Clinical Profiles of Asians with NAFLD: A Systematic Review and Meta-Analysis

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Keywords

Nonalcoholic fatty liver disease · Epidemiology · Liver function tests · Obesity · Fibrosis

Abstract

Introduction: NAFLD is increasingly prevalent in Asia, where people suffer more metabolic comorbidities at a lower body mass index (BMI), suggesting potential differences in their clinical profile. Therefore, we attempted to characterize the clinical profile of Asians with NAFLD via a meta-analytic approach. **Methods:** We searched PubMed, EMBASE, and Cochrane databases from January 1, 2000, to January 17, 2019. Two authors independently reviewed and selected 104 ar-

ticles (2,247,754 persons) that identified NAFLD in Asians and reported relevant data, especially BMI and ALT, and excluded individuals with other liver disease and excessive alcohol consumption. Individual patient-level data were obtained from seven cohorts in Asia to complement meta-analyzed data. **Results:** Overall, the mean age was 52.07 (95% CI: 51.28–52.85) years, with those from Southeast Asia (42.66, 95% CI: 32.23–53.11) being significantly younger. The mean BMI was 26.2 kg/m², higher in moderate-severe versus mild hepatic steatosis (28.3 vs. 25.7) patients and NFS ≥ –1.455 versus < –1.455 (27.09 vs. 26.02), with 34% having nonobese NAFLD. The mean ALT was 31.74 U/L, higher in NFS < –1.455 versus ≥ –1.455 (33.74 vs. 27.83), though no differences were found by obesity or steatosis severity. The majority of males

(85.7%) and females (60.7%) had normal to minimally elevated ALT ($1-1.5 \times 95\%$ ULN). Individual patient-level data analysis ($N = 7,668$) demonstrated similar results. **Conclusion:** About one-third of Asians with NAFLD were nonobese, and the majority did not have markedly elevated ALT. Therefore, abnormal ALT or BMI is not recommended as a criterion for NAFLD screening in this population. Additionally, there were significant differences in the clinical profiles of NAFLD among the different regions of Asia.

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Introduction

Nonalcoholic fatty liver disease (NAFLD) is considered a metabolic disorder of the liver associated with increased body mass index (BMI) that can progress to nonalcoholic steatohepatitis (NASH), cirrhosis, hepatocellular carcinoma, and death [1]. In recent decades, NAFLD has also become more prevalent in Asia [2]. In fact, the overall prevalence of NAFLD in Asia is about 30%, closely tracking that of the West [1]. However, obesity is defined at a lower BMI for Asians, as the risk of metabolic comorbidities is known to rise at these lower BMI cutoffs [3]. In addition, ALT thresholds for normal ALT may also be lower in Asians [4, 5]. Therefore, it is important to profile the Asian NAFLD population to provide ethnic and region-specific data to inform local practice and public health policy. This is particularly relevant as a recent population-based study from the USA reported very poor liver disease awareness in people affected by NAFLD in general and especially among the Asian group [6]. This disparity could be due to underdiagnosis by care providers, as well as a misperception of being well by patients because of a lack of disease knowledge specific to Asian patients with NAFLD.

Through a systematic review and meta-analytic approach, we characterized the demographic, anthropometric, and laboratory characteristics, as well as the severity of hepatic steatosis and fibrosis in Asians with NAFLD, with a focus on BMI and ALT distributions. We also obtained individual patient-level data to complement our meta-analyzed results.

Methods

Search Strategy

This study was carried out using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses and was not registered (online suppl. File; for all online suppl. material, see www.karger.com/doi/10.1159/000521662). The search was conducted using PubMed, EMBASE, and Cochrane databases from January 1, 2000, to January 17, 2019, and details of the search strategy were previously published and provided in the online supplementary material. We included studies that provided data for specific characteristics of NAFLD patients, especially BMI and ALT. Excluded studies included individuals with other liver diseases (e.g., viral hepatitis and autoimmune hepatitis) or excessive alcoholic consumption (>30 g/day for men and >20 g/day for women).

Systemic Literature Review, Data Extraction, and Quality Assessment

Two authors independently reviewed, selected, and extracted relevant data using a standardized form. Studies using duplicate cohorts were excluded. Discordance between the two reviewers was resolved by discussion between the two reviewers and/or by consultation with a senior investigator (M.H.N.).

