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Supplemental information

Impact of metabolic risk factors on hepatic and cardiac outcomes in patients with alcohol- and non-alcohol-related fatty liver disease

Jihye Lim, Hyunji Sang, and Ha Il Kim

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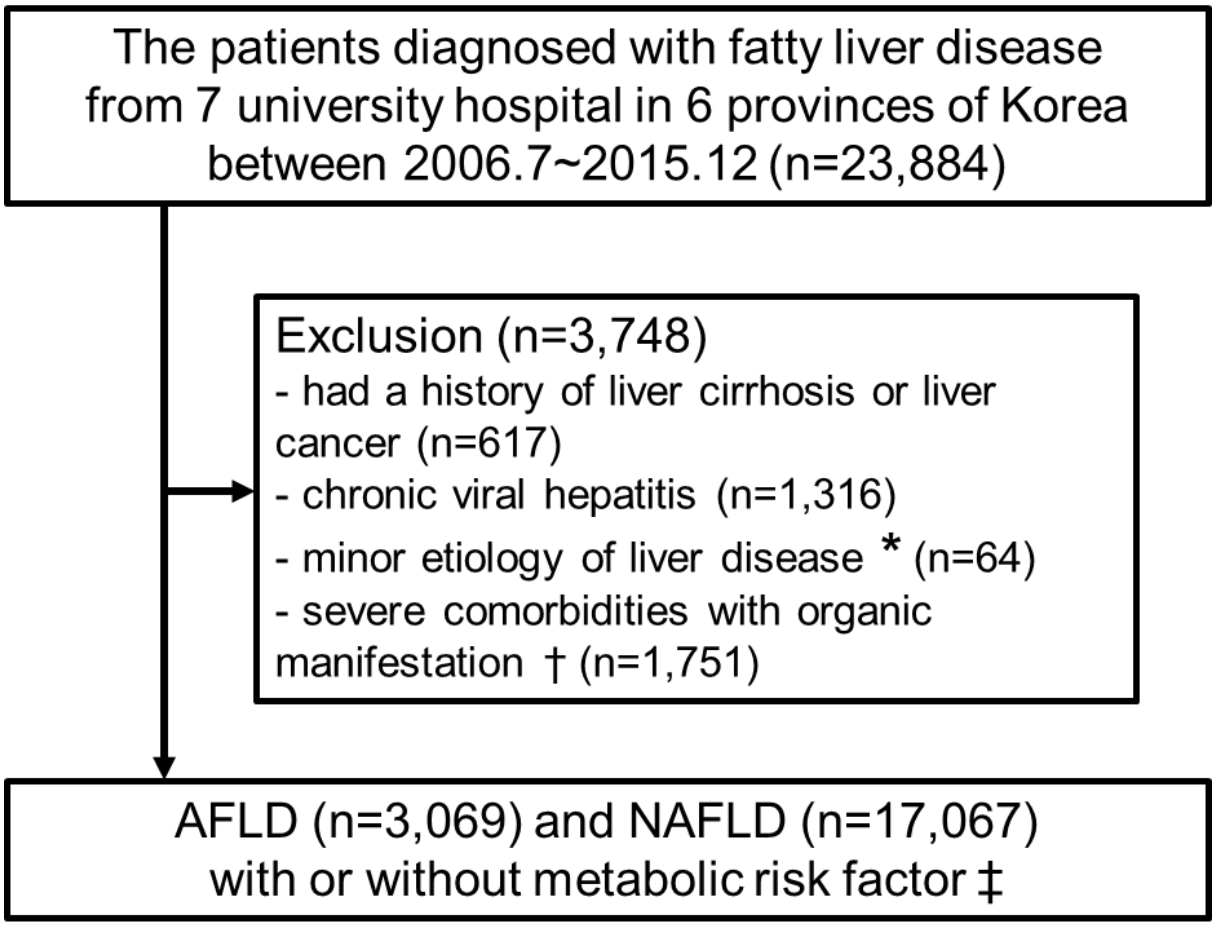
Fig. S1. Flow chart of study population

