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Original article

Ethnic differences in metabolic and histologic features among White, Hispanic, Black and Asian patients with metabolic-associated Steatotic liver disease: A network meta-analysis

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ABSTRACT

Introduction and Objectives: Current evidence on the impact of ethnic disparities on metabolic-associated steatotic liver disease (MASLD) is limited to individual studies with small sample sizes from specific regions. This network meta-analysis aimed to assess variations in metabolism and histological characteristics of MASLD among four ethnicities.

Materials and Methods: Observational studies on MASLD involving at least two ethnic groups (White, Black, Asian, and Hispanic) were identified from PubMed, Embase, and Web of Science databases up to May 7th, 2024, for inclusion in this study. The results were reported as unstandardized mean differences (MDs) and odds ratios (ORs) with 95% confidence intervals (CIs).

Results: A total of twenty-seven articles involving 14,440 non-Hispanic Whites, 4,927 non-Hispanic Blacks, 5,254 Asians, and 8,344 Hispanic MASLD patients were included in this study. The prevalence of type 2 diabetes mellitus of all ethnic groups combined was 33%, without significant difference among the four ethnicities. Asians showed higher levels of total cholesterol compared to the other groups, while Blacks had the lowest levels of alanine aminotransferase. Among biopsy-proven MASLD patients, Blacks individuals had a lower risk of significant fibrosis compared to Whites (OR=0.63, 95% CI: 0.45 to 0.87), as well as lower risks of liver inflammation (OR=0.53, 95% CI: 0.29 to 0.95) and nonalcoholic steatohepatitis (NASH) (OR=0.53, 95% CI: 0.29 to 0.95) compared to Hispanics.

Conclusions: Asians MASLD patients had higher risk of suffering from abnormal lipid metabolism while Black MASLD patients presented milder liver histologic features than both Whites and Hispanics individuals.

1. Introduction

Continuing research efforts have led to the renaming of Non-alcoholic fatty liver disease (NAFLD) as Metabolic dysfunction-associated fatty liver disease (MAFLD), and it now carries the latest nomenclature—Metabolic dysfunction-associated steatotic liver disease (MASLD). The diagnosis of MASLD is based on the presence of steatosis indicated by imaging or histology, along with at least one cardiometabolic criterion. MASLD includes different histological presentations, ranging from a mild form of simple steatosis to a progressive form of metabolic dysfunction-associated steatohepatitis (MASH) with varying degrees of fibrosis or cirrhosis [1,2]. MASLD confers an increasing health burden globally because of its high prevalence (approximately 38%) and an increasing epidemic trend [3]. The etiology of MASLD is multifaceted and stems from the complex interplay between environmental and genetic factors. Therefore, targeted, instead of generalized, identifications and treatments for patients or cultures with highly susceptible genetic backgrounds would increase the awareness of MASLD and its prevention.

Emerging evidence has demonstrated the ethnic heterogeneity for MASLD prevalence and incidence. A meta-analysis in the USA including 34 studies with 368,569 participants found that Hispanic individuals had a significantly higher pooled MASLD prevalence (22.9%, 95% CI 21.6−24.1%) than White individuals (14.4%, 95% CI 14.0−14.8%) or Black individuals (13.0%, 95% CI 12.2−13.9%) [4]. Furthermore, the almost two-

Abbreviations: ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; BMI, Body mass index; CHOL, total cholesterol; FBG, Fasting blood glucose; HOMA-IR, Homeostasis model assessment of insulin resistance; HDL-C, High-density lipoprotein cholesterol; LDL-C, low-density lipoprotein- cholesterol; MAFLD, Metabolic dysfunction-associated fatty liver disease; MASLD, Metabolic dysfunction-associated steatotic liver disease; MASH, Metabolic dysfunction-associated steatohepatitis; NAFLD, Non-alcoholic fatty liver disease; NASH, Nonalcoholic steatohepatitis; MetS, Metabolic syndrome; TG, Triglyceride; T2DM, Type 2 diabetes mellitus

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folds higher MASLD burden in Hispanic individuals compared to individuals of other ethnicities supports the existence of ethnic differences. Additionally, susceptible genetic alleles (PNPLA3-rs738409 + rs6006460, TM6SF2-rs58542926, HSD17B13-rs80182459 + rs72613567, MBOAT7/TMC4-rs641738, and GCKR-rs1260326) known to be involved in disease progression are not equally distributed among multiethnic groups of MASLD patients. Hispanic individuals carry more risk alleles, whereas Black individuals contain fewer of these alleles than White individuals [5–10]. However, all these studies were mainly conducted in the USA, and limited data have been presented for Asian individuals. Resmetirom, the sole FDA-approved drug for NASH with liver fibrosis, enrolled approximately 90% of White patients in this clinical trial, leaving the efficacy for other ethnic groups uncertain [11]. The global rise in NAFLD prevalence has been unprecedented across all regions. Given the substantial disease burden, addressing the unknown ethnic clinical variations poses a significant obstacle in drug development. Therefore, tailored clinical interventions and ongoing management for diverse ethnic groups should be guided by their distinct clinical profiles. It would be of great significance to perform a comprehensive meta-analysis with convincing evidence derived from multiethnic groups, including Asian individuals, to elaborate the ethnic differences in the clinical features of MASLD.

In the current study, we conducted this systematic review and meta-analysis of observational studies to investigate the ethnic metabolic and histological discrepancies among patients with MASLD from non-Hispanic White individuals, non-Hispanic Black individuals, Asian individuals, and Hispanic individuals.

This manuscript is written following the Systematic Reviews and Meta-Analysis (PRISMA) 2009 checklist.

2. Materials and Methods

This network meta-analysis was registered in the PROSPERO registry (registration number: CRD42022377699). It was designed, performed, and reported in accordance with the Preferred Reporting Items for PRISMA [12].

2.1. Literature and search strategy

We searched eligible studies indexed in the PubMed, Embase, and Web of Science databases from the establishment of each database to May 7th 2024. The details of search strategy was described in Table S1 and included the following keywords: “nonalcoholic fatty liver disease” or “nonalcoholic steatohepatitis” or “NAFLD” or “NASH” or “NAFL” or “fatty liver” or “liver steatosis” or “hepatic steatosis” or “metabolic dysfunction-associated fatty liver disease” or “metabolic dysfunction-associated steatotic liver disease” or “MAFLD” or “MASLD” or “MASH” combined with the terms “race” or “ethnicity” or “ethic” or “racial” or “ethnical” or “Caucasian” or “non-Hispanic Whites” or “Whites” or “non-Hispanic Blacks” or “Blacks” or “African American” or “Hispanics” or “Asians”. The reference lists of the included articles were also manually searched.

2.2. Eligibility criteria and study selection

The inclusion criteria of the literature were as follows: [1] cross-sectional, case-control, or cohort studies; [2] including individuals diagnosed with NAFLD/MAFLD/MASLD with at least one of the serum scores, radiologic, or histologic evidence; and [3] any studies reporting clinical parameters in NAFLD/MAFLD/MASLD patients of no less than two ethnicities (White, Black, Asian, and Hispanic). Studies were excluded from this systematic review and meta-analysis according to the following criteria: [1] reviews, editorials, case reports, unpublished articles; [2] studies on animals; [3] coexisting with other liver diseases (e.g., alcoholic liver disease and viral hepatitis); and [4] non-English language [5] insufficient information to extract data.

2.3. Quality assessment

Study quality was evaluated by two investigators (L.M and Y.J) according to the Newcastle–Ottawa Scale (NOS) criteria that appraises the quality of published nonrandomized studies in meta-analysis [13]. The NOS consists of eight items categorized into three main criteria: selection, comparability, and outcome (cohort studies) or exposure (case-control studies). The quality score ranged from zero to nine grading the articles as follows: poor quality: poor quality (0–3), moderate quality [4–6], and high quality [7–9].

2.4. Data extraction

Two authors (LM L and JM L) independently selected and extracted data from eligible studies. In case of disagreement on the extractions, the corresponding authors (JZ Y and BH Z) participated in the discussion to reach a final agreement. A standardized data extraction form was used to extract the following information: first author, year of publication, country, ethnicity, study design, study group (children or adults), disease severity of the study group (NAFLD/MAFLD/MASLD and NASH/MASH), diagnostic methods, sample size, age, sex, and quality score. If important data could not be obtained directly from the article, we contacted the corresponding or first author by e-mail to obtain primary reports; if they did not respond, the article was excluded. If data transformations were necessary during the analysis, we also contacted the authors for assistance; if original data were not available, we applied standard statistical formulas [14]. All studies included in the analysis provided essential data in both the main text or supplementary materials. We also extracted data on type 2 diabetes mellitus (T2DM) prevalence and the following biochemical and histological parameters in different ethnic groups: [1] liver enzyme: alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-glutamyl transpeptidase (GGT); [2] blood lipids: total cholesterol (CHOL), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C); [3] glycemic indices: fasting blood glucose (FBG), glycosylated hemoglobin (HbA1c), Insulin resistance index (HOMA-IR); and [4] histologic features: steatosis, fibrosis hepatocyte ballooning, lobular and portal inflammation. In this study, we used the NASH clinical research network system to score steatosis (graded 0–3), inflammation (graded 0–3), and ballooning (graded 0–2) and the METAVIR fibrosis scoring system to evaluate fibrosis (graded 0–4) [15,16] to extract liver histological data from included articles with biopsy. The significant steatosis (moderate-severe) was defined as a steatosis score $\geq$2, and significant fibrosis was defined as a fibrosis stage $\geq$2 for the analyses as well as inflammation and ballooning were defined as score $\geq$1. NASH was defined as NAS score $\geq$4. The fibrosis score comparisons were only based on histology and not non-invasive tests.