Baseline characteristics recorded included age, BMI, ALT, aspartate aminotransferase (AST), gamma-glutamyl transferase, alkaline phosphatase, total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein, and triglycerides. We also collected data on diabetes mellitus, degree of hepatic steatosis, and fibrosis scores when available. Characteristics of NAFLD patients were further categorized by sex, BMI, severity of NAFLD, or presence of fibrosis. Obesity in Asians was defined as $\text{BMI} \geq 25 \text{ kg/m}^2$ as this was the cutoff most often used in the studies included in this meta-analysis. For the purpose of this study, we defined severity of hepatic steatosis using the following ultrasound criteria, since ultrasound is the most commonly used diagnostic method for NAFLD [7]. Mild steatosis was defined as a mild increase in liver echogenicity with normal or slightly increased visualization of the diaphragm and intrahepatic vessel borders, moderate steatosis as moderate increase in liver echogenicity with decreased visualization of the diaphragm and intrahepatic vessel borders, and severe steatosis as gross increase in liver echogenicity with poor visualization of the diaphragm, intrahepatic vessel borders, and posterior section of the right lobe. We assessed for the presence of fibrosis by NAFLD fibrosis score (NFS) and Fibrosis-4 (FIB-4) index [8, 9]. We used $\text{NFS} < -1.455$ to define the absence of advanced fibrosis (negative predictive value = 93%) and $\text{NFS} > 0.676$ as a cutoff for advanced fibrosis. We used $\text{FIB-4} \geq 2.67$ as the cutoff for advanced fibrosis, since it has been shown to have a highly positive predictive value for advanced fibrosis among NAFLD patients [10, 11].

The quality assessment tool was based on the Newcastle-Ottawa scale (NOS) to evaluate the risk of bias and methodological quality of the included studies [12]. Each article was evaluated for its representativeness, comparability, and outcome. Studies with 7 or more stars were considered to have low risk of bias, 4–6 stars as moderate risk of bias, and 3 or less stars as high risk of bias.

Individual Patient Data

In addition to study-level data, we obtained individual patient-level data from seven centers for additional analysis (Taichung Veterans General Hospital, Taichung, Taiwan; University of Hong Kong, Hong Kong; Kumamoto University, Kumamoto, Japan; Ogaki Municipal Hospital, Ogaki, Japan; Eguchi Hospital, Saga, Japan; Kawamura Clinic Health Center, Hiroshima, Japan; and Kochi Medical School Hospital, Kochi, Japan). All patients were diagnosed with NAFLD by ultrasound. The data derived from Ku-

mamoto University were obtained from a health screening program performed by the Japanese Red Cross Kumamoto Health Center, Kumamoto (May 2003–April 2012) [13]. The data derived from Ogaki Municipal Hospital were obtained from clinic records of consecutive patients who presented for either health screening or a medical visit (March 2010–September 2015). The data derived from Saga Prefecture (Eguchi Hospital Health Center from 2009 to 2010), Kawamura Clinic Health Center, Hiroshima (April 2009–March 2010), and Kochi Medical School Hospital, Kochi (April 2009–March 2010) were all obtained from general health checkup clinics. The data derived from Taichung Veterans General Hospital were collected from the Medical Screening Center (January–December 2009) [14]. The data derived from the University of Hong Kong were obtained from blood donors from the Hong Kong Red Cross Blood Transfusion Center and volunteers from the general population (August 2010–March 2012) [15]. The study was performed in accordance with the Declaration of Helsinki and was approved by the institutional review board at each study center that provided individual patient-level data.

Statistical Analysis

We calculated the pooled estimates for mean values of characteristics of NAFLD patients using a random-effects model. For studies reporting only median values, interquartile range values were used to calculate the mean and standard deviation based on the assumption that the distribution of data was symmetrical with large sample size and with other liver diseases excluded. We performed subanalysis for the following populations: male, female, obese, nonobese, Western Pacific, Southeast Asian, Eastern Mediterranean, mild steatosis, moderate steatosis, severe steatosis, moderate to severe steatosis, $\text{NFS} \geq -1.455$, and $\text{NFS} < -1.455$ (as data were generally reported using these cutoffs in the studies included in this meta-analysis).

We determined the ALT distribution among males and females with NAFLD using a bootstrap model with 10,000 resamples from the included study cohorts. Based on the corresponding mean and standard deviations of ALT values in the included studies, we estimated the proportion of patients with ALT <95% upper limit of normal (ULN), ALT (defined as 30 and 19 U/L in males and females, respectively), $1-1.5 \times 95\%$ ULN ALT (30–45 and 19.1–28.5 U/L), $1.5-2 \times 95\%$ ULN ALT (45–60 and 28.5–38 U/L), and $>2 \times 95\%$ ULN ALT (60 and 38 U/L) [16].

Heterogeneity was assessed using I^2 statistic, and estimates with $I^2 \geq 50\%$ and p value of <0.05 in Q -statistic were considered to have moderate to severe heterogeneity. We used Egger's test to evaluate for publication bias.

All meta-analyses were conducted using the meta-analysis package in R statistical software (version 3.5.1). Bootstrap modeling was performed with SAS (version 9.4; Cary, NC, USA).

