IJC Heart & Vasculature 56 (2025) 101602

Contents lists available at ScienceDirect

IJC Heart & Vasculature

journal homepage: www.sciencedirect.com/journal/ijc-heart-and-vasculature

Sudden cardiac death associated with fatty liver disease

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ARTICLE INFO

Keywords:
Sudden cardiac death
Fatty liver disease
Coronary artery disease
Healthcare disparities

ABSTRACT

Background: Fatty liver disease or steatotic liver disease (SLD) affects 25% of the global population and has been associated with heart disease. However, there is a lack of postmortem studies in the context of sudden cardiac death (SCD).
Objectives: To investigate the relationship between SLD and SCD.
Methods: A post-mortem case-case study was conducted in victims of SCD from an ongoing community-based study in Southern California (Ventura, CA, 2015–2023). Diagnosis of SLD was determined from post-mortem liver histopathology reports. For each patient, demographic variables, laboratory values, and presence of co-morbidities were ascertained from medical records and were compared between patients with and without SLD.
Results: Of 162 individuals with SCD, there were 101 SLD cases and 61 without SLD. Individuals with SLD were found to have higher BMI (31.6 ± 7.6 vs. 26.7 ± 5.7, $p < 0.001$), higher prevalence of heavy drinking (28 % vs. 12 %, $p = 0.008$), heavier liver weights (2433.6 g ± 940.6 vs 1934.7 g ± 505.3, $p < 0.001$), and were more often Hispanic (37 vs. 18 %, $p = 0.01$). Patients with SLD had lower prevalence of coronary artery disease (CAD) (49 % vs. 70 %). Multivariable logistic regression analysis showed that CAD was a negative predictor of SCD with SLD (OR = 0.35, 95 % CI 0.14 – 0.83).
Conclusion: Among adults with SCD, SLD was associated with higher prevalence of Hispanic ethnicity and lower prevalence of CAD. Given the major rise in SLD burden, these ethnicity-based differences as well as the specific nature of non-ischemic SCD etiologies warrant urgent further investigation.

1. Introduction

Steatotic liver disease (SLD) is one of the most common causes of liver disease with an estimated overall global prevalence of at least 25 % [1]. Metabolic dysfunction-associated steatotic liver disease (MASLD), which has replaced the previous term of non-alcoholic fatty liver disease (NAFLD), is a subcategory of SLD and is defined as the presence of hepatic steatosis plus one cardiometabolic risk factor and no other causes of SLD [2]. Prior studies have shown an association between MASLD and heart failure [3,4], atherosclerosis [5], and cardiovascular events [6–8]. Further research has additionally shown links between MASLD and prolonged QTc interval [9,10], atrial fibrillation [11,12], and ventricular arrhythmias [13,14]. Although the gold standard for diagnosing SLD has been histological examination, most published studies have utilized an ultrasonography or laboratory-based diagnosis [15,16]. Additionally, no studies have examined the pathophysiology of SCD among individuals with histologically confirmed SLD. Therefore, we performed a postmortem analysis of individuals with SCD and histologically confirmed SLD compared to individuals who also suffered SCD, but in the absence of SLD.

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https://doi.org/10.1016/j.ijcha.2025.101602
Received 10 December 2024; Received in revised form 30 December 2024; Accepted 3 January 2025

2. Methods

2.1. Study population

We conducted a retrospective case-case study using the ongoing PRESTO (PREdiction of Sudden death in mulTi-ethnic cOmmunities) study in Ventura County, CA (population ~ 850,000 in 2018). Detailed methods of the PRESTO study have been published previously [17]. For this study, we identified individuals from February 1, 2015 to February 1, 2023 who experienced SCD and then further limited our analysis to the subset of patients who underwent autopsy with histologic liver microscopic examination. SCD was defined as a sudden, pulseless collapse likely attributed to a cardiac cause occurring after the onset of symptoms when witnessed or within 24 h of the individual last being seen in their usual state of health [18]. Non-cardiac causes of death, including trauma, drowning, overdose/substance abuse, known terminal illness, a malignancy not in remission, and pulmonary embolism, were excluded. We also excluded patients aged < 18 and patients who did not have medical records available. The study design is shown in Fig. 1.