2.5. Statistical analysis

In this network meta-analysis, data analysis was conducted utilizing the Review Manager version 5.3 and Stata 12.0 software. Following data extraction and transformation, serum levels of hepatic liver enzymes, blood lipids, and glycemic indices were expressed as mean and standard deviation (SD), and the effect size among MASLD patients of four ethnic groups was determined through calculation of unstandardized mean differences (MDs) with 95% confidence intervals (CIs). Furthermore, the associations between ethnicity and moderate to severe steatosis, inflammation, ballooning and significant fibrosis were evaluated through the calculation of odds ratios (ORs) with 95% CIs. We inspected the potential for publication bias by funnel plot asymmetry and further quantified the asymmetry using Egger’s and Begg’s tests, which considered bias as significant for P values < 0.05. The corrected effect size for significant bias was calculated using the Duval and Tweedie’s trim-and-fill method. The surface under the cumulative ranking (SUCRA) was

calculated as a numerical measure to overview which ethnicity had the most marked features with the order of four ethnic groups with a hierarchy of probabilities for network meta-analysis [17]. As for the heterogeneity across these studies, we tested it via I^2 statistics, indicating substantial heterogeneity with value of greater than 50%. Moreover, a random-effects meta regression analysis was further performed to investigate the impact of several continuous variables (including the mean age, male proportion and BMI) on the metabolic parameters and histological characteristics of MASLD patients. Because the small sample size of included studies may lead to an unreliable value of the heterogeneity test, a random-effects model and sensitivity analysis were performed to validate the stability of the conclusions in our meta-analysis.

3. Results

3.1. Characteristics of the included studies

We initially retrieved a total of 8822 records; excluded 1416 duplicate records, and removed 6953 records based on title and abstract review; and reviewed the full text of 453 articles remaining for retrieval and assessment eligibility for this meta-analysis. Among these articles, we excluded 361 articles for providing only ethnic proportion but not ethnic groups, 52 articles for subjects involved in ethnic subgroups were not all MASLD, and 13 articles for categorizing multiple target ethnicities as "others". Finally, 27 articles consisting of 32,965 patients (14,440 White, 4927 Black, 5254 Asian and 8344 Hispanic) with MASLD were included in this meta-analysis (Fig. 1) [6,7,10,18–41]. Only 9 studies out of the 27 (33%) had actual liver biopsies for all patients. The detailed characteristics of 27 included articles were outlined in Table 1. Among these articles, three were performed in children, and the others were in adults; twenty-two were conducted in the United States (USA), one was conducted in India, one was six-center study, one was two-center study conducted in USA and UK, one was multi-center study conducted in 18 countries, and one was an analysis of the of the STELLAR-3 (NCT03053050) and STELLAR-4 (NCT03053063) trials. In terms of their quality, 24 articles were considered to be of high quality, and 3 articles were considered as moderate quality while none was excluded for low quality. Table S2 showed the score results of NOS quality assessment.

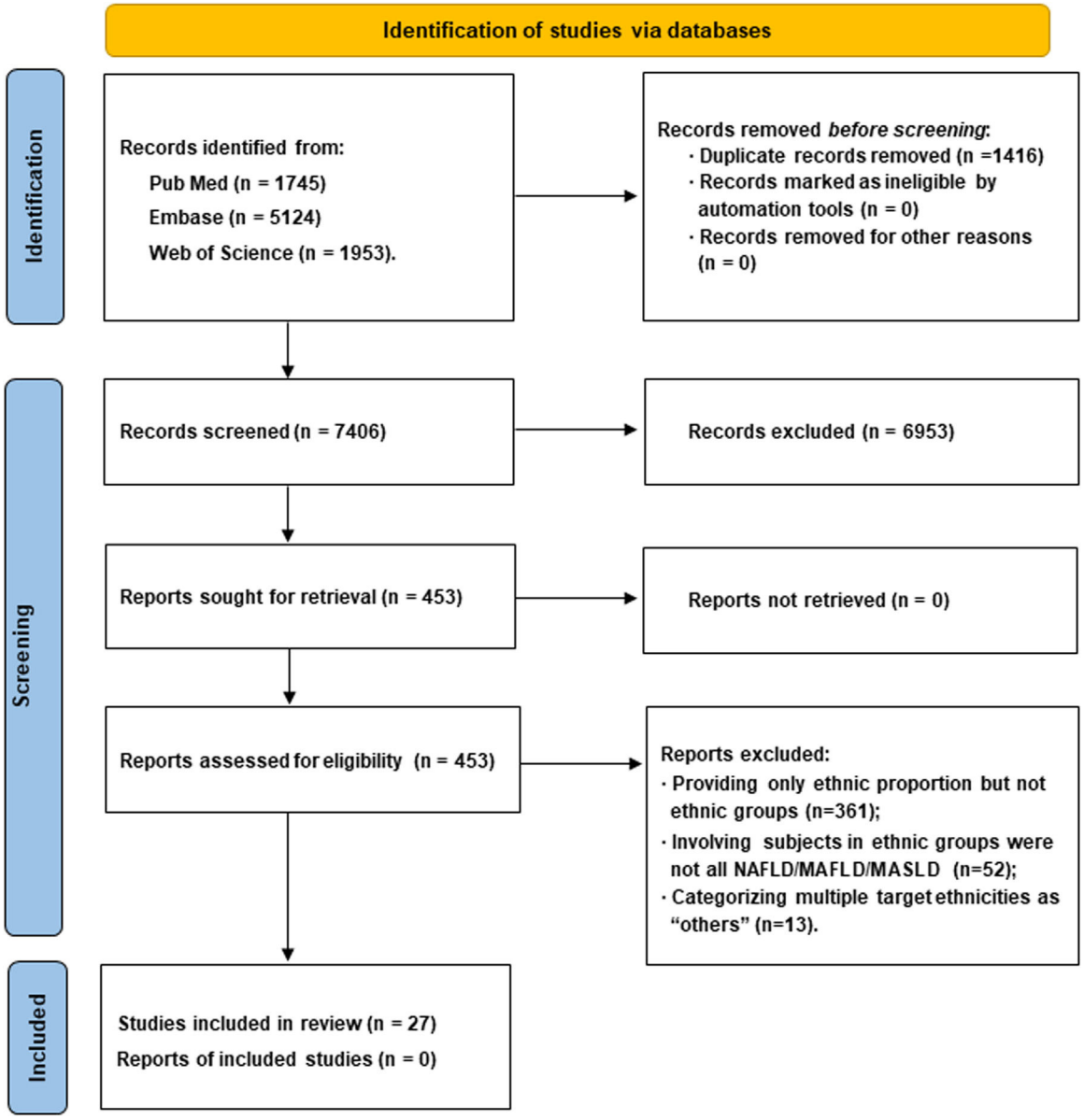

Fig. 1. Flowchart of the study selection process.

Table 1
Characteristics of the included studies.