Results

Study-Level Analysis

As described in Figure 1, 4,995 citations were initially identified with our search strategy where 104 articles (2,247,754 participants) met study criteria and were included in study analysis. Of these, 103 studies ($n =$

2,245,083 participants) provided BMI data, and 87 studies ($n = 2,204,503$ participants) provided ALT data for participants with NAFLD. Seven studies used either CT, MRI, controlled attenuation parameter, or the fatty liver index to diagnose NAFLD while the remaining studies were diagnosed by ultrasound. All were from January 1, 2000, to January 17, 2019 (online suppl. Table 1). Overall, the pooled mean age of NAFLD participants was 52.07 (95% CI: 51.28–52.85) years, the mean BMI was 26.2 kg/m² (95% CI: 25.94–26.46), the mean ALT was 31.74 U/L (95% CI: 30.75–32.72), and the prevalence of diabetes was 16.7% (95% CI: 13.6–20.1) (Table 1a).

There was no difference between males or females in the pooled mean age (49.33 vs. 53.43, $p = 0.07$) or BMI (26.01 vs. 26.73, $p = 0.36$), though males had a higher ALT level (37.91 vs. 27.84, $p < 0.001$) (Table 1b). While 74% of males compared to 53% of females had ALT levels between 1 and $1.5 \times 95\%$ ULN, more females than males (37% vs. 12%) had a higher degree of ALT elevation $1.5-2 \times 95\%$ ULN (shown in Fig. 2a).

We also found that 66% of NAFLD participants were considered obese while 34% were nonobese (Table 1c). Obese and nonobese patients had similar mean age ($p = 0.78$), but the obese group had a higher mean ALT level and a lower mean HDL ($p = 0.01$ for both) (Table 1c).

For subanalysis by region, there were 94 studies ($n = 2,244,590$) from the Western Pacific, 5 studies ($n = 1,981$) from Southeast Asia, and 5 studies ($n = 1,183$) from the Eastern Mediterranean (Table 1d). The ages of those from Southeast Asia (42.66, 95% CI: 32.23–53.11) were significantly younger than those from the Western Pacific (52.80, 95% CI: 51.85–53.75) or the Eastern Mediterranean regions (47.83, 95% CI: 46.62–49.04, $p < 0.001$), but there was no significant difference in the pooled mean ALT or AST levels among the regions ($p = 0.79$ and 0.16, respectively) (Table 1d).

For analysis of steatosis severity, 4 studies provided data for mild, moderate, and severe steatosis and 6 for mild versus moderate-severe steatosis. In total, 6,262 patients with mild steatosis, 1,576 patients with moderate steatosis, 543 patients with severe steatosis, and 3,952 patients with moderate-severe steatosis were included in this analysis (Table 2). NAFLD participants with severe steatosis had a significantly higher pooled mean BMI (29.89, 95% CI: 27.94–31.84) compared to those with moderate (27.85, 95% CI: 26.66–29.06) and mild steatosis (25.71, 95% CI: 24.90–26.53, $p < 0.001$), as well as a significantly higher pooled mean ALT level (50.34 vs. 49.61 vs. 34.62, respectively, $p = 0.01$) (Table 2a; online suppl. Table 2). We found similar results in analysis comparing

Fig. 1. Flowchart of systemic literature search and screening for analysis of characteristics in Asian NAFLD patients.

Table 1. Pooled means for participant characteristics: (a) overall; (b) by sex; (c) by BMI; and (d) by geographic region