2.2. Definition of SLD, comorbidities, and demographic data

Within this cohort, we identified individuals with hepatic steatosis based on liver histology. Two physicians reviewed the liver histology reports to adjudicate SLD and no-SLD. This adjudication process was done with a keyword search method using the following keywords: "fatty metamorphosis," "steatosis," "fatty liver," "steatohepatitis," "fibrosis," "cirrhosis," and "vacuoles." Using this approach, Cohen's kappa statistic was calculated to be 1 for the adjudication of SLD vs non-SLD.

Demographic information was obtained including data on age, sex, race, ethnicity, and BMI. Laboratory values including aspartate transaminase (AST), alanine transaminase (ALT), albumin, platelet counts, alkaline phosphatase (ALP), and total protein were extracted based on the most recent results prior to onset of SCD. Based on these laboratory data, Fibrosis-4 index (FIB-4) values were calculated for each patient. FIB-4 is a well-validated scoring system for prediction of liver fibrosis using non-invasive laboratory markers [19,20]. Presence of co-morbidities including asthma, chronic obstructive pulmonary disease (COPD), hyperlipidemia, hypertension, diabetes, and chronic kidney disease (CKD) were also extracted from medical records. Presence of CAD (any degree) and left ventricular wall thickness were determined based on autopsy reports.

Coronary artery disease was additionally divided into obstructive CAD and non-obstructive CAD by autopsy reports. Obstructive CAD was defined as > 50 % stenosis in the left main coronary artery or > 70 % stenosis in any other coronary vessel. Nonobstructive CAD was defined as any CAD with < 50 % stenosis in the left main coronary artery or < 70 % stenosis in any other coronary vessel [21]. Heart weight was also ascertained from autopsy reports. See (Fig. 2).

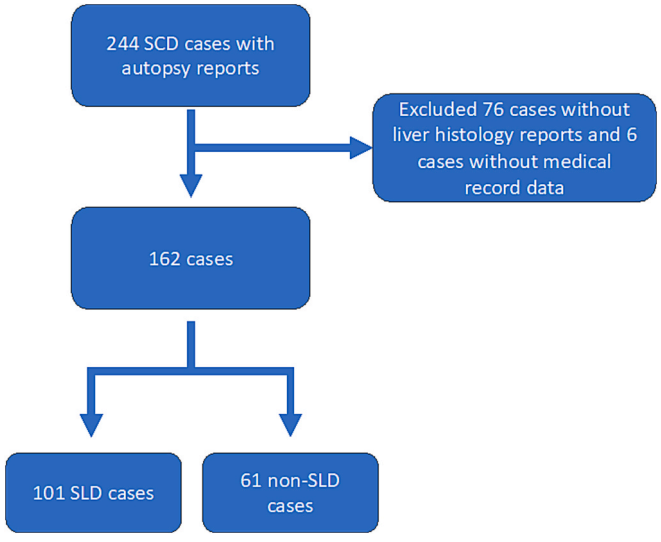

Fig. 1. Study population selection of sudden cardiac death (SCD) patients with and without steatotic liver disease (SLD).

2.3. Statistical analysis

Comparisons between the SLD and no-SLD groups were made using independent t-tests for continuous variables and Fisher's exact test for categorical variables. Age was compared with the Mann-Whitney test since a non-normal distribution was observed using the Kolmogorov-Smirnov test. Other continuous variables are normally distributed and reported as mean ± standard deviation. Categorical variables are reported as frequency (percentages). Significance was determined at a threshold of p-value < 0.05, and all reported p-values are two-sided. Categorical variables included in this analysis were presence of co-morbidities, race, ethnicity, gender, and presence of CAD. Continuous variables included age, BMI, laboratory values, and FIB-4 scores. We also performed multivariable logistic regression using a model that included ethnicity, age, BMI, sex, CAD, asthma, COPD, hyperlipidemia, hypertension, and CKD with SLD as the outcome. These variables were selected to adjust for individual co-morbidities that have been shown to be independently associated with SLD in prior studies [22–26]. Receiver operating characteristic (ROC curves and area under the curve (AUC) values were calculated for FIB-4 in discriminating between patients with SLD and no-SLD, fibrosis and no fibrosis, and cirrhosis and no cirrhosis. All analyses were done using R (version 4.3.2, R Foundation for Statistical Computing, Vienna, Austria).