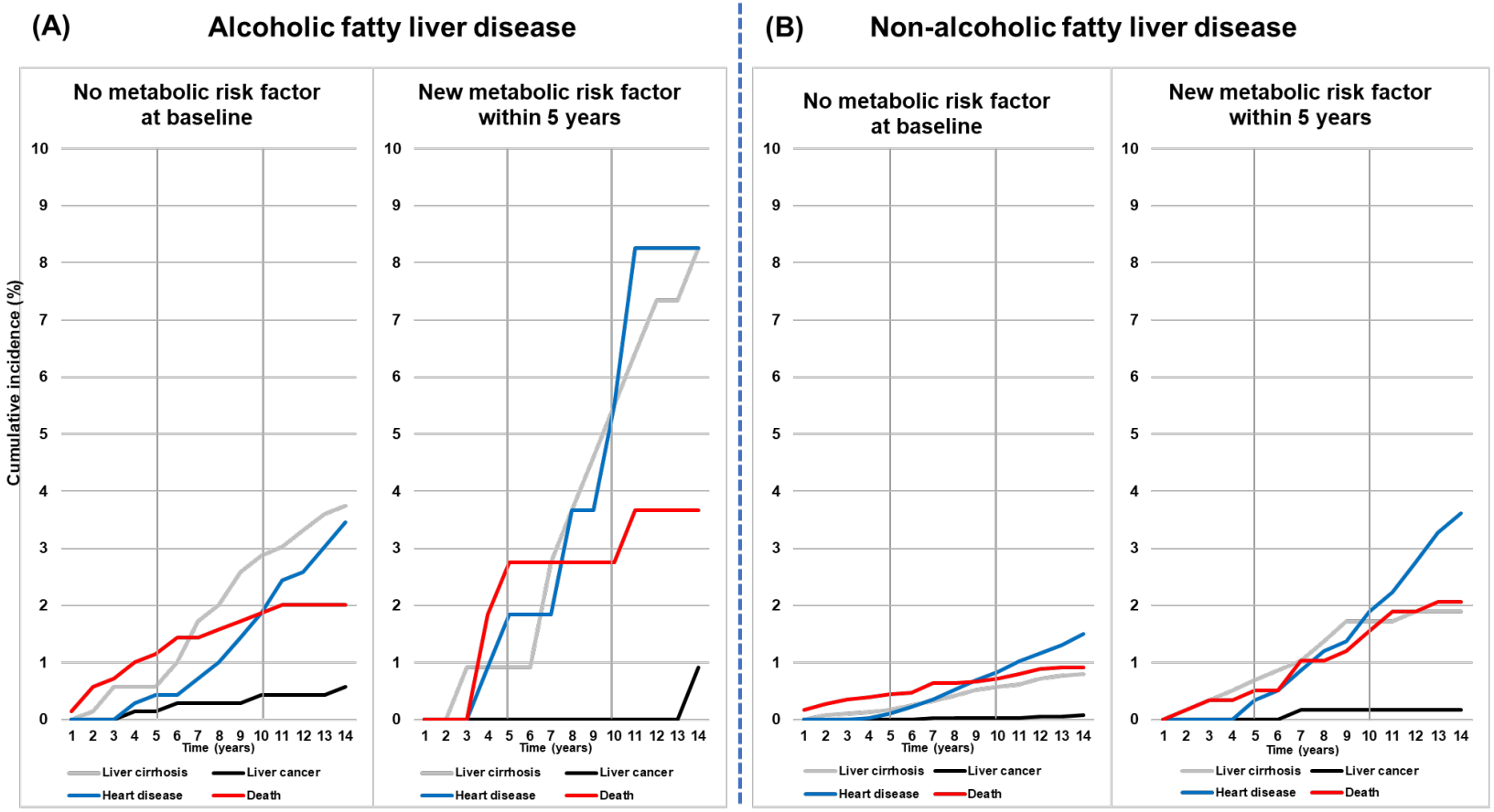


* Including primary biliary cholangitis, primary sclerosing cholangitis, Wilson's disease, hemochromatosis, and autoimmune hepatitis.

† Heart failure, ischemic heart disease, atrial fibrillation, chronic obstructive lung disease, cerebral infarction, and chronic kidney disease.

‡ Diabetes mellitus, hypertension, dyslipidemia, and obesity

Fig. S2. The trend of incidence of cirrhosis, liver cancer, heart disease, and death between the patients without MetR and newly developed MetR within 5 years compared (A) in AFLD group and (B) in NAFLD group



AFLD, alcoholic fatty liver disease; NAFLD, non-alcoholic fatty liver disease; MetR, metabolic risk factor

Fig. S3. Cumulative incidence patterns of heart disease and stroke in patients with alcoholic fatty liver disease and non-alcoholic fatty liver disease.