(a) Overall	Studies, <i>n</i>	Participants, <i>n</i>	Pooled mean	95% CI		
Age	102	2,245,268	52.07	51.28–52.85		
BMI, kg/m ²	103	2,245,083	26.20	25.94–26.46		
ALT, U/L	87	2,204,503	31.74	30.75–32.72		
AST, U/L	73	2,158,655	27.07	25.44–28.70		
GGT, U/L	58	2,122,760	38.53	33.04–44.04		
ALP, U/L	9	18,607	135.52	123.44–147.58		
TC, mg/dL	82	2,221,329	201.21	199.19–203.23		
HDL, mg/dL	84	224,546	47.85	47.44–48.25		
LDL, mg/dL	66	169,691	120.46	115.97–124.96		
TG, mg/dL	86	2,229,552	163.13	154.26–172.00		
(b) By sex	Male		Female		<i>p</i> value	
	studies, ¹ <i>n</i>	participants, <i>n</i>	pooled mean	95% CI		
Age	20	53,591	49.33	50.15–56.72	0.07	
BMI, kg/m ²	21	2,056,100	26.01	25.27–28.19	0.36	
ALT, U/L	20	35,502	37.91	26.59–29.09	<0.001	
AST, U/L	12	10,951	31.31	22.82–31.22	0.18	
GGT, U/L	7	3,306	48.15	10.09–57.94	0.38	
TC, mg/dL	11	9,064	205.71	206.45–210.1	0.73	
HDL, mg/dL	14	13,005	44.22	50.12–56.94	<0.001	
LDL, mg/dL	8	2,858	129.83	119.84–37.51	0.85	
TG, mg/dL	15	13,525	165.37	129.04–53.94	0.004	
(c) By BMI	Obese (BMI ≥25)		Nonobese (BMI <25)		<i>p</i> value	
	studies, ² <i>n</i>	participants, <i>n</i>	pooled mean	95% CI		
Age	8	12,171	51.12	49.02–54.16	0.78	
BMI, kg/m ²	9	13,366	27.55	22.63–23.5	<0.001	
ALT, U/L	9	13,366	33.49	25.91–30.68	0.009	
AST, U/L	7	12,870	26.99	23.47–26.44	0.14	
GGT, U/L	6	8,328	41.38	30.69–39.51	0.06	
ALP, U/L	2	1,158	141.80	4.19–280.86	0.99	
TC, mg/dL	7	9,146	200.70	199.86–205.2	0.29	
HDL, mg/dL	7	11,886	48.29	48.69–53.58	0.01	
LDL, mg/dL	6	8,861	122.24	118.68–125.59	0.97	
TG, mg/dL	8	12,171	165.70	135.69–176.63	0.43	
(d) By geographic region	Western Pacific		Southeast Asia		<i>p</i> value	
	studies, <i>n</i>	participants, <i>n</i>	pooled mean	95% CI		
Age	92	2,242,104	52.80	51.85–53.75	<0.001	
BMI, kg/m ²	94	2,241,919	26.00	25.73–26.27	0.07	
ALT, U/L	80	2,202,907	31.40	30.39–32.41	0.79	
AST, U/L	66	2,157,059	26.86	25.15–28.59	0.16	
ALP, U/L	6	18,076	97.93	85.63–110.23	<0.001	
TC, mg/dL	77	2,220,399	201.63	199.55–203.71	<0.001	
HDL, mg/dL	79	223,616	48.52	48.1–48.94	<0.001	
LDL, mg/dL	64	170,880	138.11	133.42–142.81	<0.001	
TG, mg/dL	82	2,228,795	162.62	153.54–171.71	0.008	

¹ Some articles did not present data on each characteristic resulting in a lower number of studies presented for each characteristic compared to the total number of studies used in the male or female subgroup. ² Some articles did not present data on each characteristic resulting in a lower number of studies presented for each characteristic compared to the total number of studies used in the obese or nonobese subgroup.

Fig. 2. ALT distribution of the overall population: by bootstrap modeling of data derived from meta-analysis (a); by individual patient-level data (b).

NAFLD participants with moderate to severe steatosis to those with mild steatosis (Table 2b).

In analysis of fibrosis, there were three studies with 16,729 patients with NFS < -1.455 and 3,008 patients with NFS ≥ -1.455 . Those with an NFS < -1.455 had a significantly lower BMI (26.02, 95% CI: 25.66–26.40) compared to those with an NFS ≥ -1.455 (27.09, 95% CI: 26.36–27.83, $p < 0.001$), but a higher pooled mean ALT level

(33.74 vs. 27.83, respectively, $p = 0.01$) (Table 2c). As mentioned above, most studies provided NFS data using cutoff of -1.455 but not for the 0.676 cutoff.

Online supplementary Tables 3a–g and 4a–e provide the quality assessment of the studies included in the overall and subanalyses with overall scores of 7.45 and 8.83 indicating that the majority of included studies had a low risk of bias and used sound methodology in their respec-

Table 2. Pooled means for characteristics by severity of NAFLD: (a) mild, moderate, and severe steatosis by ultrasound; (b) mild versus moderate-severe steatosis by ultrasound; and (c) no fibrosis versus fibrosis by NFS