Study	Country	Diagnostic methods	Sex (Male/Total)				Age (years)				BMI (kg/m^2)				NOS score
			White	Black	Hispanic	Asian	White	Black	Hispanic	Asian	White	Black	Hispanic	Asian	
Solga 2005 [6]	USA	Biopsy	28/149	1/17	-	-	44.0 ± 9.5	37.2 ± 7.8	-	-	54.4 ± 11.4	61.5 ± 14.7	-	-	8
Weston 2005 [7]	USA	Biopsy /Ultrasound /CT	31/71	0/5	23/45	22/28	52.0	61.0	46.0	46.0	34.0	36.6	34.2	26.8	9
Nelson 2007 [10]	USA/CAN	Biopsy	50/98	-	7/12	7/12	48.7 ± 11.1	-	50.1 ± 11.8	43.9 ± 12.6	32.7 ± 5.3	-	32.4 ± 3.9	29.0 ± 3.6	6
Kallwitz 2009 [18]	USA	Biopsy	32/110	21/92	7/36	-	44.0 ± 10.0	42.0 ± 9.0	39.0 ± 8.0	-	56.3 ± 11.0	55.4 ± 8.4	53.6 ± 9.3	-	7
Mohanty 2009 [19]	USA	Biopsy	59/154	13/36	13/32	10/16	45.5 ± 11.5	47.4 ± 11.5	40.0 ± 13.3	46.7 ± 16.7	38.8 ± 12.5	36.2 ± 9.4	37.1 ± 9.6	29.3 ± 5.5	7
Lomo-co 2011 [20]	USA	Biopsy /MRI	21/56	-	36/96	-	53.0 ± 1.0	-	50.0 ± 1.0	-	34.0 ± 1.0	-	34.0 ± 1.0	-	7
Tabibian 2011 [21]	USA	Biopsy	22/47	-	7/18	10/16	51.6 ± 9.4	-	41.6 ± 13.2	49.4 ± 10.1	32.3 ± 7.5	-	32.3 ± 6.1	26.1 ± 5.9	7
Bambha 2012 [22]	USA	Biopsy	285/785	3/27	45/118	32/54	48.4 ± 1.9	51.6 ± 10.9	38.0 ± 5.9	43.3 ± 7.6	34.1 ± 1.0	38.1 ± 5.3	33.7 ± 2.9	27.4 ± 2.4	9
Foster 2013 [23]	USA	CT	94/189	36/106	94/208	-	61.5 ± 9.2	63.5 ± 9.3	59.3 ± 9.9	-	31.4 ± 5.1	32.8 ± 5.8	31.7 ± 5.3	-	8
Garcia 2015 [24]	USA	Biopsy /MRI	0/54	0/16	-	-	43.4 ± 1.2	39.5 ± 2.2	-	-	43.8 ± 0.8	43.9 ± 2.0	-	-	7
Panigrah 2015 [25]	India	Biopsy /Ultrasound	253/451	-	-	519/633	47.5	-	-	45.6	32.6 ± 5.3	-	-	26.2 ± 3.4	5
Goffredo 2016 [26]	USA	MRI	24/64	7/18	35/76	-	13.8 ± 3.7	13.4 ± 3.4	12.8 ± 3.7	-	32.7 ± 7.4	34.4 ± 8.0	31.9 ± 7.1	-	8
Lee 2017 [27]	USA	MRI	8/8	5/5	-	-	15.1 ± 1.4	14.4 ± 2.1	-	-	36.5 ± 5.7	38.1 ± 3.3	-	-	7
Remigio 2017 [28]	USA	CT	34/64	6/19	28/69	45,616	61.5 ± 8.3	62.9 ± 9.7	60.3 ± 9.1	65.2 ± 11.3	31.0 ± 4.6	30.9 ± 5.3	31.2 ± 4.7	25.6 ± 2.9	9
Trico 2018 [29]	USA	Biopsy /MRI	39/82	12/21	61/106	-	13.2 ± 2.8	14.1 ± 2.6	13.1 ± 2.8	-	33.9 ± 5.5	38.5 ± 6.0	32.7 ± 6.1	-	9
Kim 2020 [30]	USA	Biopsy	9/21	4/6	85/180	33/69	46.5	48.6	45.3	48.4	31.4	32.6	34.2	29.5	7
Marella 2020 [31]	USA	Ultrasound /CT /MRI	83/309	28/172	-	-	43.8 ± 10.8	42.1 ± 8.7	-	-	44.0 ± 6.8	45.7 ± 7.8	-	-	5
Hullar 2021 [32]	USA	MRI	31/67	15/38	67/143	78/178	41.7	43.4	42.3	47.5	33.1	31.3	32.4	28.6	8
Kubiliun 2022 [33]	USA	Biopsy /Ultrasound /CT /MRI	206/429	21/57	287/668	-	56.9 ± 12.1	53.9 ± 10.6	52.3 ± 11.4	-	31.9 ± 7.6	32.9 ± 7.2	32.9 ± 7.1	-	9
Li 2022 [34]	USA/UK	Biopsy /Ultrasound /CT /MRI	48/83	10/14	-	47/80	55.0 ± 13.6	47.9 ± 11.8	-	49.3 ± 11.3	35.5 ± 8.6	33.3 ± 8.9	-	29.8 ± 4.8	8
Younossi 2022 [35]	Multi-center[a]	Biopsy /Ultrasound /CT /MRI	690/1500	-	-	577/946	54.4 ± 11.1	49.0 ± 11.3	52.5 ± 14.1	44.2 ± 11.5	40.8 ± 8.8	33.6 ± 6.2	28.2 ± 4.8	27.0 ± 4.0	8
Zhou 2022 [36]	USA	FibroScan	360/642	161/336	293/514	147/249	53.0 ± 19.5	50.0 ± 24.9	45.0 ± 29.9	49.0 ± 23.2	33.9 ± 12.7	36.4 ± 9.2	33.1 ± 9.1	29 ± 4.7	8
Nguyen 2023 [37]	USA	Ultrasound/CT/MRI	2387/4115	83/214	982/2604	1336/2407	54.1 ± 14.9	51.4 ± 15.2	44.5 ± 15.2	48.3 ± 15.4	32.3 ± 6.7	36.1 ± 9.9	33.5 ± 7.5	28.0 ± 5.0	8
Wong 2023 [38]	Six-center[b]	Biopsy	751/1734	-	221/539	403/762	59.0 ± 8.9	-	57.0 ± 9.6	58.0 ± 11.1	34.2 ± 6.2	-	32.8 ± 6.0	28.2 ± 4.6	9
Bril 2024 [39]	USA	FibroScan	1121/2242	806/1714	753/1568	409/835	52.0 ± 20.0	48.0 ± 18.0	45.0 ± 17.0	46.0 ± 16.0	29.7 ± 7.2	31.1 ± 8.3	30.0 ± 6.2	25.8 ± 4.8	7
Elsaid 2024 [40]	USA	Ultrasound	475/1029	288/756	483/1115	-	46.3 ± 0.6	41.2 ± 0.5	39.4 ± 0.6	-	28.6 ± 0.4	30.0 ± 0.4	29.3 ± 0.3	-	8
Samala 2024 [41]	USA	Biopsy	745/1910	27/109	-	-	51.4 ± 11.9	51.6 ± 11.3	-	-	35.1 ± 6.7	36.9 ± 6.6	-	-	9

Abbreviations: BMI: body mass index; NOS: Newcastle–Ottawa Scale; USA: the United States; CAN: Canada; UK: the United Kingdom; CT: computed tomography; MRI: magnetic resonance imaging; SD: standard deviation. Data are presented as number or (Mean ± SD).

[a] This study was conducted in 23 sites located in 18 countries (Australia, China, Cuba, Egypt, Greece, India, Italy, Japan, Saudi Arabia, Malaysia, Mexico, Pakistan, Russia, Spain, Turkey, and the United States).

[b] This study was conducted in 6 countries (the United States, China, Japan, India, the United Kingdom and Spain).

3.2. Meta-analysis on the T2DM prevalence among four ethnic groups

As presented in Figure S1, Asian MASLD patients had a pooled T2DM prevalence of 32% (95% CI 23 to 40%) with significant heterogeneity (I^2 = 96.88%) from 13 studies involving 5501 participants. Black MASLD patients showed a pooled T2DM prevalence of 33% (95% CI 27 to 42%) with substantial heterogeneity (I^2 = 95.91%) from 16 studies with 5031 participants. Hispanic MASLD patients had a pooled T2DM prevalence of 34% (95% CI 27 to 40%) with substantial heterogeneity (I^2 = 97.25%) from 16 studies with 8849 participants. White MASLD patients exhibited a pooled T2DM prevalence of 33% (95% CI 26 to 40%) with substantial heterogeneity (I^2 = 98.62%) from 21 studies involving 14,736 participants. Overall, the meta-analysis showed that the pooled T2DM prevalence among the four ethnic MASLD patients was 33% (95% CI 30 to 37%) with substantial heterogeneity (I^2 = 97.64%). Importantly, there was no significant difference in T2DM prevalence among the four ethnic groups of MASLD patients (p = 0.98).

3.3. Meta-analysis of the effects on metabolic parameters and histological characteristics in MASLD

An evaluation of serum levels of liver enzymes, blood lipids, and glucose metabolism was conducted in this meta-analysis to gain insight into the differences between various ethnic groups with MASLD. The raw data of median values of metabolic indicators and percentage of patients with various histological features were presented in Table 2. The comparison of these biochemical parameters was performed between every two ethnic groups, and the results are displayed in Figs. 2-7 and Tables S3–4. The funnel plots of liver enzymes (ALT and AST), blood lipids (CHOL, TG, HDL-C and LDL-C), and glucose metabolism (FBG, HbA1c, and HOMA-IR) are included in the supplementary materials (Figure S2, S5, S8, S11, S14, S17).

The study also investigated the histological features of MASLD in different ethnic groups by utilizing liver biopsy results. Twelve out of the twenty-seven included studies were able to provide data on hepatocellular steatosis (6 studies), ballooning (6 studies), lobular and portal inflammation (7 studies), fibrosis (12 studies) and NAS score (6 studies).

3.3.1. Comparisons of Asians vs. Whites

Due to limited data, comparisons of the HOMA-IR index were not possible. However, Asians showed slightly higher serum ALT, AST, and CHOL levels with total random-effects MDs of 3.21 [95% CI 0.10 to 6.33 in ALT (U/L), Fig. 2A], 3.87 [95% CI 1.45 to 6.28 in AST (U/L), Figure S2B], and 4.14 [95% CI 0.98 to 7.30 in CHOL (mg/dL), Figure S2C]. Additionally, they had lower risks of liver significant fibrosis (OR= 0.63, 95% CI 0.53 to 0.75, Fig. 2G) and NASH (OR= 0.77, 95% CI 0.64 to 0.93, Fig. 2H). No significant differences were noted in the remaining comparisons (Table S3).

3.3.2. Comparisons of Asians vs. Blacks

Asians had higher serum ALT, AST, CHOL and TG levels compared to Blacks, with a total random-effects MDs of 11.06 [95% CI 6.63 to 15.50 in ALT (U/L), Fig. 3A], 3.52 [95% CI 0.35 to 6.70 in AST (U/L), Figure S5B], 10.67 [95% CI 4.22 to 17.11 in CHOL (mg/dL), Figure S5C] and 48.02 [95% CI 39.85 to 56.20 in TG (mg/dL), Fig. 3B]; but lower HbAc1 level than Blacks with MDs of -0.09 [95% CI -0.17 to -0.01 (%), Figure S5H]. No significant differences were observed in the comparison of histological features between the two ethnic groups. Limited literature was available for comparing the HOMA-IR index, as well as significant steatosis and NASH, between Asians and Blacks (Table S3).

3.3.3. Comparisons of Asians vs. Hispanics

Asians exhibited higher serum CHOL and HDL-C levels compared to Hispanics (total random-effects MD of 5.76 [95% CI 1.72 to 9.79 in CHOL (mg/dL), Figure S8C] and 3.28 [95% CI 2.26 to 4.30 in HDL-C (mg/dL), Figure S8E]. Due to limited studies, a comparison of HOMA-IR index between the two ethnic groups could not be conducted. There were no significant differences observed in other laboratory indicators or liver histological features among the comparisons (Table S3).