2.4. Ethics statements

This study was conducted in compliance with ethical guidelines, following the principles outlined in the Declaration of Helsinki. The institutional review boards of Cedars-Sinai Medical Center and all relevant hospitals/health systems have approved the study protocol.

3. Results

3.1. Baseline characteristics of SCD patients

We identified 2689 total SCD cases, of which 244 (9.1 %) underwent autopsy in a single medical examiner's office. Of these 244 autopsy cases, we excluded 76 cases without microscopic liver examination and 6 cases without medical history. These 76 excluded cases had a median age of 56.0 (47.8–63.8), 61 (80 %) males, 48 non-Hispanic White (63 %), 21 Hispanic (28 %), 4 undetermined White (5.3 %), 1 Black/AA (1.3 %), and 1 Asian (1.3 %). We identified 162 individuals who underwent autopsy with liver histologic examination within the PRESTO cohort between February 1, 2015, to February 1, 2023. Of these 162 individuals, there were 101 (62.3 %) patients with SLD and 61 (37.7 %) patients without SLD (Fig. 1). Patient characteristics are shown in Table 1. Between both groups, the SLD group had a significantly higher BMI (SLD 31.6 ± 7.6; no-SLD 26.7 ± 5.7, $p < 0.001$), higher percentage of heavy drinkers (SLD 28 %; no-SLD 12 %, $p = 0.008$), younger age (SLD 52.0 years-old; no-SLD 55.8 years-old, $p = 0.02$) and higher percentage of Hispanic patients (SLD 37 %; no-SLD 18 % group, $p = 0.01$). Sex distribution was similar between the two groups.

3.2. Comorbidities

Patient co-morbidities are shown in Table 2. Other co-morbidities were not significantly different between the two groups.

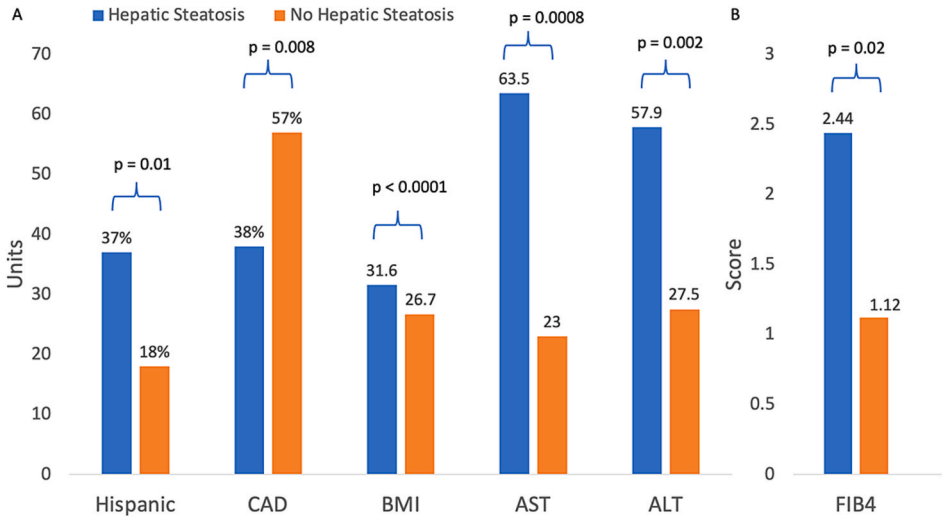

Fig. 2. Significant demographic and clinical differences between sudden cardiac death (SCD) patients with and without steatotic liver disease (SLD). (A) Y-axis units vary based on variable. Hispanic and coronary artery disease (CAD) variables are in units of percentage. Body mass index (BMI) is in units of kg/m [2]. Aspartate aminotransferase (AST) and Alanine aminotransferase (ALT) are in units of units per liter. Fibrosis-4 score (FIB-4). (B) Y-axis is in units of score.

Table 1
Demographic characteristics of sudden cardiac death (SCD) victims with and without steatotic liver disease (SLD).