	Mild				Moderate				Severe				p value
	studies, n	participants, n	pooled mean	95% CI	studies, n	participants, n	pooled mean	95% CI	studies, n	participants, n	pooled mean	95% CI	
Age	5	5,175	49.06	45.68–52.46	4	1,576	49.03	47.14–50.94	4	543	52.32	48.35–56.3	0.33
BMI, kg/m ²	6	6,262	25.71	24.9–26.53	4	1,576	27.85	26.66–29.06	4	543	29.89	27.94–31.84	<0.001
ALT, U/L	6	6,262	34.62	27.12–42.13	4	1,576	49.61	23.65–75.58	4	543	50.34	44.26–56.44	0.006
AST, U/L	4	2,499	33.49	14.61–52.39	3	1,034	45.74	3.26–88.22	3	474	36.50	23.21–49.79	0.087
TC, mg/dL	5	5,175	199.98	192.26–207.7	4	1,576	209.19	183.63–234.75	4	543	213.22	179.91–246.54	0.62
HDL, mg/dL	5	5,175	46.49	43.84–49.15	4	1,576	47.23	43.11–51.35	4	543	38.46	27.27–49.66	0.38
LDL, mg/dL	4	3,674	117.53	108.33–126.74	4	1,576	127.77	122.88–132.67	4	543	137.23	118.29–156.19	0.08
TG, mg/dL	5	5,174	151.98	133.33–170.64	4	1,576	169.98	138.9–201.08	4	543	186.20	155.26–217.15	0.16
(b) By steatosis degree Mild													
	Moderate and severe												p value
	studies, n	participants, n	pooled mean	95% CI	studies, n	participants, n	pooled mean	95% CI	studies, n	participants, n	pooled mean	95% CI	
Age	5	5,175	49.06	45.68–52.46	5	3,096	50.61	48.7–52.54					0.44
BMI, kg/m ²	6	6,262	25.71	24.9–26.53	6	3,952	28.28	27.31–29.25					<0.001
ALT, U/L	6	6,262	34.62	27.12–42.13	6	3,952	48.20	35.97–60.44					0.06
AST, U/L	4	2,499	33.49	14.61–52.39	3	1,508	41.78	11.41–72.17					0.65
TC, mg/dL	5	5,175	199.98	192.26–207.7	5	3,096	209.69	187.73–231.65					0.43
HDL, mg/dL	5	5,175	46.49	43.84–49.15	5	3,096	43.03	41.73–44.34					0.02
LDL, mg/dL	4	3,674	117.53	108.33–126.74	4	2,119	131.00	121.66–140.36					<0.001
TG, mg/dL	5	5,174	151.98	133.33–170.64	5	3,096	181.74	158.33–205.15					0.05
(c) By fibrosis level													
	NFS < –1.455				NFS ≥ –1.455								p value
	studies, n	participants, n	pooled mean	95% CI	studies, n	participants, n	pooled mean	95% CI	studies, n	participants, n	pooled mean	95% CI	
Age	3	16,729	42.80	35.67–49.94	3	3,008	53.36	40.96–65.78					0.15
BMI, kg/m ²	3	16,729	26.02	25.66–26.4	3	3,008	27.09	26.36–27.83					<0.001
ALT, U/L	3	16,729	33.74	32.24–35.25	3	3,008	27.83	23.62–32.05					0.0096
AST, U/L	2	15,600	26.79	25.23–28.37	2	2,507	28.04	24.03–32.06					0.57
GGT, U/L	2	12,343	39.49	30.67–48.31	2	939	42.59	33.78–51.42					0.63
TC, mg/dL	3	16,729	204.64	202.17–207.12	3	3,008	205.99	191.8–220.18					0.86
HDL, mg/dL	3	16,729	44.97	41.6–48.34	3	3,008	45.91	42.92–48.91					0.68
LDL, mg/dL	3	16,729	127.46	120.11–134.83	3	3,008	124.92	112.91–136.93					0.72
TG, mg/dL	3	16,729	154.61	149.45–159.77	3	3,008	161.26	153.52–169.01					0.16

Mild, mild increase in liver echogenicity with normal or slightly increased visualization of the diaphragm and intrahepatic vessel borders. Moderate, moderate increase in liver echogenicity with decreased visualization of the diaphragm and intrahepatic vessel borders. Severe, gross increase in liver echogenicity with poor visualization of the diaphragm, intrahepatic vessel borders, and posterior section of the right lobe. Insufficient data available for NFS 0.676 cutoff.

Table 3. Characteristics of patients from the individual patient dataset: (a) overall and by sex; (b) by obesity and fibrosis

(a)	Overall (n = 7,668)	Male (n = 4,499)	Female (n = 3,169)	p value
Age	55.1±13	55.5±13.1	57.3±12.5	<0.001
BMI, kg/m ²	25.5±3.4	25.6±3.3	25.5±3.6	0.45
ALT, U/L	29 (20–43)	31 (22–47)	25 (18–36)	<0.001
AST, U/L (n = 6,615; 3,938; 2,677)	23 (19–30)	23 (19–30.75)	22 (18–30)	0.30
GGT, U/L (n = 7,168; 4,194; 2,974)	33 (23–53)	38 (27–52.88)	26 (19–41)	<0.001
ALP, U/L (n = 2,016; 263; 3,766)	218 (181–263)	215 (181–257)	225.5 (183–281)	<0.001
TC, mg/dL (n = 6,470; 3,766; 2,604)	206.1±37.7	202.9±37.3	210.7±37.8	<0.001
HDL, mg/dL (n = 5,937; 3,564; 2,373)	50±12.5	47.25±11.1	54.2±13.3	<0.001
LDL, mg/dL (n = 5,567; 3,303; 2,264)	124.1±36.9	123.5±36.6	124.9±37.4	0.17
TG, mg/dL (n = 6,109; 3,369; 2,440)	133 (96–189)	141 (101–201)	122 (89–172)	<0.001
Albumin, g/dL (n = 4,089; 2,198; 1,871)	4.4±0.4	4.4±0.4	4.3±0.4	<0.001
Platelet, 10 ³ /μL (n = 6,085; 3,622; 2,463)	234 (194–283)	232.9 (189–298)	246 (204–298)	<0.001
Diabetes, % (n = 6,615; 3,938; 2,677)	1.743 (26.3)	1.028 (26.1)	715 (26.7)	<0.001
FIB-4 with 2.67 cutoff, %	(n = 6,085)	(n = 3,622)	(n = 2,463)	0.58
FIB-4 ≤ 1.45	4,341 (71.3)	2,661 (73.5)	1,680 (68.2)	
FIB-4 1.45 < x < 2.67	1,360 (22.4)	747 (20.6)	613 (24.9)	
FIB-4 ≥ 2.67	384 (6.3)	214 (5.8)	170 (6.9)	
FIB-4 with 3.25 cutoff, %	(n = 6,085)	(n = 3,622)	(n = 2,463)	<0.001
FIB-4 ≤ 1.45	4,341 (71.3)	2,661 (73.5)	1,680 (68.2)	
FIB-4 1.45 < x < 3.25	1,489 (24.5)	816 (22.5)	673 (27.3)	
FIB-4 ≥ 3.25	255 (4.2)	145 (4.0)	110 (4.5)	
NFS, %	(n = 4,069)	(n = 2,198)	(n = 1,871)	0.07
NFS < −1.455	2,664 (65.5)	1,464 (66.6)	1,200 (64.1)	
NFS −1.455 ≥ x ≥ 0.676	1,267 (31.1)	671 (30.5)	596 (31.9)	
NFS > 0.676	138 (3.4)	63 (2.9)	75 (4)	