3.3.4. Comparisons of Blacks vs. Whites

As presented in Table S4, Black participants exhibited lower serum levels of ALT, AST, CHOL and TG but higher HDL-C and HOMA-IR index compared to white participants, as demonstrated by total random-effects mean differences of -6.24 [95% CI -8.96 to -3.53 in ALT (U/L), Fig. 5A], -2.21 [95% CI -3.80 to -0.62 in AST (U/L), Figure S11B], -4.63 [95% CI -6.52 to -2.73 in CHOL (mg/dL), Figure S11C], -50.00 [95% CI -60.35 to -39.66 in TG (mg/dL), Fig. 5B), 2.26 (95% CI

Table 2
The median values of metabolic indicators and percentage of patients with various histological features in MASLD patients from four ethnic groups.

	Asian	White	Black	Hispanic
Metabolic indicators				
ALT (U/L)	55.44 (47.78, 63.10)	48.94 (42.92, 54.96)	34.21 (28.25, 40.18)	51.60 (43.05, 60.16)
AST (U/L)	41.19 (35.12, 47.25)	37.61 (32.76, 42.46)	33.06 (29.30, 36.83)	40.81 (34.55, 47.07)
CHOL (mg/dL)	196.73 (192.18, 201.28)	187.80 (184.23, 191.38)	181.64 (174.01, 189.26)	185.73 (179.68, 191.78)
TG (mg/dL)	180.81 (162.12, 199.51)	170.72 (162.63, 178.81)	122.88 (108.71, 137.06)	162.93 (144.65, 181.20)
HDL-C (mg/dL)	46.84 (42.10, 51.58)	43.85 (41.82, 45.87)	46.83 (43.10, 50.56)	42.79 (39.54, 46.04)
LDL-C (mg/dL)	111.87 (109.75, 113.98)	107.70 (103.68, 111.72)	108.64 (103.30, 113.97)	107.89 (103.52, 112.25)
FBG (mg/dL)	110.08 (101.31, 118.85)	110.01 (105.59, 114.42)	110.62 (102.14, 119.09)	114.04 (104.58, 123.51)
HbAc1 (%)	6.38 (6.01, 6.76)	6.24 (5.96, 6.51)	6.20 (5.96, 6.45)	6.00 (5.76, 6.24)
HOMA-IR	4.31 (3.33, 5.29)	4.29 (3.41, 5.17)	5.28 (3.43, 7.13)	4.37 (3.06, 5.67)
Percentage of histological features				
Significant steatosis (%)	54 (31, 77)	52 (22, 82)	28 (4, 60)	46 (3, 90)
Inflammation (%)	58 (35, 81)	69 (47, 91)	54 (11, 97)	66 (40, 92)
Ballooning (%)	68 (53, 82)	77 (63, 92)	63 (39, 87)	78 (59, 96)
Significant fibrosis (%)	38 (15, 62)	37 (21, 53)	19 (13, 26)	39 (24, 54)
NASH (%)	73 (70, 76)	54 (22, 87)	38 (4, 73)	71 (66, 77)

The median values of metabolic indicators and percentage of histological features were derived from the raw data.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CHOL, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein- cholesterol; FBG, fasting blood glucose; HOMA-IR, homeostasis model assessment of insulin resistance; NASH, nonalcoholic steatohepatitis.
The significant steatosis (moderate-severe) was defined as a steatosis score ≥2, and significant fibrosis was defined as a fibrosis stage ≥2 for the analyses as well as inflammation and ballooning were defined as score ≥1. NASH was defined as NAS score ≥4.

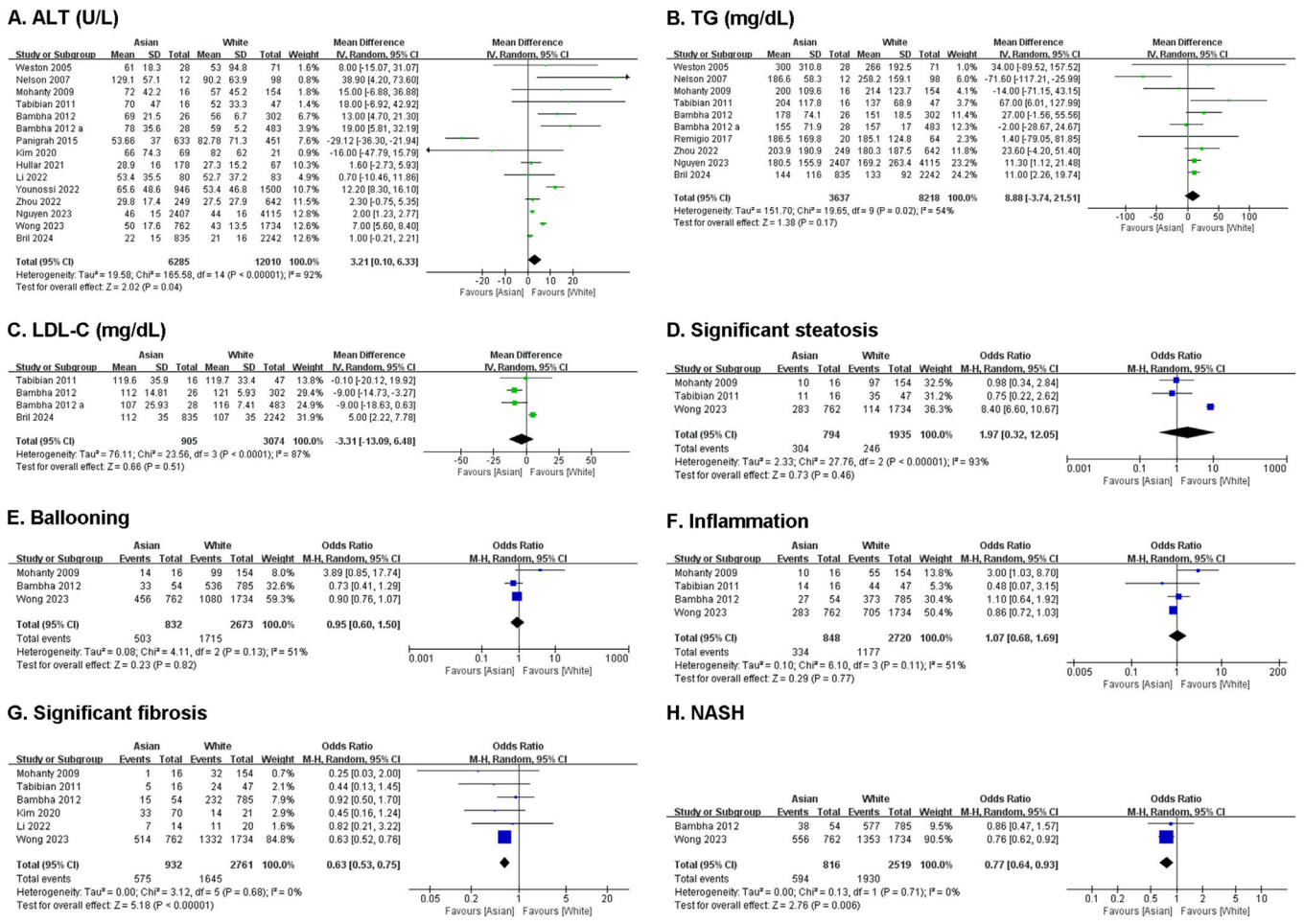

Fig. 2. Forest plot of the included trials comparing Asian and White MASLD patients regarding biochemical indicators (A-C) and histological features (D-H).
A. ALT (U/L); B. TG (mg/dL); C. LDL-C (mg/dL; D. Significant steatosis; E. Ballooning; F. Inflammation; G. Significant fibrosis; H. NASH.
[a] Patients diagnosed as NASH from the same research enrolling patients with simply NAFLD.

0.48 to 4.03 in HDL-C (mg/dL), Figure S11E] and 0.85 (95% CI 0.03 to 1.67 in HOMA-IR, Fig. 5D). Additionally, a lower risk of liver significant steatosis (OR=0.30, 95% CI 0.11 to 0.76, Fig. 5E) and fibrosis (OR=0.63, 95% CI 0.45 to 0.87, Fig. 5H), as well as a similar risk of NASH (OR=0.69, 95% CI 0.43 to 1.09, Fig. 5I) was observed in Black participants compared to White participants (Table S4).

3.3.5. *Comparisons of Blacks vs. Hispanics*

When compared to Hispanics, Black individuals exhibited significantly lower levels of serum ALT, AST and TG but higher levels of HDL-C and HOMA-IR index, as indicated by mean differences of −9.11 [95%CI −12.01 to −6.21 in ALT (U/L), Fig. 6A], -3.80 [95% CI -6.34 to -1.27 in AST (U/L) , Figure S14B], −41.73 [95%CI −53.73 to −29.74 in TG (mg/dL), Fig. 6C], 3.25 [95% CI 0.69 to 5.81 in HDL-C (mg/dL) , Figure S14E] and 0.23 (95% CI 0.05 to 0.42 in HOMA-IR index, Fig. 6D), respectively. Also, Black individuals tend to be with a lower risk of liver inflammation (OR=0.53, 95% CI 0.29 to 0.95, Fig. 6F) and NASH (OR=0.43, 95% CI 0.23 to 0.78, Fig. 6H) than those of Hispanics. And Black and Hispanic individuals had a similar risk of significant fibrosis (OR=0.76, 95% CI 0.28 to 2.06, Fig. 6G). The comparing of liver significant steatosis could not be performed due to insufficient studies (Table S4).

3.3.6. *Comparisons of Hispanics vs. Whites*

As demonstrated in Table S4, The Hispanic population exhibited higher levels of serum ALT (U/L) (MDs = 2.83, 95% CI 0.35 to 5.30, Fig. 7A) and HOMA-IR index (MDs = 0.80, 95% CI 0.32 to 1.28, Fig. 7D) compared to Whites. However, there were no significant differences in liver histological features between the Hispanic and Whites MASLD patients (Table S4).

