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Letter to the Editor

Differences in major adverse cardiovascular events of metabolic dysfunction-associated steatotic liver disease by race and ethnicity: Letter to the editor on "Differences in liver and mortality outcomes of non-alcoholic fatty liver disease by race and ethnicity: A longitudinal real-world study"

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Keywords: Race disparity; MACE; MASLD; Cohort; Electronic medical records

Dear Editor,

The interplay between race and long-term complications of metabolic dysfunction-associated steatotic liver disease (MASLD) is intriguing. A recent US study by Nguyen et al.[1] found significantly higher risks for liver-related outcomes and mortality in Black individuals compared to White individuals. MASLD is associated with various systemic outcomes, including dementia, autoimmune diseases, and major adverse cardiovascular events (MACE).[2-4] People with hepatic steatosis have over a 60% higher risk of developing MACE compared to controls. A recent cross-sectional study indicated potential racial disparities, with Hispanics having a lower odds ratio (0.88) for MACE compared to

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Whites.[5] However, the impact of race on MACE onset in a longitudinal design remains uncertain. Therefore, we analyzed data from the TriNetX research network to assess the risk of new-onset MACE among MASLD patients of different racial groups.

The TriNetX research network, widely used in epidemiological studies, offers de-identified electronic medical records, including diagnoses, medications, procedures, and lab data.[6-8] For our analysis, we utilized the "Global Collaborative Network" subset, containing 126 institutions across 19 countries and data from over 120 million patients. The TriNetX database is updated monthly for current information. We included participants aged 18 and older with a diagnosis of MASLD (ICD-10-CM K75.81, K76.0) between January 1, 2005, and December 31, 2017, with more than two visit records. The control group consisted of White MASLD patients. Individuals with a prior history of MACE, liver cirrhosis, liver cancer, or those deceased before the index date were excluded. The case group included Black, Hispanic, and Asian MASLD patients. Before matching, there were 283,063 White, 31,039 Black, 72,342 Hispanic, and 21,941 Asian patients. Propensity score matching in a 1:1 ratio accounted for covariates such as age, sex, body mass index, socioeconomic status, substance abuse, comorbidities, and medical utilization status. The main outcome was the risk of MACE, evaluated by Cox proportional hazards regression models. Participants were monitored starting three months after the index date until MACE occurrence, their last visit, or July 12, 2024, whichever came first. Sensitivity analyses were conducted to ensure reliability. These analyses involved: (1) Follow-up period: We looked at how long we tracked participants after index date —5, 10, or 15 years—to see if it affected the results on the occurrence of MACE. (2) Matching methods: To avoid potentially skewing the results by overmatching participants, we compared different models in covariate selection. (3) Washout period: To address the possibility that a recent event might be influencing the results, we excluded data from participants who had the event of interest within the past 12 or 24 months. Cox proportional hazards models were employed to estimate hazard ratios (HR) and their corresponding 95% confidence intervals. The analyses were conducted using the TriNetX analytical platform. Propensity score matching was implemented using greedy nearest neighbor algorithms with a caliper width of 0.1. Baseline information of respective groups was presented in Supplementary tables (Supplementary Tables 1–3). Research performed in TriNetX system was waived from IRB approval.

For Black people compared to White people, the HR for MACE varies slightly over different follow-up periods: 1.341 (5 years), 1.295 (10 years), and 1.312 (15 years). Matching algorithms show a consistent increased risk, with the crude model at 1.426 and more detailed models (considering socioeconomic status, substance abuse, and Nonsteroidal Anti-Inflammatory Drug [NSAID] use) ranging from 1.452 to 1.510. Wash-out periods of 12 and 24 months yield HRs of 1.325 and 1.332, respectively. For Hispanic people versus White people, the risk of MACE is lower. The HR over follow-up periods is approximately 0.819 (5 years), 0.829 (10 years), and 0.830 (15 years). The crude model shows an HR of 0.599, and detailed models range from 0.835 to 0.859. Wash-out periods of 12 and 24 months show HRs of 0.831 and 0.827, respectively. For Asian people versus White people, the risk is also lower. The HR over follow-up periods is 0.550 (5 years), 0.563 (10 years), and 0.555 (15 years). The crude model shows an HR of 0.538, while detailed models range from 0.538 to 0.585. Wash-out periods of 12 and 24 months show HRs of 0.551 and 0.555, respectively (Fig. 1).