(b)	Obese (n = 3,952)	Nonobese (n = 3,716)	p value	NFS ≥ −1.455 (n = 1,405)	NFS < −1.455 (n = 2,664)	p value
Age	54.6±13.2	55.6±12.8	<0.001	68.2±8.8	54.8±13.3	<0.001
Males, %	2,365 (59.8)	2,134 (57.4)	0.03	734 (52.2)	1,464 (55)	0.10
BMI, kg/m ²	28±2.8	22.9±1.6	<0.001	26.6±4.1	24.9±3.3	<0.001
ALT, U/L	30 (20–45)	28 (19–41)	<0.001	23 (16–36)	28 (19–46)	<0.001
AST, U/L (n = 3,747; 3,421; 1,401; 2,660)	23 (19–31)	23 (19–30)	0.97	24 (19–34)	23 (19–32)	0.02
GGT, U/L (n = 3,747; 3,421; 1,401; 2,660)	34 (23–54)	32 (22–52)	0.50	30 (20–51)	34 (22–57)	0.10
ALP, U/L (n = 1,015; 1,001)	220 (183.5–262)	217 (179–264)	0.43	–	–	–
TC, mg/dL (n = 3,099; 3,271; 1,403; 2,660)	206.2±38.1	206±37.3	0.86	198.2±40.4	207.4±37.7	<0.001
HDL, mg/dL (n = 2,969; 2,773; 1,247; 2,144)	49.5±12.7	50.5±12.2	<0.001	47.2±13.1	49.5±12.4	<0.001
LDL, mg/dL (n = 2,794; 2,773; 1,256; 2,173)	125.2±37.7	123±36.1	0.02	119.6±35.8	129.7±36	<0.001
TG, mg/dL (n = 2,060; 3,049; 1,295; 2,268)	135 (97–191)	132 (95–188)	0.27	128 (92.5–185)	137 (96–193.2)	0.36
Albumin, g/dL (n = 2,075; 1,994)	4.4±0.4	4.4±0.4	0.02	4.2±0.4	4.5±0.3	<0.001
Platelet, 10 ³ /μL (n = 3,090; 2,995)	235 (195–282)	234 (193–283)	0.89	202 (175–233)	270 (233–314)	<0.001
Diabetes, % (n = 3,313; 3,302; 1,405; 2,664)	899 (27.1)	844 (25.6)	0.15	784 (55.8)	470 (17.6)	<0.001
FIB-4 with 2.67 cutoff, %	(n = 3,090)	(n = 2,995)		–	–	–
FIB-4 ≤ 1.45	2,236 (72.4)	2,105 (70.3)	<0.001	–	–	–
FIB-4 1.45 < x < 2.67	635 (20.6)	725 (24.2)	–	–	–	–
FIB-4 ≥ 2.67	219 (7.1)	165 (5.5)	–	–	–	–
FIB-4 with 3.25 cutoff, %	(n = 3,090)	(n = 2,995)	0.01	–	–	–
FIB-4 ≤ 1.45	2,236 (72.4)	2,105 (70.3)		–	–	–
FIB-4 1.45 < x < 3.25	712 (23)	777 (25.9)	–	–	–	–
FIB-4 ≥ 3.25	142 (4.6)	113 (3.8)	–	–	–	–
NFS, %	(n = 2,075)	(n = 1,994)	<0.001	–	–	–
NFS < −1.455	1,214 (58.5)	1,450 (72.7)		–	–	–
NFS −1.455 ≥ x ≥ 0.676	754 (36.3)	513 (25.7)		–	–	–
NFS > 0.676	107 (5.2)	31 (1.6)		–	–	–

Values as mean ± SD or median (IQR). Obese defined as BMI ≥ 25. Nonobese defined as BMI < 25.

tive studies, respectively (online suppl. Tables 3–4). However, heterogeneity was considerable for the majority of studies included with $I^2 > 50$ for most analyses and >70 for subanalyses for liver steatosis and liver fibrosis. There was no significant publication bias found using Egger's test for the analysis of ALT in the overall population ($p = 0.15$).