	Steatotic liver disease (n = 101)	No Steatotic liver disease (n = 61)	P-value
Male, n (%)	70 (69)	49 (80)	0.14
Age, median (interquartile), year	53.3 (44.6–61.1)	60.8 (47.2–65.4)	0.017[†]
BMI, mean ± SD, kg/m^2	31.6 ± 7.6	26.7 ± 5.8	0.001
Heavy drinker, n (%)	28 (28)	7 (12)	0.008
Race and ethnicity, n (%)			0.17
Am Ind/Alaska Native	1 (1)	0 (0)	
Asian	2 (2)	2 (3.3)	
Black/AA	3 (3)	4 (6.6)	
Hispanic, n(%)	37 (37)	11 (18)	
Non-Hispanic White	57 (57)	43 (71)	
Undetermined White	1 (1)	1 (1.6)	
Hispanic, n(%)	37 (37)	11 (18)	0.01

[†] Analyzed by using Mann–Whitney *U* test.

Table 2
Comorbidities of sudden cardiac death (SCD) victims with and without steatotic liver disease (SLD).

	Steatotic liver disease (n = 101)	No Steatotic liver disease (n = 61)	P-value
DM, n(%)	26 (25)	12 (20)	0.44
Asthma, n(%)	7 (6.9)	3 (4.9)	0.74
COPD, n(%)	9 (8.9)	5 (8.2)	1
HLD, n(%)	22 (22)	11 (18)	0.69
HTN, n(%)	55 (54)	30 (49)	0.52
Renal Insufficiency, n(%)	14 (14)	11 (18)	0.51
Missing[†]	1		

Abbreviations: CAD: coronary artery disease; DM: diabetes mellitus; COPD: chronic obstructive pulmonary disease; HLD: hyperlipidemia; HTN: hypertension.

[†] For variables with missing values, proportions and P values are calculated with the non-missing data used as the denominator.

3.3. Laboratory and pathology features

Patient laboratory values and calculated FIB-4 scores are shown in Table 3. Mean liver weight (SLD 2433.6; no-SLD 1934.7, p < 0.001), (SLD 63.5; no-SLD 23.0p < 0.001), ALT (SLD 57.9; no-SLD 27.5, p < 0.01), ALP (SLD 103.1; no-SLD 80.4, p < 0.01), and FIB-4 scores (SLD 2.44; no-SLD 1.12, p < 0.03) were significantly higher in the SLD group. CAD of any degree (SLD 49 %; no-SLD 71 %, p < 0.01) and obstructive CAD (SLD 38 %; no-SLD 57 %, p = 0.016) were significantly higher in the no-SLD group.

Resuscitation characteristics of SCD subjects are shown in Table 4. SLD was associated with a significantly higher percentage of non-shockable initial rhythms as compared to no-SLD (SLD 84 %; no-SLD 62 %, p = 0.002).

AUC values of FIB4 for SLD, liver fibrosis and liver cirrhosis were 0.64, 0.67, and 0.91, respectively (Fig. 3).

Results of multivariable logistic regression (Fig. 4) including co-morbidities, ethnicity, age, sex, and BMI showed that CAD had a statistically significant negative association with SLD (OR = 0.31, CI 0.11 – 0.90) and BMI had a statistically positive association (OR = 1.1, CI 1.1 – 1.2).

4. Discussion

In this study, we compared demographic and clinical characteristics among SCD victims with and without autopsy-proven SLD. We report that patients with SLD had higher rates of initial non-shockable rhythm, higher BMI, and were more likely to be of Hispanic ethnicity. Additionally, patients with SLD had higher AST/ALT/ALP and higher FIB-4 scores. Interestingly though, patients with SLD had lower rates of both obstructive CAD as well as any degree of CAD seen on autopsy. Moreover, we did not find any significant difference in prevalence of other

Table 3
Laboratory and pathologic features of sudden cardiac death (SCD) victims with and without steatotic liver disease (SLD).

	Steatotic liver disease (n = 101)	No Steatotic liver disease (n = 61)	P-value
CAD (any degree), n(%)*	49 (49)	43 (71)	<0.01
Obstructive CAD, n(%)*	38 (38)	35 (57)	0.02
Non-obstructive CAD, n (%)*	11 (11)	8 (13)	0.8
Underlying cardiac pathology, n(%)*			0.008
CAD	49 (49)	43 (71)	
Cardiomyopathy	14 (14)	4 (7)	
Congestive heart failure	10 (10)	3 (5)	
Others‡	5 (5)	6 (10)	
Wall thickness, mm	15.1 ± 3.3	14.8 ± 2.9	0.68
Missing†	9	11	
Liver weight, g*	2433.6 ± 940.6	1934.7 ± 505.3	<0.001
Missing†	1	3	
AST	63.5 ± 79.9	23.0 ± 9.88	<0.001
Missing†	51	31	
ALT	57.9 ± 65.3	27.5 ± 15.6	<0.01
Missing†	51	31	
Alkaline phosphatase	103.1 ± 47	80.4 ± 24.5	<0.01
Missing†	53	34	
Platelets	245.6 ± 97.3	250.3 ± 111.1	0.84
Missing†	47	29	
FIB-4 index	2.44 ± 3.84	1.12 ± 0.99	0.03
Missing†	52	31	