3.3.7. *Publication bias*

Funnel plots were generated to assess publication bias for liver enzyme levels, serum lipid levels, glycometabolism, and histological characteristics, as presented in supplementary materials (Figures S3, S6, S9, S12, S15, S18). Our analysis revealed a minimal presence of publication bias, as the plots were largely symmetrical. This was confirmed through Egger's and Begg's tests, except for ALT levels in the comparison between Blacks and Hispanics (p = 0.020 and 0.350 in Table S5, respectively), HDL-C levels in the comparison between Hispanics and Whites (p = 0.018 and 0.592 in Table S5, respectively), HOMA-IR levels in the comparison between Blacks and Whites (p = 0.020 and 0.296 in Table S4, respectively), and ballooning in the comparison between Blacks and Whites (p = 0.033 and 0.308 in Table S7, respectively). The corrected effect size was 2.170 (95% CI: 0.432 −10.909) for ALT levels in the comparison between Blacks and Hispanics, although this was not statistically significant (p value not altered). Therefore, it can be concluded that the presence of publication bias had a minimal effect on the statistical significance of the pooled results.

3.3.8. *Sensitivity analysis*

We sequentially excluding each individual study and then recalculating the total estimates for the remaining studies. As shown in

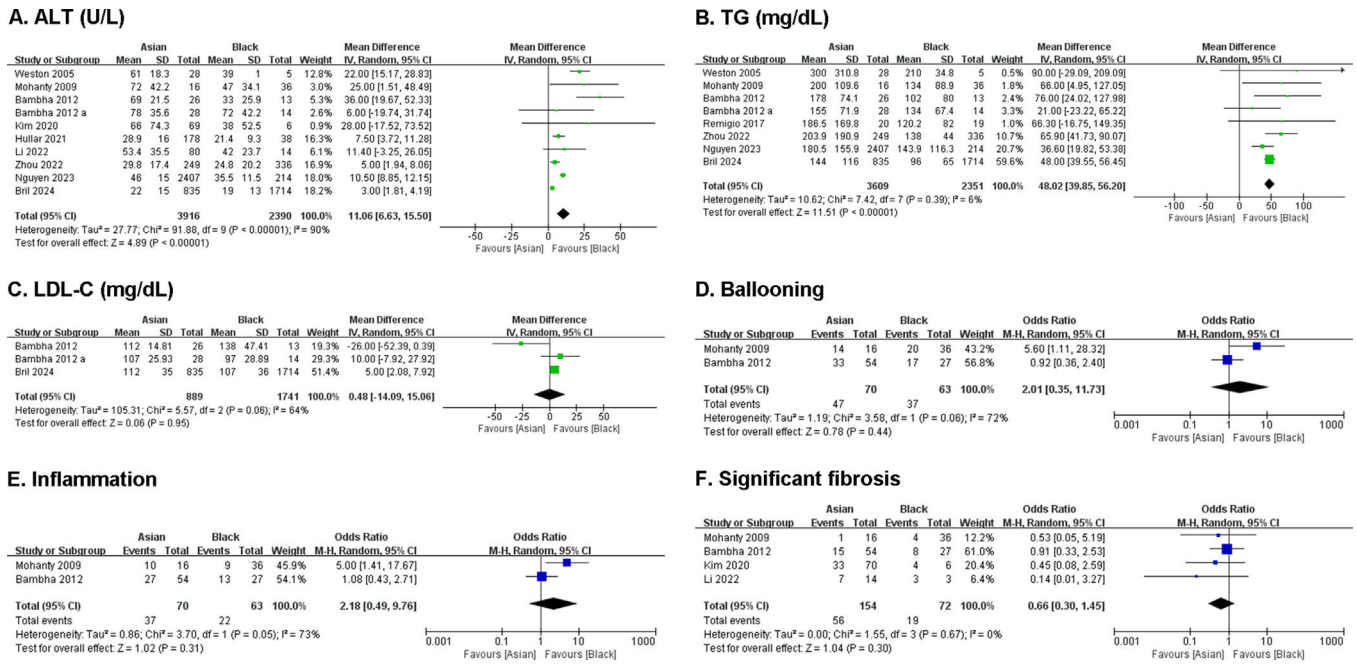

Fig. 3. Forest plot of the included trials comparing Asian and Black MASLD patients regarding biochemical indicators (A-C) and histological features (D-F).
A. ALT (U/L); B. TG (mg/dL); C. LDL-C (mg/dL); D. Ballooning; E. Inflammation; F. Significant fibrosis.
[a] Patients diagnosed as NASH from the same research enrolling patients with simply NAFLD.

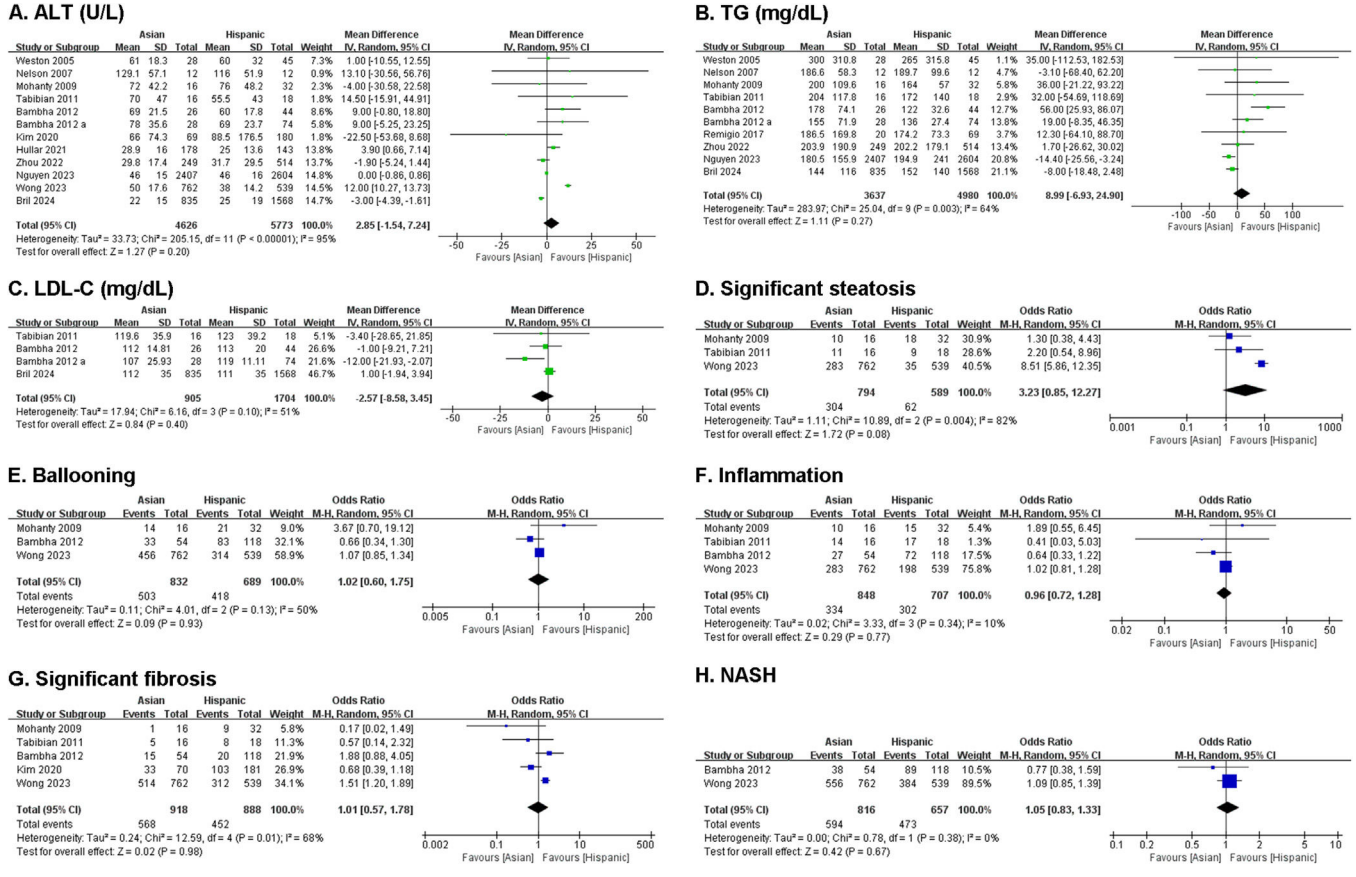

Fig. 4. Forest plot of the included trials comparing Asian and Hispanic MASLD patients regarding biochemical indicators (A-C) and histological features (D-H).
A. ALT (U/L); B. TG (mg/dL); C. LDL-C (mg/dL); D. Significant steatosis; E. Ballooning; F. Inflammation; G. Significant fibrosis; H. NASH.
[a] Patients diagnosed as NASH from the same research enrolling patients with simply NAFLD.