The findings reveal a racial disparity in the relationship between MASLD and MACE. The racial disparity of MACE risk could be associated with socioeconomic and lifestyle factors. Differences in access to healthcare, diet, and lifestyle behaviors contribute to varying prevalence and severity of MASLD and related comorbidities across racial and ethnic groups.[5,9] Similar to the Nguyen et al.[1] study, Black patients with MASLD showed a higher risk of developing MASLD-associated outcomes. Desai et al.[5] noted a slight reduction in MACE risk among Hispanics based on cross-sectional data. In our longitudinal report, the reduced risk of MACE remained significant across various sensitivity

Abbreviations:

CI, confidence interval; HR, hazard ratios; MACE, major adverse cardiovascular events; MASLD, metabolic dysfunction-associated steatotic liver disease

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models. However, potential misclassification bias and residual confounders warrant further investigation to clarify the mechanisms behind these racial variations.

Statement of ethics

The TriNetX database was previously approved by the Western Institutional Review Board (Western IRB). The subsequent determination regarding the de-identification process attested on December 2020 replaced the need of Western IRB approval in TriNetX studies. Ethical approval was not required for the study involving humans in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and the institutional requirements.

"This retrospective study is exempt from informed consent. The data reviewed is a secondary analysis of existing data, does not involve intervention or interaction with human subjects, and is de-identified per the de-identification standard defined in Section §164.514(a) of the HIPAA Privacy Rule. The process by which the data is de-identified is attested to through a formal determination by a qualified expert as defined in Section §164.514(b)(1) of the HIPAA Privacy Rule. This formal determination by a qualified ex-

Outcome: MACE	Study cohort, n (%)		Hazard ratio (95% CI)
	Case group	Control group	
Black people (case) vs White people (control)			
Applying various follow-up periods			
5 year	2,848 (9.2)	2,147 (6.9)	1.341 (1.267, 1.418)
10 year	4,954 (16.0)	3,824 (12.3)	1.295 (1.242, 1.351)
15 year	4,892 (15.9)	3,728 (12.1)	1.312 (1.257, 1.369)
Applying various matching algorithms			
Crude Model	4,858 (16.0)	28,937 (11.1)	1.426 (1.383, 1.470)
Matching Model 1	4,857 (16.0)	3,251 (10.7)	1.510 (1.445, 1.579)
Matching Model 2	4,858 (16.0)	3,345 (11.0)	1.463 (1.400, 1.529)
Matching Model 3	4,848 (16.0)	3,360 (11.1)	1.452 (1.390, 1.518)
Applying various wash-out periods			
12 months	4,628 (15.2)	3,473 (11.4)	1.325 (1.268, 1.385)
24 months	4,344 (14.3)	3,243 (10.7)	1.332 (1.273, 1.394)
Hispanic people (case) vs White people (control)			
Applying various follow-up periods			
5 year	2,551 (3.5)	3,179 (4.4)	0.819 (0.778, 0.863)
10 year	4,150 (5.7)	5,258 (7.3)	0.829 (0.796, 0.863)
15 year	4,329 (6.1)	5,597 (7.9)	0.830 (0.797, 0.863)
Applying various matching algorithms			
Crude Model	4,153 (6.0)	28,256 (10.8)	0.599 (0.580, 0.619)
Matching Model 1	4,329 (6.1)	5,558 (7.8)	0.835 (0.803, 0.869)
Matching Model 2	4,355 (6.1)	5,385 (7.6)	0.872 (0.838, 0.908)
Matching Model 3	4,329 (6.1)	5,416 (7.6)	0.859 (0.825, 0.894)
Applying various wash-out periods			
12 months	4,093 (5.8)	5,310 (7.5)	0.831 (0.798, 0.866)
24 months	3,759 (5.3)	4,939 (7.0)	0.827 (0.792, 0.863)
Asian people (case) vs White people (control)			
Applying various follow-up periods			
5 year	739 (3.4)	1,254 (5.8)	0.550 (0.502, 0.602)
10 year	1,315 (6.1)	2,065 (9.5)	0.563 (0.525, 0.603)
15 year	1,482 (6.8)	2,263 (10.4)	0.555 (0.519, 0.592)
Applying various matching algorithms			
Crude Model	1,482 (6.8)	30,215 (10.9)	0.538 (0.510, 0.567)
Matching Model 1	1,450 (6.9)	2,249 (10.7)	0.538 (0.504, 0.575)
Matching Model 2	1,482 (6.8)	2,164 (10.0)	0.581 (0.543, 0.620)
Matching Model 3	1,482 (6.8)	2,143 (9.9)	0.585 (0.547, 0.625)
Applying various wash-out periods			
12 months	1,407 (6.5)	2,146 (9.9)	0.551 (0.515, 0.589)
24 months	1,329 (6.1)	1,992 (9.2)	0.555 (0.517, 0.595)