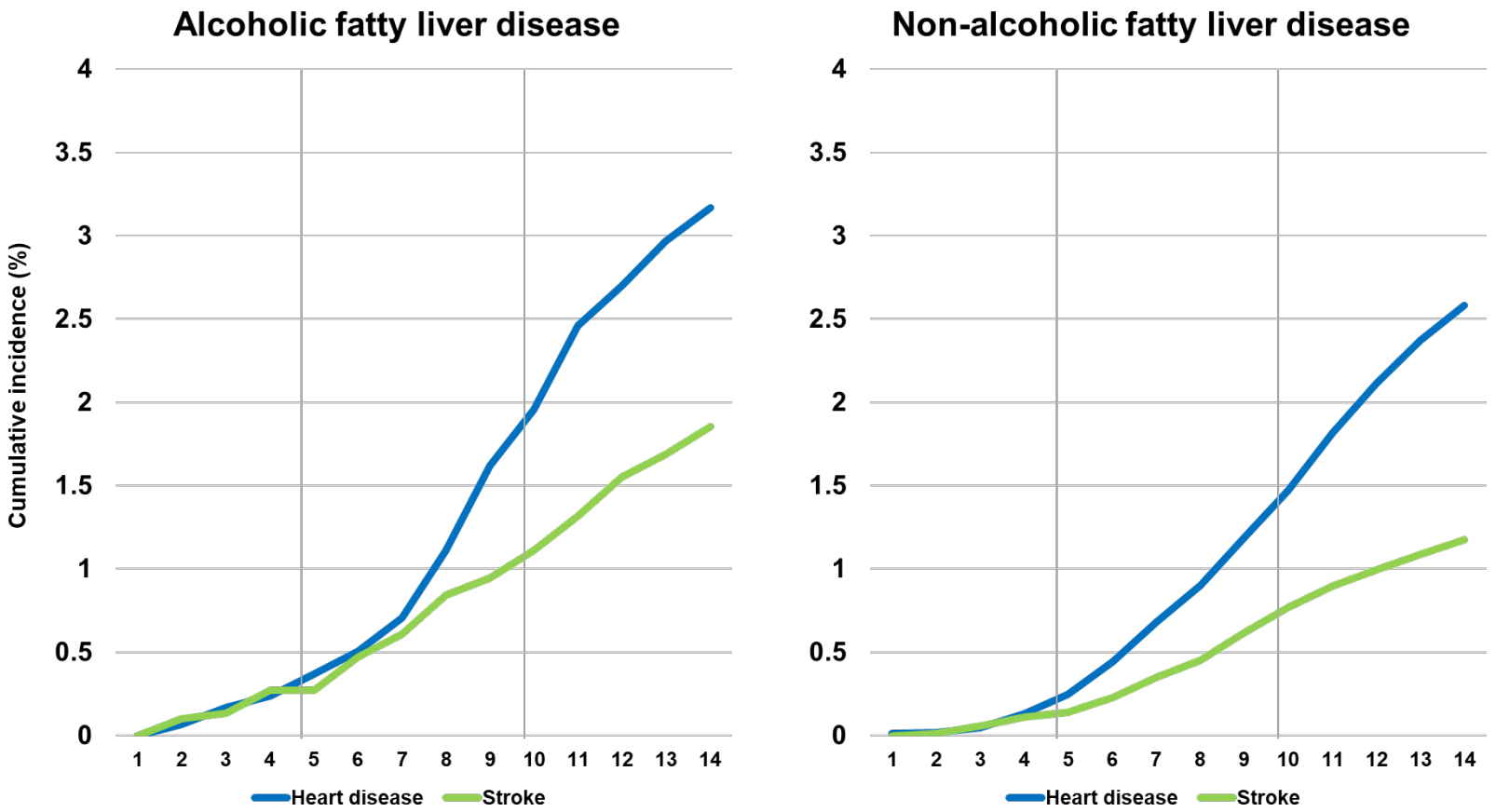


Fig. S4. Cumulative incidence patterns of heart disease and stroke in patients without metabolic risk factors, risk factor ≥ 1, and risk factor ≥ 2: (A) alcoholic fatty liver disease, (B) non-alcoholic fatty liver disease

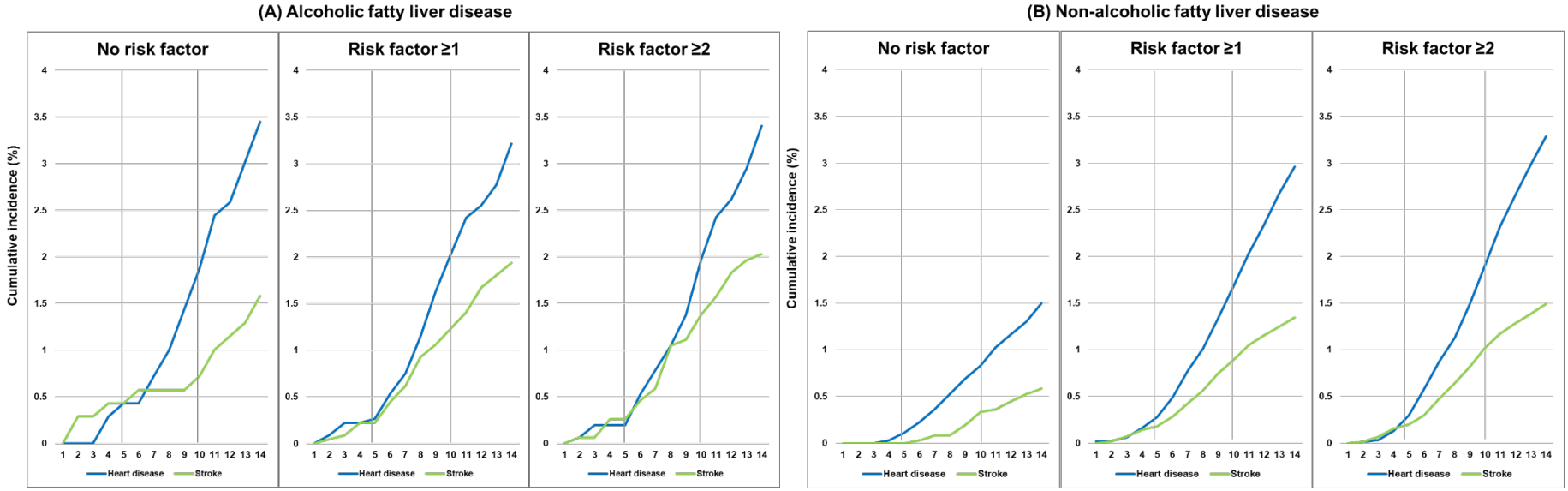
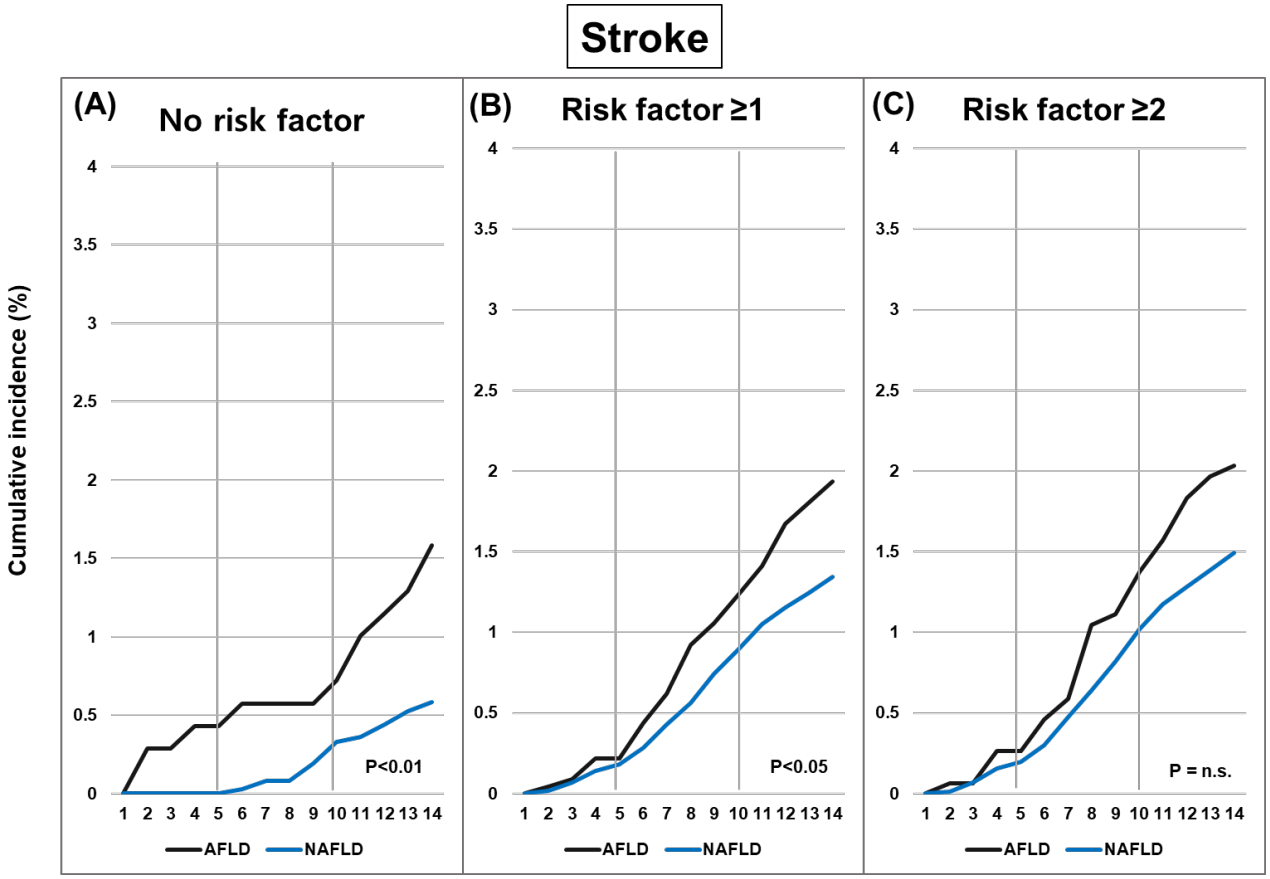


