable regression model 2

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