Continuous data were reported as mean ± SD.
Abbreviations: LVH: left ventricular hypertrophy; AST: aspartate aminotransferase; ALT: alanine aminotransferase; FIB-4: Fibrosis-4.
* Autopsy results.
† For variables with missing values, proportions and P values are calculated with the non-missing data used as the denominator.
‡ Others include infective endocarditis, mitral valve prolapse, congenital bicuspid aortic valve stenosis, abnormal origin of coronary artery, and arrhythmogenic Right Ventricular Cardiomyopathy.

comorbidities between the SLD and no-SLD group.

Multiple prior studies have shown an independent association between SLD and CKD [23], diabetes [27], asthma [24], COPD [25], and cardiovascular disease [6,22,28]. We did not detect any difference in prevalence of CKD, diabetes, asthma, COPD, HLD, or HTN between SLD or no-SLD though this may be confounded by the fact that our study population is comprised of SCD victims, and these conditions have also been shown to be independently associated with SCD. Also, we detected lower rates of CAD in the SLD sub-group. Furthermore, in our logistic regression model, CAD was negatively associated with SLD after controlling for co-morbidities and demographic factors. This may be due to two reasons. One possible explanation is that patients with SLD are younger compared to the no-SLD group. This may make it more likely for patients with SLD to have SCD prior to developing significant CAD. This argument is also supported by the finding that obstructive CAD was more common in the no-SLD group, but rates of non-obstructive CAD were similar between both groups. However, another possible explanation is that for patients with SLD, CAD is not a significant contributor or cause of SCD. This is in contrast to the general population of patients with SCD where CAD is known to be the most common cause of SCD, even amongst young patients [29]. Our findings highlight the potential significance of non-ischemic etiologies in SCD with SLD, suggesting the possibility of an independent pathophysiologic association between SLD and SCD.

Steatotic liver disease could lead to SCD through multiple postulated mechanisms. One possible mechanism is through the metabolic syndrome associated with SLD, which can lead to non-ischemic cardiomyopathy by provoking myocardial interstitial fibrosis and fatty infiltration leading to cardiac remodeling and dysfunction [30]. Additionally, metabolic syndrome induces a state of constant low-level inflammation through increased release of pro-inflammatory adipokines which leads to increased sympathetic activation and a pro-arrhythmogenic state [31]. However, independent of metabolic syndrome, SLD itself is

Table 4
Resuscitation characteristics of sudden cardiac death subjects with and without steatotic liver disease reported in Utstein style.

	Steatotic liver disease (n = 101)	No Steatotic liver disease (n = 61)	p-value
Location, n (%)			0.03
Home	86 (85.1)	41 (67.2)	
Care facilities	1 (1.0)	2 (3.3)	
Public	14 (13.9)	16 (26.2)	
Other	0 (0.0)	2 (3.3)	
Witnessed collapse, n (%)	30 (29.7)	23 (37.7)	0.29
Bystander CPR, n (%)	55 (54.5)	38 (62.8)	0.33
Response Time, mean ± SD, minute	6.6 ± 2.9	6.5 ± 3.6	0.76
Initial presenting rhythm n(%)			0.002
VFVT	16 (16)	23 (38)	
PEA/Asystole	85 (84)	38 (62)	
Resuscitation attempted	101 (100.0)	61 (100.0)	1
ROSC	13 (12.9)	2 (3.3)	0.04
STHD	0 (0)	0 (0)	1

CPR: Cardiopulmonary resuscitation, VFVT: Ventricular fibrillation and ventricular tachycardia; PEA: Pulseless electrical activity; ROSC: Return of spontaneous circulation; STHD: Survive to hospital discharge; SD: Standard Deviation.