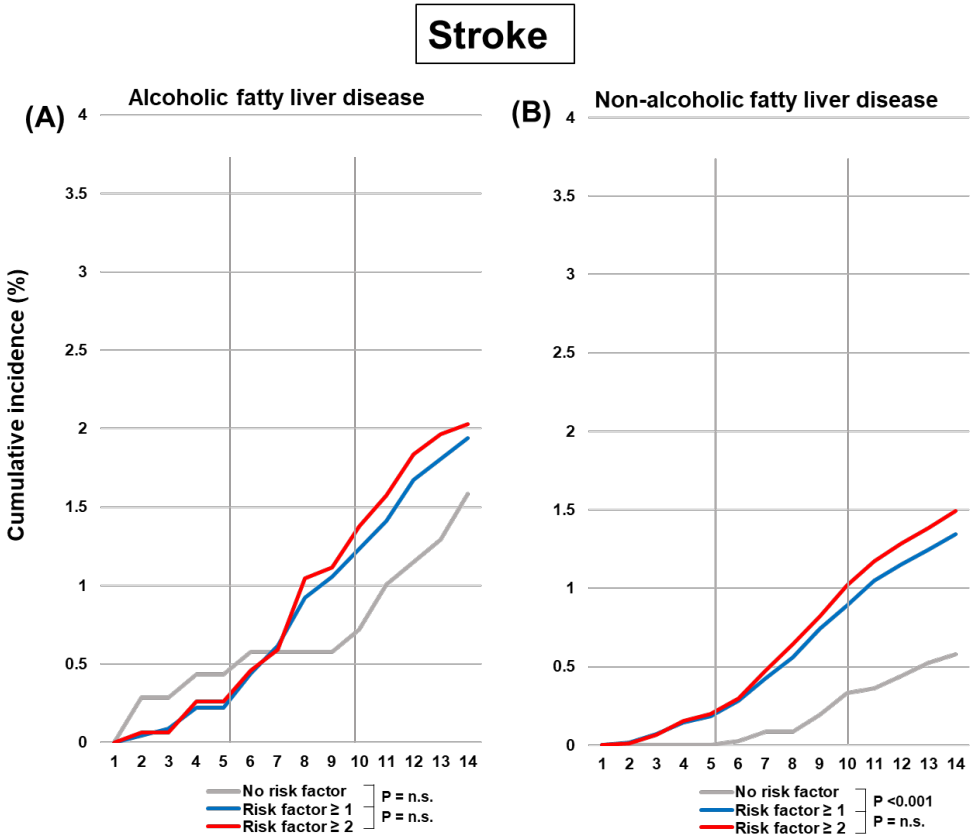
Fig. S5. Intergroup comparison of cumulative incidence of stroke in (A) patients without metabolic risk factors, (B) risk factor ≥ 1, and (C) risk factor ≥ 2.