Individual Patient Data Analysis

Overall ($n = 7,668$), the mean age was $55.1 (\pm 13)$ years, the mean BMI was $25.5 (\pm 3.4)$ kg/m², the median ALT was 29 (range 20–43) U/L, 26.3% were diabetic, 4.2% had FIB-4 ≥ 3.25 , and 3.4% had NFS > 0.676 (Table 3a). Females ($n = 3,169$) were significantly older than males ($n = 4,499$) (57.3 ± 12.5 vs. 53.5 ± 13.1 , $p < 0.001$), had significantly lower median ALT levels (25 vs. 31, $p < 0.001$), were significantly less likely to have FIB-4 ≤ 1.45 (68.2% vs. 73.5%), and were more likely to have FIB-4 ≥ 2.67 (6.9% vs. 5.8%, $p < 0.001$) and FIB-4 ≥ 3.25 (4.5% vs. 4%, $p < 0.001$) (Table 3a). However, ALT levels were low for both males and females (shown in Fig. 2b), as 46% of males and 32% of females had ALT levels $< 95\%$ ULN.

About half (48.5%) were obese, and obese NAFLD participants were younger ($p < 0.001$), more likely male ($p = 0.03$), and had a higher median ALT ($p < 0.001$), low-density lipoprotein ($p = 0.02$), and a lower HDL ($p < 0.001$) (Table 3b). Obese patients were also more likely to have lower FIB-4 ($p < 0.001$).

When comparing participants with high versus low FIB-4, high FIB-4 participants using the FIB-4 cutoff of 2.67 were about 10 years older (67.4 ± 10.7 years vs. 56.1 ± 12.8 years, $p < 0.001$), had higher BMIs (26 ± 3.8 vs. 25.5 ± 3.5 kg/m², $p = 0.01$), higher ALT levels (34 vs. 26 U/L, $p < 0.001$), and a greater proportion of diabetes (36.7% vs. 24.2%, $p < 0.001$). We found similar findings for those with an FIB-4 of 3.25 or above (online suppl. Table 5).

Discussion

Our study found that patients with NAFLD in Asia were approximately 52 years old, overweight by Asian cutoffs, about 34% nonobese, with slightly elevated ALT and total cholesterol levels, around 17% diabetic, and 85% with NFS < -1.455 indicating a very low probability of having advanced fibrosis. Males tended to be approximately 4 years younger than females, but their BMIs were similar. As with other populations, neither the absence of obesity nor an elevated ALT should be used to guide the screening or diagnosis of NAFLD for Asians [2, 17, 18].

We also found different clinical phenotypes of NAFLD among the various Asian subregions. Those with NAFLD in Southeast Asia were significantly younger, with mean age only 43 years, suggesting that the possibility of NAFLD should not be excluded in young patients. Those from the Western Pacific were older by 10 years and 5 years than those from Southeast Asia or the Eastern Mediterranean, respectively. Those from the Eastern Mediterranean had the highest BMIs though there was no statistical difference among regions. However, all three regions demonstrated only slightly elevated ALT levels without regional differences, again showing that ALT levels should not be a criterion for detecting the presence of NAFLD. Notably, ALT levels were also lower in subgroups with higher likelihood for advanced fibrosis, which is likely due to the increase in the AST/ALT ratio that is part of the NFS, and AST/ALT ratio has been shown to correlate with liver fibrosis in chronic liver disease [19].

Notably, when we reviewed the characteristics of patients by classification of their hepatic steatosis as mild, moderate, and severe by ultrasound, we found those with severe steatosis on average had BMIs that were 14% greater than those with mild hepatic steatosis and 7% greater than those with moderate steatosis. In addition, those with severe steatosis demonstrated average ALT levels that were increased at $1.5\text{--}2 \times 95\%$ ULN ALT and were 31% higher than those with mild steatosis. Such a finding suggests that if an elevated ALT level is found in one suspected of having NAFLD, that patient may in fact have severe steatosis and require further assessment.