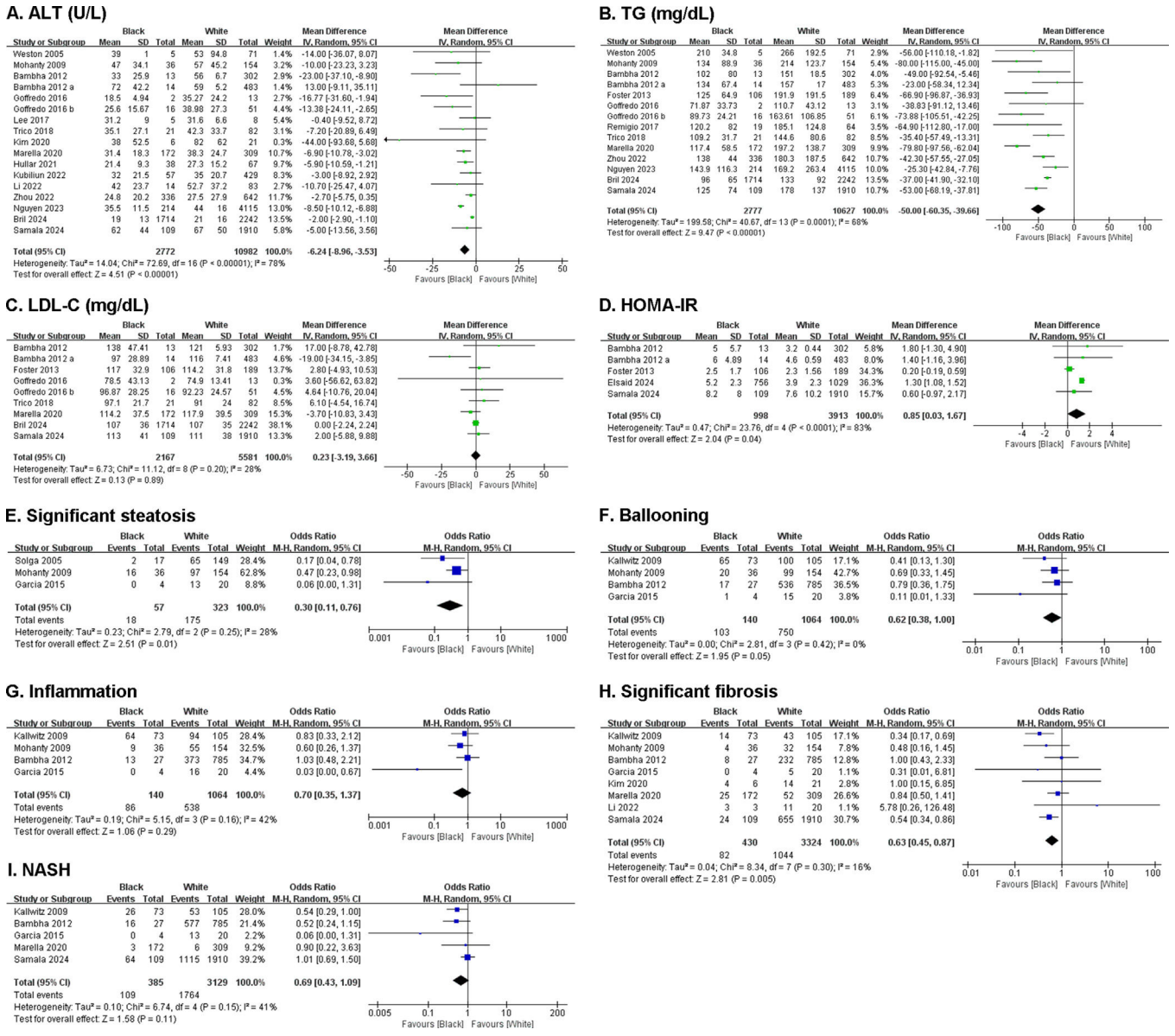

Fig. 5. Forest plot of the included trials comparing Black and White MASLD patients regarding biochemical indicators (A-D) and histological features (E-I).
A. ALT (U/L); B. TG (mg/dL); C. LDL-C (mg/dL); D. HOMA-IR; E. Significant steatosis; F. Ballooning; G. Inflammation; H. Significant fibrosis; I. NASH.
[a] Patients diagnosed as NASH from the same research enrolling patients with simply NAFLD. [b] NAFLD patients with single-nucleotide polymorphism TM6SF2 rs58542926 CC genotype from the same research enrolling patients with CT/TT genotype.

supplementary materials (Figure S4, S7, S10, S13, S16, S19), none of the studies significantly changed the conclusion in the analysis for liver enzymes, serum lipids, FBG, HbA1c and histological features, suggesting that our statistics were relatively robust and reliable.

3.4. Summary of metabolic parameters and histological characteristics in four ethnic groups

The SUCRA of network meta-analysis indicated that Asians had the highest probability of elevated serum ALT levels (84.4%, Fig. 8A), followed by Hispanics (79.2%), Whites (35.8%), and Blacks (0.6%). Asians also ranked highest in serum CHOL (98.5%, Fig. 8C) and TG (89.2%, Fig. 8D) levels. Hispanics were ranked highest in serum LDL-C levels (74.5%), followed by Whites (72.1%), Asians (35.0%), and Blacks (18.4%), as well as FBG levels (78.1%), followed by Blacks (53.1%), Asians (40.6%), and Whites (28.2%). Blacks had the lowest rankings in liver enzymes and lipid metabolism but the highest probabilities of HbA1c (80.2%, Fig. 8H) and HOMA-IR (82.3%, Fig. 8I) levels.

In terms of liver histological features, Whites had the highest risks for significant liver steatosis (86.9%, Fig. 8J) and significant fibrosis (86.2%, Fig. 8M). Hispanics were ranked highest in risks for liver inflammation (87.2%, Fig. 8J) and NASH (79.0%, Fig. 8M), while Asians were ranked highest in the risk of liver ballooning with 77.6%.

3.5. Meta-regression analysis

A random-effects meta-regression analysis was conducted using available data to examine the influence of mean age, the proportion of men and BMI on the metabolic and histological characteristics of patients with MASLD. The findings of the univariate meta-regression are outlined in Table S8. When comparing the risk of significant steatosis between Asian and White individuals, the proportion of men

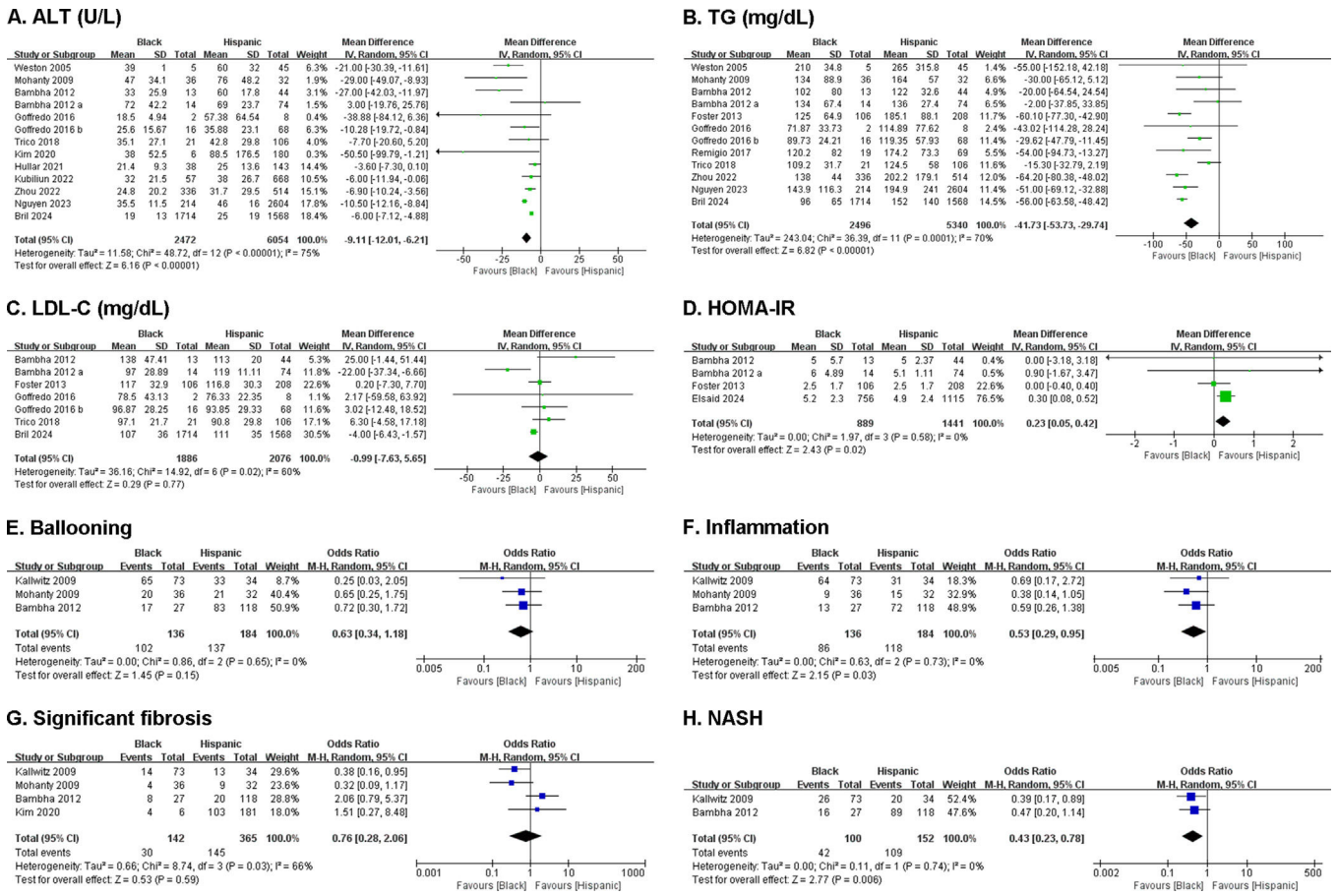

Fig. 6. Forest plot of the included trials comparing Black and Hispanic MASLD patients regarding biochemical indicators (A-D) and histological features (E-H).
A. ALT (U/L); B. TG (mg/dL); C. LDL-C (mg/dL); D. HOMA-IR; E. Ballooning; F. Inflammation; G. Significant fibrosis; H. NASH.
[a] Patients diagnosed as NASH from the same research enrolling patients with simply NAFLD. [b] NAFLD patients with single-nucleotide polymorphism TM6SF2 rs58542926 CC genotype from the same research enrolling patients with CT/TT genotype.

was identified as a slight but significant confounding factor (regression coefficient beta = -78.14, p = 0.036). Additionally, age was found to be a confounding factor in the comparison of serum ALT (regression coefficient beta = 0.049, p = 0.041) and the risk of significant steatosis (regression coefficient beta = 0.667, p = 0.047), while the proportion of men was a confounding factor for significant steatosis (regression coefficient beta = -70.937, p = 0.047) between Asian and Hispanic individuals. In the comparison between Hispanic and White individuals, age was identified as a confounding factor for the risk of liver inflammation (regression coefficient beta = -0.044, p = 0.033), while BMI affected serum HbA1c (regression coefficient beta = -0.056, p = 0.030). Notably, no significant correlation was found in any other pair of comparisons.