AFLD, alcoholic fatty liver disease; NAFLD, non-alcoholic fatty liver disease

Log-rank tests used to examine the differences in cumulative risks, level of significance, p <0.05

Fig. S6. Intergroup comparison of cumulative incidence of stroke in (A) patients without metabolic risk factors, (B) risk factor ≥ 1, and (C) risk factor ≥ 2.



Log-rank tests used to examine the differences in cumulative risks, level of significance, p <0.05

Table S1. Concept identification and concept codes for concept sets

Concept sets		Concept identification	Concept code	Name
Fatty liver disease	Alcoholic fatty liver disease	193256	50325005	Alcoholic fatty liver
	Non-alcoholic fatty liver disease	4059290	197321007	Steatosis of liver
Drinking pattern	Current drinker at baseline	4074035, 4038558, 4336673	219006, 228279004, 86933000	Current drinker, Very heavy drinker, Heavy drinker
	Non-drinker at baseline	4022664	105542008	Non-drinker
Liver cirrhosis	Definition of pre-existing liver cirrhosis	4064161, 194643, 192675, 4046123, 4340394, 4340385	19943007, 420054005, 1761006, 12368000, 235899008, 23588004	Cirrhosis of liver, Alcoholic cirrhosis, Biliary cirrhosis, Secondary biliary cirrhosis, Hepatic sclerosis, Alcoholic fibrosis and sclerosis of liver
	Definition of newly diagnosed **Liver cirrhosis**	4064161, 194643	19943007, 420054005	Cirrhosis of liver, Alcoholic cirrhosis
Liver cancer	Definition of pre-existing primary liver cancer	4001171, 201519	109841003, 95214007	Hepatocellular carcinoma, Primary malignant neoplasm of liver
	Definition of newly diagnosed **Liver cancer**	4001171	109841003	Hepatocellular carcinoma
Chronic viral hepatitis		439674, 192240, 197493, 198964, 4012113	186639003, 235869004, 235865005, 128302006, 10295004	Chronic viral hepatitis B without delta-agent, Hepatitis D superinfection of hepatitis B carrier, Chronic viral hepatitis B with hepatitis D, Chronic hepatitis C, Chronic viral hepatitis
Minor etiologies for chronic liver disease		4135822,40577758,	31712002,4032000,	Primary biliary cholangitis, Primary sclerosing

		4229262, 4163735,200762	88518009, 399187006, 408335007	cholangitis, Wilson's disease, Hemochromatosis, Autoimmune hepatitis
Metabolic risk factor	Diabetes mellitus	4193704, 201826, 3004410, 3037110	313436004, 44054006, 4548-4, 1558-6	Type 2 diabetes mellitus without complication, Type 2 diabetes mellitus, Hemoglobin A1c/Hemoglobin.total in Blood, Fasting glucose [Mass/volume] in Serum of Plasma
	Hypertension	316866, 320128, 3004249, 21490853, 3012888, 21490851	38341003, 56921000, 8480-6, 76215-3, 8462-4, 76213-8	Hypertensive disorder, Essential hypertension, Systolic blood pressure, Invasive systolic blood pressure, Diastolic blood pressure, Invasive diastolic blood pressure
	Dyslipidemia	432867, 4159131, 3027114, 3022192, 3007070, 3028437, 3028288	55822004, 370992007, 2093-3, 2571-8, 2085-9, 2089-1, 13457-7	Hyperlipidemia, Dyslipidemia, Cholesterol [Mass/volume] in Serum of Plasma, Triglyceride [Mass/volume] in Serum or Plasma, Cholesterol in HDL [Mass/volume] in Serum or Plasma, Cholesterol in LDL [Mass/volume] in Serum or Plasma, Cholesterol in LDL [Mass/volume] in Serum or Plasma by calculation
	Obesity	3038553	39156-5	Body mass index (BMI) [Ratio]
Comorbidities		319835, 315286, 313217, 321318, 312327, 319844,	42343007, 413838009, 49436004, 194828000,	Congestive heart failure, chronic ischemic heart disease, atrial fibrillation, angina

	255573, 443454, 46271022	57054005, 413439005, 13645005, 432504007, 709044004	pectoris, acute myocardial infarction, acute ischemic heart disease, chronic obstructive lung disease, ischemic stroke, chronic kidney disease
Hepatic outcomes	4064161, 194643, 4001171	19943007, 420054005, 109841003	Cirrhosis of liver, Alcoholic cirrhosis, hepatocellular carcinoma
Cardiac outcomes (heart disease)	319835, 315286, 313217, 321318, 312327,	42343007, 413838009, 49436004, 194828000, 57054005,	Congestive heart failure, chronic ischemic heart disease, atrial fibrillation, angina pectoris, acute myocardial infarction, acute ischemic heart disease,
Death (all-cause mortality)	4249566, 4052310, 4306655	409651001, 16100001, 419620001	Mortality rate, Death diagnosis, Death

Table S2. Amounts and patterns of alcohol consumption in patients with AFLD and NAFLD from the EMR of KHUG