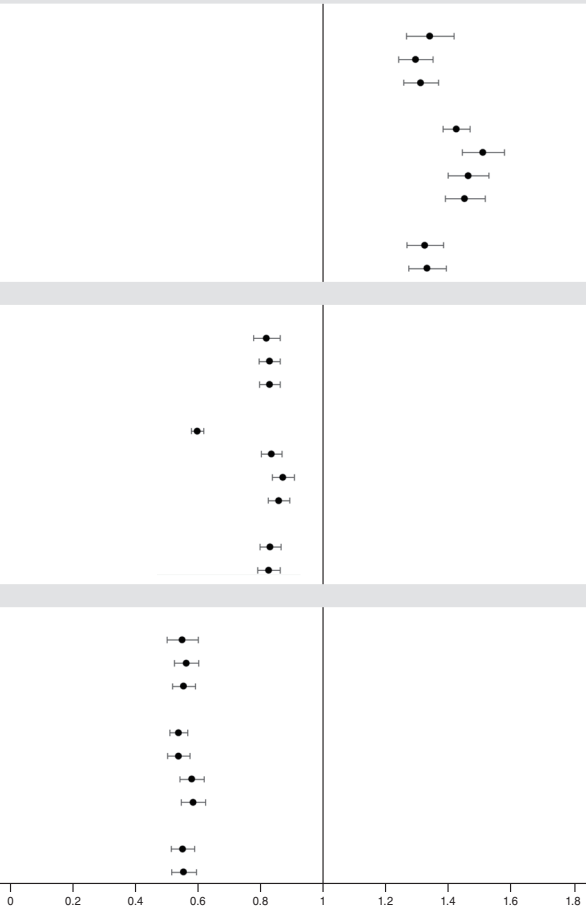

Figure 1. Risk of MACE in MASLD patients with different races. Propensity score matching was reperformed in each analysis. All analysis was followed from 3 months after index date to 15 years after index date if not specifically stated. Matching model 1: matching covariates include age, sex, BMI; Matching model 2: matching covariates include age, sex, BMI, socioeconomic status, substance abuse. Matching model 3: matching covariates include age, sex, BMI, socioeconomic status, substance abuse, NSAIDs use. MACE, major adverse cardiovascular events; CI, confidence interval; BMI, body mass index.

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pert refreshed on December 2020."

Authors' contribution

All the authors involved in drafting or revising the article and approved of the submitted version. Study conception and design: Chang HC, Liao WC, Fang YJ, Chen SJ, Gau SY. Data acquisition: Chang HC and Gau SY. Data analysis and demonstration: Chang HC, Chen SJ and Gau SY. Original draft preparation: Chang HC, Liao WC, Fang YJ, Chen SJ, Gau SY

Conflicts of Interest

The authors have no conflicts to disclose.

SUPPLEMENTAL MATERIAL

Supplementary material is available at Clinical and Molecular Hepatology website (http://www.e-cmh.org).

Data in this study were retrieved from TriNetX Research Network. All data available in the database were administrated by the TriNetX platform. Detailed information can be retrieved at the official website of the research network (https://trinetx.com).

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