4. Discussion

With the surging global epidemic of MASLD, the number of studies about MASLD continues to grow [42]. To our knowledge, this study is the first comprehensive meta-analysis to pool the discrepancies in metabolic profiles and histological features among Caucasian White, Black, Asian, and Hispanic populations. In the pair comparisons between each pair of ethnicities, we confirmed the existence of diverse ethnicity in MASLD and specifically demonstrated that Asian individuals have lower LDL-C levels than Caucasian individuals, more severe hyperlipidemia than Black individuals, and a comparative metabolic dysfunction phenotype to Hispanic individuals. Distinct patterns in the MASLD histological characteristics were observed among Hispanic individuals, White individuals and Black individuals. Hispanic individuals tended to present with more severe liver inflammation, but Black individuals presented with less severe liver inflammation. Also, our findings provide a strong evident for the view that there is more severe liver ballooning in Asian MASLD patients than in the other three ethnicities. The results of meta-regression analysis indicated that the mean age, male proportion, and BMI had no significant impact on the metabolic and histological characteristics on the majority of comparisons across different ethnic groups of MASLD patients. Therefore, the results of this study were statistically reliable.

It is notable that although Asian patients with MASLD exhibited higher serum CHOL and TG levels than other three ethnic groups. The discrepancies in the serum lipid profiles might indicate that Asian MASLD patients had a higher risk of MetS; this suggests distinct serum and hepatic lipid associations between Asian MASLD patients and patients from other ethnic groups. A meta-analysis of 80 studies from 20 countries revealed a global MASLD prevalence of 55.5% (95% CI 47.3–63.7) among T2DM patients, with the highest prevalence (68.0%, 95% CI 62.1–73.0%) reported in European studies [43]. The study also found that MASLD patients of four ethnicities all had a T2DM prevalence of around 30%. MASLD and MetS are closely linked to insulin resistance and are often complicated by T2DM and cardiovascular disease (CVD), which are major causes of mortality among MASLD patients [44]. The use of anti-hyperglycemic drugs such as GLP-1 receptor agonists has been shown to effectively reduce body weight, liver injury indices, and liver fat content [45].

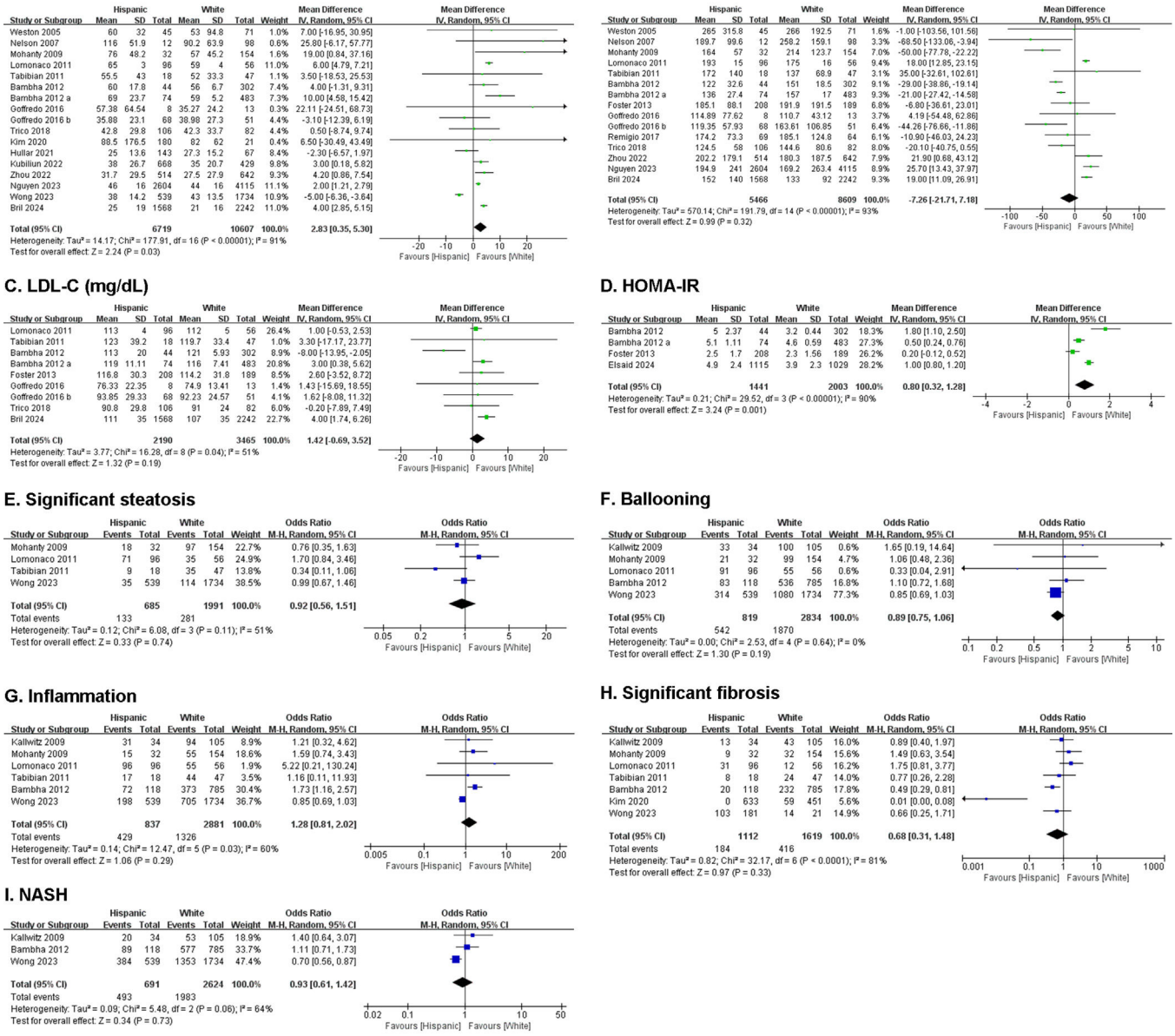

Fig. 7. Forest plot of the included trials comparing Hispanic and White MASLD patients regarding biochemical indicators (A-D) and histological features (E-I).
A. ALT (U/L); B. TG (mg/dL); C. LDL-C (mg/dL); D. HOMA-IR; E. Significant steatosis; F. Ballooning; G. Inflammation; H. Significant fibrosis; I. NASH.
[a] Patients diagnosed as NASH from the same research enrolling patients with simply NAFLD. [b] NAFLD patients with single-nucleotide polymorphism TM6SF2 rs58542926 CC genotype from the same research enrolling patients with CT/TT genotype.

MASLD and CVD share similar cardiometabolic conditions such as abnormal lipid metabolism, oxidative stress, systemic inflammation, hepatic insulin resistance, and adipose tissue dysfunction. MASLD patients exposed to these risk factors are at an increased risk of CVD [46]. Desai et al. studied 409,130 hospitalizations of MASLD patients from various ethnicities and did not find a significant difference in the risk of CVD or CVD-related mortality. However, there are limitations in the study including disparities in ethnicity representation and a lack of long-term follow-up in hospitalizations [47].

A trial study of 822 participants conducted in Canada adopted CT scans to assess abdominal adipose tissue and total body fat and found that Asian individuals tended to have more visceral and subcutaneous abdominal fat than European individuals for a given body fat mass [48]. Another study of 4504 patients from 5 ethnic groups (White individuals, African Caribbean Black individuals, Hispanic individuals, East Asian individuals, and Southeast Asian individuals) also revealed that East Asian individuals had more fat accumulation in viscera by CT scan than European individuals and African Black individuals [49]. Both studies assumed that increased visceral fat and subcutaneous fat contribute to the high prevalence of MetS in Asian individuals [49,50]. Zhang et al. found that American individuals, albeit having less visceral fat than Chinese individuals, and MetS were associated with the absence of advanced hepatic fibrosis in MASLD individuals after matching for age, sex, and BMI category, and MetS was associated with moderate or severe hepatic steatosis [51]. Furthermore, these results might be different from the previous