	Alcoholic fatty liver disease	**Non-alcoholic fatty liver disease**
Number of patients*	N=439	N=2,814
Male, number	407 (92.7%)	1,760 (62.5%)
Age, mean (SD)	49.59 (10.78)	45.38 (12.90)
Alcohol consumption		
Non-drinker	0 (0%)	2,344 (83.3%)
Current drinker †	439 (100%)	470 (16.7%)
Light drinker (< 3 unit/day)	2 (<0.1%)	292 (10.4%)
Moderate drinker (3–6 unit/day)	7 (1.6%)	145 (5.2%)
Heavy drinker (7–9 unit/day)	94 (21.4%)	18 (<0.1%)
Very heavy drinker (> 9 unit/day)	191 (43.5%)	15 (<0.1%)
Recorded on EMR as “heavy drinker” or “binge drinker” in the electronic medical record	145 (33.0%)	-
Agreement between clinical diagnostic code and CDM concept code	Any drinker: 439/439 (100%) Heavy or very heavy drinker: 430/439 (97.9%)	Any non-drinker: 2,344/2,814 (83.3%) Equal to or less than moderate drinker: 2,781/2,814 (98.8%)
Proportion of “Gray zone” ‡	9 (2.1%)	437 (15.5%)

Pattern of drinking		
No change during follow-up period	420/439 (95.7%)	Non-drinker: 2,200/2,814 (78.2%) Drinker: 454/470 (96.6%)
No follow-up data of alcohol consumption	6/439 (1.4%)	
Stopped drinking during follow-up period	13/439 (3.0%)	16/470 (3.4%)
Started drinking during follow-up period	-	144/2,344 (6.1%)

AFLD, alcoholic fatty liver disease; NAFLD, non-alcoholic fatty liver disease; KHUG, Kyung Hee University Hospital at Gangdong; SD, standard deviation; CDM, common data model; EMR, electronic medical record

* Data from KHUG, extracted by same inclusion criteria as CDM: total of 3,253/3,869 patients (84.1%) data could be accessible for manual chart review

† One unit= 10 g of alcohol

‡ Patients with light to moderate amount of alcohol consumption

Table S3. Study population data from each hospital

Hospital	KHUG		KDH		KWMC		DCMC		PNUH		WKUH		AJMC	
Group	AFLD	NAFLD	AFLD	NAFLD	AFLD	NAFLD	AFLD	NAFLD	AFLD	NAFLD	AFLD	NAFLD	AFLD	NAFLD
Patients with or without metabolic risk factor														
Patient number	618	3,251	320	1,342	238	1,103	729	3,417	160	1,977	398	2,011	606	3,966
Male, number	569	2,043	288	818	225	667	661	1,999	147	1,276	356	1,197	552	2,782
Age, mean (SD)	49.38 (10.66)	45.64 (13.02)	49.37 (11.53)	45.34 (13.77)	49.51 (10.94)	47.33 (13.99)	49.65 (10.97)	48.85 (13.67)	52.63 (10.41)	50.06 (12.50)	49.13 (10.46)	49.12 (13.51)	47.42 (10.29)	45.40 (11.53)
Age group (years)														
20–24	2	164	7	82	4	69	4	147	1	51	1	89	9	132
25–29	18	238	9	119	3	92	19	189	1	58	8	92	12	182
30–34	38	353	24	160	16	88	41	263	8	132	20	150	46	389
35–39	59	374	30	158	22	83	69	315	8	196	44	160	58	555
40–44	87	380	32	127	29	99	103	310	18	207	63	227	121	626
45–49	97	384	47	122	45	116	134	426	18	239	84	253	108	677
50–54	113	462	61	192	45	186	126	566	34	317	64	295	107	588
55–59	104	412	52	150	36	157	97	421	27	311	51	273	74	379
60–64	54	258	25	120	16	94	60	337	32	224	26	212	38	191
65–69	29	127	20	63	12	63	41	212	6	136	23	128	21	139
Patients with metabolic risk factor														
Diabetes mellitus														
Patient number	78	407	94	389	30	111	103	497	49	420	101	535	100	638
Male, number	74	236	83	226	30	59	96	281	43	259	90	290	92	440
Age, mean (SD)	52.1 (10.5)	52.6 (11.6)	50.2 (11.0)	49.7 (12.4)	53.7 (10.8)	55.2 (11.7)	53.4 (9.9)	52.6 (13.3)	53.3 (7.5)	53.5 (12.6)	52.8 (10.0)	54.2 (12.1)	50.8 (8.7)	48.6 (11.5)

Hypertension														
Patient number	205	904	78	324	37	123	133	775	25	406	101	604	199	1,126
Male, number	190	591	73	184	37	75	120	430	24	249	92	332	180	797
Age, mean (SD)	51.0 (10.0)	48.6 (13.5)	49.0 (10.9)	49.1 (13.9)	55.6 (9.9)	55.4 (11.1)	51.7 (10.8)	52.6 (14.5)	54.4 (8.0)	55.4 (11.3)	53.1 (10.1)	53.8 (13.3)	49.2 (9.8)	49.4 (11.8)
Dyslipidemia														
Patient number	282	1,702	169	803	169	781	552	2,584	103	1,576	236	1,329	421	2,388
Male, number	261	1,045	151	485	161	486	505	1,543	95	1,042	216	784	391	1,727
Age, mean (SD)	49.7 (10.5)	47.3 (12.0)	50.1 (10.2)	46.6 (13.1)	49.6 (10.8)	49.1 (13.0)	49.0 (10.4)	49.2 (13.2)	51.2 (10.2)	49.8 (12.0)	48.7 (9.9)	49.5 (13.1)	47.4 (9.5)	46.1 (11.5)
Obesity														
Patient number	151	1,118	18	215	NA	NA	NA	NA	NA	NA	42	353	95	559
Male, number	141	744	16	125	NA	NA	NA	NA	NA	NA	33	206	94	418
Age, mean (SD)	49.6 (10.2)	45.6 (12.7)	51.3 (9.3)	45.7 (13.9)	NA	NA	NA	NA.	NA	NA	49.5 (9.8)	48.1 (14.1)	48.7 (9.2)	46.4 (10.1)
Patients without metabolic risk factor														
Patient number, (% of the total number)	204 (33.0%)	952 (29.3%)	96 (30.0%)	369 (27.5%)	58 (24.4%)	301 (27.3%)	138 (18.9%)	606 (17.7%)	35 (21.9%)	272 (13.8%)	104 (26.1%)	439 (21.8%)	111 (18.3%)	1,007 (25.4%)
Male, number	184	589	87	235	53	178	120	326	32	162	89	279	95	668
Age, mean (SD)	47.39 (10.95)	42.80 (13.46)	47.80 (13.39)	41.80 (14.16)	49.10 (12.12)	42.19 (15.17)	50.76 (12.49)	46.81 (14.47)	56.09 (11.53)	47.78 (14.35)	48.08 (11.17)	45.74 (14.06)	46.41 (12.62)	41.95 (11.92)