To strengthen our meta-analysis findings, we used individual patient-level data from 7,668 subjects in seven Asian cities in three countries and found that overall the trends of differences between males and females, obese and nonobese, and those with NFS < -1.455 or ≥ -1.455 that we reported in our meta-analysis were similar to those in the analyzed individual patient-level data. Of particular interest are our findings on the percent of NAFLD patients with fibrosis, since fibrosis is the single most important predictor of death for those with NAFLD [20, 21]. Since we had individual data, we were able to calculate both the NFS and FIB-4 scores and found similar findings to our meta-analysis in that between 66% and 71% (respectively) fell into the low probability of having advanced fibrosis, while 3.4% and 4.2% (respectively) had a high probability of having advanced fibrosis or cirrhosis. In addition, we found that older, female, obese, and diabetic were more likely to have advanced fibrosis. Therefore, although the percentage of patients with advanced fibrosis is low, the large number of patients with NAFLD amplifies

the number of patients negatively affected, especially as the NAFLD burden continues to grow in Asia [22, 23]. Consequently, efforts must continue to raise awareness about NAFLD and its risk factors as well as its management, which includes weight loss through diet and exercise as well as management of patients' cardiometabolic risk factors [24, 25]. Furthermore, efforts must be made to raise awareness about the negative effects of NAFLD among older women as seen in this study and in light of a recent study that found that NASH is now the number one indicator for liver transplant among women [26].

This study has its strengths. First, the number of studies included is large, which provided a study population of over 2 million for many of the analyses. As a result, the majority of our reported findings have a good level of precision as noted in our relatively tight 95% confidence intervals. In addition, the quality of our included studies overall was high. Besides published data, we also obtained individual patient data from seven centers for additional patient-level data. We also recognize that there are several limitations. One was the lack of data to determine the NFS >0.676 for the meta-analysis. We are aware that a score between -1.455 and 0.676 is in the indeterminate zone, where certainty of the presence or absence of advanced fibrosis is not available, but we were able to determine the level of fibrosis with data from our patient-level data, which indicate that the vast majority of patients are at low risk for having advanced fibrosis. Another limitation is that the severity of steatosis was determined by ultrasound which may have interobserver variability. To account for this limitation, we included analyses of mild versus moderate versus severe steatosis as well as mild versus moderate-severe steatosis and found that the trends presented were similar. Third, a few of our subanalyses were from only a few studies; however, these studies provided a large number of patients such that our confidence in our reported findings is relatively high, especially as the majority of our findings were replicated using individual data. Lastly, for both our study level and individual patient-level data analyses, the majority of the data were from the Western Pacific region, so our data may be most representative of the Western Pacific region, and thus additional studies are needed for other regions of Asia.

Conclusion

In Asia, using a BMI of 25 or greater as an indicator of obesity, 66% of the studied population with NAFLD were obese, while 34% were nonobese. ALT levels were not

found to be elevated except in cases with combined moderate-severe as well as severe steatosis, with the majority of both males and females presenting with ALT within $1-1.5 \times 95\%$ ULN or lower, suggesting that ALT levels should not be used as a screening or diagnostic criterion for the presence of NAFLD. Among the three regions, Southeast Asians were significantly younger, Western Pacific Asians had the lowest BMIs, and Eastern Mediterranean Asians had the highest BMIs. Additional efforts to raise awareness about NAFLD among Asians are needed.

Statement of Ethics

The study was performed in accordance with the World Medical Association Declaration of Helsinki. The individual patient-level database was approved by each study center that provided individual patient-level data, received written informed consent, and the study protocol was approved by the Institutional Review Board at their respective institution (Approval No. CF14040 from the Ethics Committee of the Taichung Veterans General Hospital; No. UW-10-325 from the Ethics Committee/IRB of the University of Hong Kong and Hospital Authority Western Cluster; No. 169 from Faculty of Life Sciences, Kumamoto University; No. 20190328-7 from Ogaki Municipal Hospital; No. 2011-06-04 from Saga University Hospital).

Conflict of Interest Statement

D.Q.H. has received grant support from Exxon Mobil-NUS Research Fellowship for Clinicians and Singapore Ministry of Health's National Medical Research Council under its NMRC Research Training Fellowship. J.F. is on the advisory board/consulting for Gilead. R.C.C. has received grant support from Gilead. T.K. has received grant support and personal speaker fees from Gilead and AbbVie. M.Y. is on the advisory board/consulting for AbbVie, Arbutus Biopharma, Assembly Biosciences, Bristol Myers Squibb, Dicerna Pharmaceuticals, GlaxoSmithKline, Gilead Sciences, Janssen, Merck Sharp and Dohme, ClearB Therapeutics, and Springbank Pharmaceuticals. H.T. has received grant support from AbbVie, Merck Sharp and Dohme, and Bayer. M.H.N. has received grant support from Pfizer, Gilead, and Enanta and is on the advisory board/consulting for Intercept and Gilead. Other authors have no disclosures.

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Author Contributions

All authors participated in data acquisition, data interpretation, and review/revision of the manuscript. L.Y.K.: study design, data analysis, and manuscript drafting. D.Q.H.: study design. Y.H.Y.: study design. S.B.: data analysis. L.H.: manuscript drafting. M.H.N.: study concept and design, data analysis, manuscript drafting, and study supervision.

Data Availability Statement

The majority of data generated or analyzed during this study are included in this article and its online supplementary files. Further enquiries can be directed to the corresponding author.

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