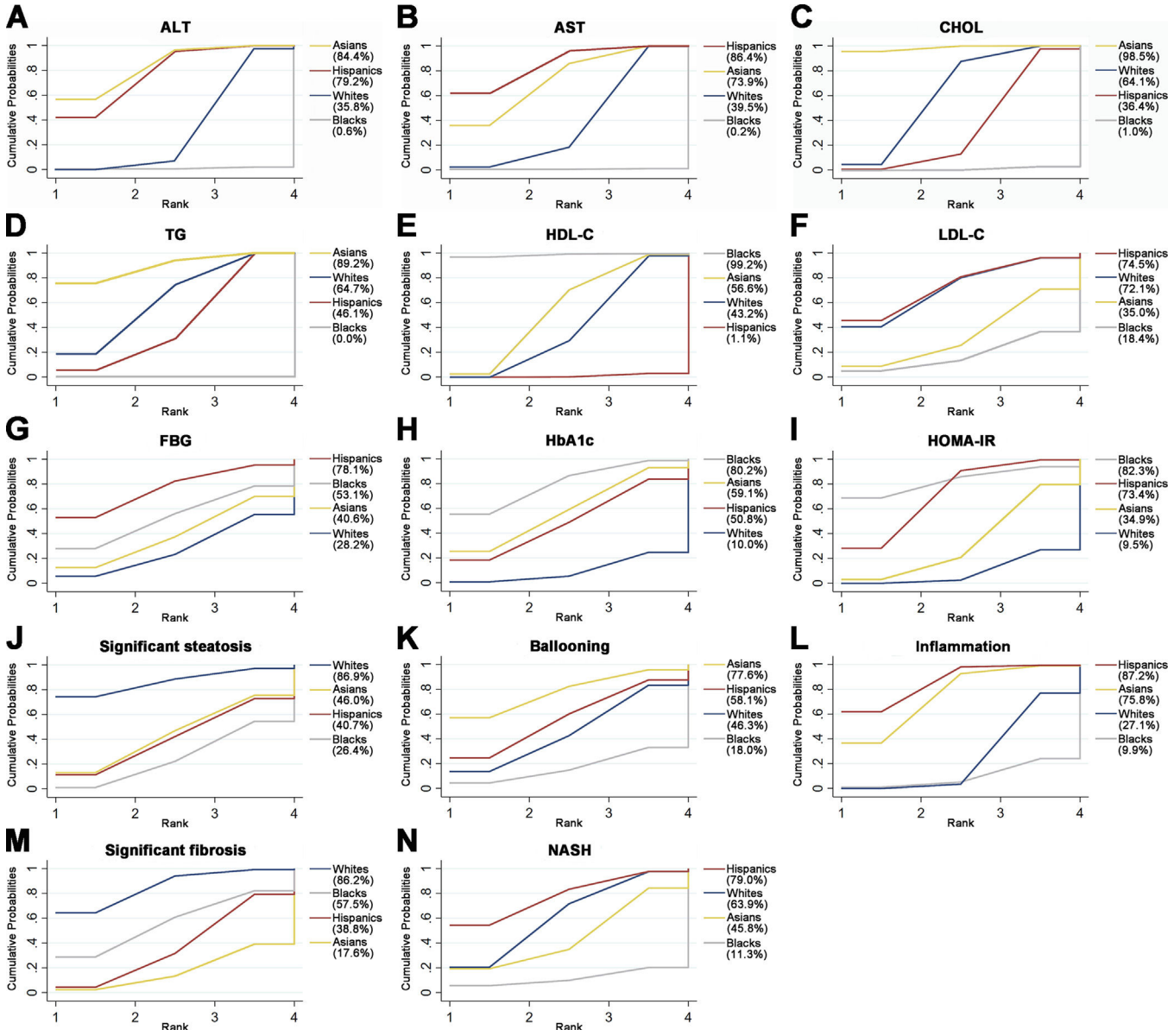

Fig. 8. Surface under the cumulative ranking curve analysis regarding biochemical indicators (A-I) and histological features (J-N) in MASLD patients from four ethnic groups.

(A) ALT (U/L); (B) AST (U/L); (C) CHOL (mg/dL); (D) TG (mg/dL); (E) HDL-C (mg/dL); (F) LDL-C (mg/dL); (G) FBG (mg/dL); (H) HbAc1(%); (I) HOMA-IR; (J) Significant steatosis; (K) Inflammation; (L) Ballooning; (M) Significant fibrosis; and (N) NASH.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CHOL, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein- cholesterol; FBG, fasting blood glucose; HOMA-IR, homeostasis model assessment of insulin resistance; NASH, nonalcoholic steatohepatitis.

phenomenon that various body fat distribution patterns differ among ethnic groups, as Asian individuals presented with a relatively greater amount of abdominal adipose tissue than European individuals, independent of BMI. And obese patients of African descent had decreased rates of visceral fat compared with patients of other ethnicities [52].

Influenced by various factors such as genes, environment and diet, gut microbiota is closely related to MetS and varies across ethnicities, which might attribute to the ethnic heterogeneity in MASLD. In a study comprising 3443 individuals (1127 Dutch, 292 Ghanaian, 324 South-Asian Surinamese, 773 African Surinamese, 366 Turk and 561 Moroccan participants) of HELIUS study for investigating fecal microbial composition, ethnic-specific associations for α-diversity and the *Ruminococcaceae, Christensenellaceae*, and *Methanobrevibacter* trophic network (higher abundance was related to better MetS outcomes) were only significant in the Dutch groups [53]. Another study of 279 Danish and 294 Indian participants showed enrichment of *Prevotella* group 9, *Megasphaera* and *Lactobacillus* in the Indian stool samples, but a higher abundance of *Bacteroides* in the Danish individuals [54]. When there is a substantial change in dietary composition, such as a marked increase in meat intake and a decrease in plant-based fiber, the abundance of the gut microbiota is significantly altered. Environmental exposures seem to have a greater influence on shaping gut microbiota than host genetics [55].

Regarding histological characteristics of biopsy-confirmed MASLD patients, our results were consistent with earlier meta-analysis findings [4], in which the Black individuals exhibit milder liver histological features such as ballooning and inflammation compared to the other three ethnic groups. Hepatocytic ballooning degeneration

might be derived from damaged hepatocyte mitochondria and related reduction under overoxidation with over load of free fatty acids [56]. Therefore, it might be hypnotized that Asians were being with more visceral adiposity compared with other ethnicities relatively at the same levels of weight [57]. Moreover, weight gain can induce worse metabolic responses in South Asian compared with White European including greater decrease in insulin sensitivity that cause free fatty acids release from visceral adiposity [58,59]. Our study indicated that Black MASLD individuals exhibited better serum lipid metabolism profiles and liver enzymes levels than other three ethnic groups with sufficient data. However, other potential pathophysiological mechanisms, genetic factors, environmental influences, or epigenetic aspects that might explain this phenomenon remain not clear.

Genes involved in lipolysis or lipogenesis pathways play an important role in how the components of MetS affect the onset and progression of MASLD in patients from different ethnic groups, particularly the most reported genetic polymorphism in PNPLA3 and TM6SF2. The PNPLA3 gene plays a key role in the secretion of very low-density lipoprotein from the liver, and its genetic variant I148M has been shown to increase the risk of fat accumulation and liver injury under environmental stress, as well as the risk factor for progress in liver histology, especially PNPLA3 G allele [60,61]. It has been reported that the prevalence of PNPLA3 G allele is highest in Americans (45%), lowest in Africans (15%), moderate among East Asians (35%) and Europeans (23%) [62]. Another study reported that the prevalence of G allele in Hispanic Americans (40%) was almost twice that of African Americans (19%) [63]. Another reported SNP is the rs58542926 (E167K) variant, which is associated with a higher risk of liver steatosis and advanced fibrosis [64]. The frequency of minor T allele of the E167K variant is higher in East Asians (34%) than that in Europeans (26%), Hispanics (10%), and Africans (6%) [65]. In summary, the differences in genetic distribution partially explain the results that Black individuals with MASLD exhibit milder liver histological features such as ballooning and inflammation compared to the other three ethnic groups.

Metabolic phenotypes may vary among different ethnic groups. A deeper understanding of the interaction between genetics and lifestyle factors could facilitate the development of tailored pharmaceuticals and provide personalized lifestyle recommendations for individuals with MASLD. Evidence-based medicine is essential in managing diseases across diverse ethnic groups, especially in preventing and delaying liver cirrhosis, as well as related complications such as T2DM and CVD. For populations with more severe histological features, such as significant liver fibrosis that may progress to cirrhosis or liver cancer, vigilant monitoring and timely intervention are crucial in clinical practice.

4.1. Study strengths and limitations

One advantage of this meta-analysis was that it is the first to investigate the metabolic and histological discrepancies of MASLD among Caucasian White patients, African American Black patients, Asian patients, and Hispanic patients. Another strength was that histopathological evaluation for MASLD liver injury is the gold standard and provided cogent evidence for the conclusion.

Certainly, limitations were inevitable. First, although a comprehensive and systematic search strategy was used, lean or nonobese MASLD patients lacked analysis. Second, the use of a random-effects model could only partially diminish but not obviate the statistical heterogeneity in this meta-analysis. Third, most of the studies in the meta-analysis lacked subgroup analysis, such as age, sex, and BMI. These studies also did not provide detailed information on potential confounding factors like socioeconomic status or lifestyle, which are known to be closely related to MASLD and can vary among different ethnic groups. Fourth, only three databases were selected in this study, so including additional databases might have been beneficial, as well as regional databases from each continent, which may affect the representativeness of the results. Furthermore, the selection bias in the inclusion of only English-language articles should not be ignored. Lastly, the pooled prevalence of T2DM in the study was 33%, and the use of anti-hyperglycemic drugs like GLP-1 receptor agonists could potentially change the clinical characteristics of MASLD.

As new related research emerges, ongoing updates to this study will help to uncover the specific reasons behind the ethnic disparities observed in the clinical characteristics of MASLD.

5. Conclusions

This meta-analysis revealed that Asian MASLD patients may have a higher risk of abnormal lipid metabolism but similar liver injury severity compared to the other groups. Hispanic and White MASLD patients exhibited more severe histological features. Further research is necessary to validate these results and to fully understand the underlying reasons for the variation in clinical features among different ethnic groups.

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Declaration of interests

None.

CRediT authorship contribution statement

Limin Lin: Data curation, Formal analysis, Writing – original draft. **Jiaming Lai:** Data curation, Formal analysis. **Ling Luo:** Formal analysis. **Junzhao Ye:** Data curation, Writing – review & editing. **Bihui Zhong:** Conceptualization, Funding acquisition, Supervision, Writing – review & editing.

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Data availability statement

The datasets generated and/or analysed during the current study are available in the [PubMed, Embase and Web of Science] repository.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.aohep.2025.101780.

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