Age group (years)														
20–24	1	74	6	33	2	44	2	36	0	18	1	26	5	68
25–29	10	107	4	51	1	41	5	53	1	15	4	38	4	88
30–34	17	121	9	54	4	29	7	59	1	22	6	43	12	124
35–39	26	107	9	56	7	28	13	61	1	29	9	49	11	171
40–44	34	87	8	30	5	25	18	51	3	27	21	61	19	154
45–49	29	105	14	27	11	23	23	70	4	27	25	37	20	143
50–54	38	115	13	36	7	43	19	81	6	34	11	57	11	112
55–59	19	124	14	30	10	25	14	66	4	36	9	48	11	65
60–64	11	33	9	25	5	16	16	61	9	29	5	36	7	34
65–69	17	53	4	15	4	14	10	31	2	19	10	27	7	31
Patients with 1 or more metabolic risk factor														
Patient number	415	2,329	224	965	178	795	591	2,808	125	1,702	295	1,572	495	2,950
Male, number	385	1,449	201	577	170	493	541	1,670	115	1,113	268	918	457	2,109
Age, mean (SD)	50.36 (10.38)	46.82 (12.65)	50.09 (10.57)	46.73 (13.38)	49.57 (10.60)	49.29 (13.00)	49.40 (10.58)	49.30 (13.45)	51.66 (9.91)	50.43 (12.14)	49.49 (10.18)	50.06 (13.20)	47.64 (9.69)	46.57 (11.17)
Patients with 2 or more metabolic risk factor														
Patient number	266	1,522	139	681	123	566	384	1,990	85	1,291	222	1,286	337	1,952
Male, number	247	968	129	402	118	354	351	1,196	79	852	201	752	312	1,432
Age, mean (SD)	50.01 (9.97)	47.84 (12.42)	50.12 (10.19)	47.95 (12.99)	49.94 (10.75)	50.31 (12.53)	49.18 (10.18)	49.53 (13.30)	51.31 (9.08)	50.81 (11.75)	49.88 (10.10)	50.48 (13.04)	48.57 (9.13)	47.07 (11.06)

Values are presented as mean±standard deviation or number (%)

KHUG, Kyung Hee University Hospital at Gangdong; KDH, Hallym University Kangdong Sacred Heart Hospital; KWMC, Kangwon National University Hospital; DCMC, Daegu Catholic University Medical Center; PNUH, Pusan National University Hospital; WKUH, Wonkwang University Hospital; AJMC, Ajou University Hospital; AFLD, alcoholic fatty liver disease; NAFLD, nonalcoholic fatty liver disease; SD, standard deviation.

* Obesity data from 3 centers (Kangwon National University Hospital, Daegu Catholic University Medical Center, Pusan National University Hospital) were not available.

Table S4. Risk of adverse cardiac and hepatic outcomes on intergroup comparisons between those with AFLD and those with NAFLD.

	Outcome incidence	Outcome incidence (Events /Follow-up time [person-year])	Adjusted risk ratio*	95% Confidence interval	*P* value
AFLD vs. NAFLD					
Any MetR †	Cardiac outcomes	66/10,851 vs. 174/34,110	1.19	0.89–1.58	0.24
	Hepatic outcomes	101/10,842 vs. 52/34,436	5.81	4.14–8.15	**<0.001**

AFLD, alcoholic fatty liver disease; NAFLD, non-alcoholic fatty liver disease; MetR, metabolic risk factor.

* Model adjusted for age and sex in each hospital data included, and meta-analyses were undertaken to obtain cumulative incidence estimates (by person-year) using a random-effects model.

†Data of hazard ratios and 95% confidence intervals for the incidence (event per person-year) of outcomes by Cox proportional hazard models were used in six hospitals, except Wonkwang University Hospital.

Table S5. Annual incidence of study outcomes according to burden of metabolic risk factors

Year since index date	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Alcoholic fatty liver disease														
Patient without metabolic risk factor														
Number at risk	485	437	405	361	321	279	237	193	149	118	84	54	29	16
Cirrhosis (Event per year)	0	1	3	0	0	3	5	2	4	2	1	2	2	1
Liver cancer (Event per year)	0	0	0	1	0	1	0	0	0	1	0	0	0	1
Heart disease (Event per year)	0	0	0	2	1	0	2	2	3	3	4	1	3	3
Overall death (Event per year)	1	3	1	2	1	2	0	1	1	1	1	0	0	0
Patient with ≥ 1 metabolic risk factor														
Number at risk	1,751	1,591	1,435	1,308	1,190	1,035	858	680	496	351	251	164	98	43
Cirrhosis (Event per year)	0	2	7	2	9	11	5	11	13	9	6	5	7	5
Liver cancer (Event per year)	0	0	0	1	0	0	3	1	1	0	0	0	1	1
Heart disease (Event per year)	0	2	3	0	1	6	5	9	11	9	9	3	5	10
Overall death (Event per year)	9	7	2	6	8	6	4	3	0	2	1	0	0	1
Patient with ≥ 2 metabolic risk factors														
Number at risk	1,214	1,103	1,004	920	831	722	587	458	341	232	161	104	60	26
Cirrhosis (Event per year)	0	2	4	1	4	7	4	7	6	8	5	3	4	2
Liver cancer	0	0	0	1	0	0	2	1	0	0	0	0	0	0

(Event per year)														
Heart disease (Event per year)	0	1	2	0	0	5	4	4	5	9	7	3	5	7
Overall death (Event per year)	6	6	2	3	3	3	3	1	0	1	1	0	0	0
Non-alcoholic fatty liver disease														
Patient without metabolic risk factor														
Number at risk	2,546	2,317	2,114	1,923	1,721	1,478	1,260	1,031	923	623	475	319	203	106
Cirrhosis (Event per year)	0	3	1	1	1	3	3	3	4	2	1	4	2	1
Liver cancer (Event per year)	0	0	0	0	0	0	1	0	0	0	0	1	0	1
Heart disease (Event per year)	0	0	0	1	3	4	5	6	6	5	7	5	5	7
Overall death (Event per year)	6	4	3	1	2	1	6	0	1	2	3	3	1	0
Patient with ≥ 1 metabolic risk factor														
Number at risk	9,930	9,141	8,406	7,665	6,789	5,796	4,642	3,712	2,823	2,109	1,510	1,010	579	308
Cirrhosis (Event per year)	0	1	4	3	7	9	18	11	8	4	9	6	9	4
Liver cancer (Event per year)	0	0	1	1	1	1	1	2	5	1	2	2	2	1
Heart disease (Event per year)	2	1	5	12	15	27	36	30	41	44	44	39	42	37
Overall death (Event per year)	19	12	11	12	18	10	15	10	8	7	7	4	3	0
Patient with ≥ 2 metabolic risk factors														
Number at risk	7,243	6,675	6,148	5,599	4,930	4,205	3,322	2,639	1,990	1,477	1,051	699	396	190
Cirrhosis (Event per year)	0	1	2	1	7	5	11	9	6	3	7	4	5	4

Liver cancer (Event per year)	0	0	1	1	2	0	0	3	3	1	0	2	1	1
Heart disease (Event per year)	0	1	2	9	15	25	27	23	33	37	38	31	29	27
Overall death (Event per year)	13	8	6	9	11	9	14	10	8	5	3	3	2	0

Table S6. Intergroup comparison of the risk of stroke between patients with AFLD and those with NAFLD according to MetR

Presence of MetR	Outcome incidence	Outcome incidence (Events /Follow-up time [person-year])	Adjusted risk ratio*	95% Confidence interval	*P* value
AFLD vs. NAFLD					
Without MetR †	Stroke	12/2,425 vs. 15/5,989	2.23	1.03-4.82	**0.04**
MetR ≥ 1 †		43/7,580 vs. 82/23,276	1.68	1.10-2.55	**0.02**
MetR ≥ 2		33/5,015 vs. 56/16,631	1.96	1.27-3.02	**0.002**

AFLD, alcoholic fatty liver disease; NAFLD, non-alcoholic fatty liver disease; MetR, metabolic risk factor.

* Model adjusted for age and sex in each hospital data included, and meta-analyses were performed to obtain cumulative incidence estimates (by person-year) using a random-effects model.

†Data of hazard ratios and 95% confidence intervals for the incidence (event per person-year) of outcomes by Cox proportional hazard models were used in six hospitals, except in Ajou University Hospital.

Table S7. Intragroup comparison of the risk of stroke between patients with AFLD and those with NAFLD according to MetR

	Outcome incidence	Outcome incidence (Events /Follow-up time [person-year])	Adjusted risk ratio*	95% Confidence interval	*P* value
AFLD					
No MetR vs. MetR ≥ 1 †	Stroke	12/2,616 vs. 27/5,732	1.10	0.56-2.17	0.78
No MetR vs. MetR ≥ 2 †		12/2,616 vs. 30/5,050	0.90	0.46-1.76	0.77
NAFLD					
No MetR vs. MetR ≥ 1 †	Stroke	17/11,912 vs. 79/24,087	0.48	0.29-0.80	**0.005**
No MetR vs. MetR ≥ 2 †		17/11,494 vs. 82/22,220	0.46	0.27-0.77	**0.003**

AFLD, alcoholic fatty liver disease; NAFLD, non-alcoholic fatty liver disease; MetR, metabolic risk factor.

* Model adjusted for age and sex in each hospital data included, and meta-analyses were performed to obtain cumulative incidence estimates (by person-year) using a random-effects model.

†Data of hazard ratios and 95% confidence intervals for the incidence (event per person-year) of outcomes by Cox proportional hazard models were used in six hospitals, except in Ajou University Hospital.