associated with increased risk of arrhythmias. This second mechanism occurs by triggering hepatotoxic stress that induces release of reactive oxygen species and pro-inflammatory and profibrogenic molecules which lead to electrical and autonomic remodeling of the heart [13,32]. Our study adds to the growing evidence behind this second mechanism given that the typical metabolic syndrome profile was not significantly different between the SLD and no-SLD groups. Additionally, our work highlights a potential non-ischemic mechanism linking SLD and SCD which requires further investigation. Given that SLD is a spectrum of disease ranging from ranging from simple steatosis to cirrhosis and cancer, late-stage complications of SLD have been especially shown to impact the pathophysiology of SCD through various mechanisms. These

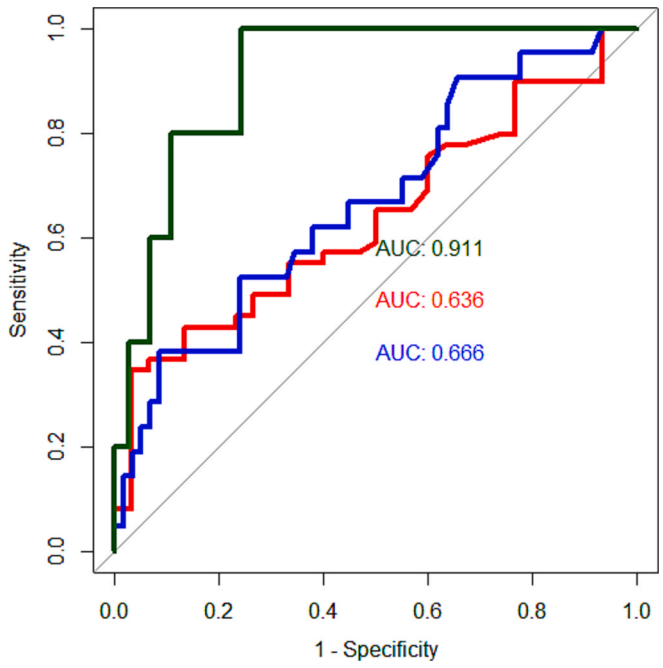

Fig. 3. The receiver operating characteristic (ROC) curves of FIB4 to diagnose SLD (Red), liver fibrosis (Blue), and liver cirrhosis (Green). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

mechanisms include autonomic dysfunction [33], ventricular arrhythmia (prolonged QT intervals and increased QT dispersion) [34], and particularly electromechanical uncoupling and chronotropic incompetence [35], which might be the cause of the high proportion of non-shockable rhythms in SCD individuals with SLD in our study. Furthermore, cirrhotic cardiomyopathy is a common long-term complication of end-stage liver disease, occurring in approximately 50 % of cases [36]. Notably, SCD is the leading cause of death in patients undergoing liver transplantation, with an incidence rate of 165 per 100,000 person-years, underscoring the critical and life-threatening role of SCD in the progression course of liver disease [37].

Our analysis also showed that patients with SLD had higher proportion of Hispanic patients compared to patients without SLD. This is in concordance with the current literature in that Hispanic patients have higher rates of SLD compared to non-Hispanic patients [38]. The underlying reasons are not well understood. One leading hypothesis is based on several studies showing increased prevalence of SLD and hepatic fat content in patients with the I48M polymorphism of the PNPLA3 gene [39]. This genetic polymorphism is known to be more common in Hispanic individuals compared to other ethnicities [39]. However, despite SLD being more common in Hispanic populations, burden of sudden cardiac arrest (SCA) remains similar between Hispanic and White patients [40]. These findings suggests that more work is required to further delineate the reasons for disparity in SLD between Hispanic and non-Hispanic patients as well as further study in possible ethnic or racial-specific protective factors in SCD.

Finally, we did find significantly higher values of traditionally liver-based laboratory markers AST, ALT, and ALP in the SLD sub-group. The well-validated liver fibrosis scoring system FIB-4 also showed a good diagnostic value for SLD, fibrotic liver disease, and cirrhosis based on AUC values, with higher AUC scores for more severe liver disease showing strong predictive value in risk-stratifying patients with liver disease. This non-invasive biomarker demonstrated excellent effectiveness in the diagnosis of liver cirrhosis. This highlights the utility of these lab-based markers and especially FIB-4 for potential screening of SLD as well as future research studies where histology-based diagnosis of SLD is

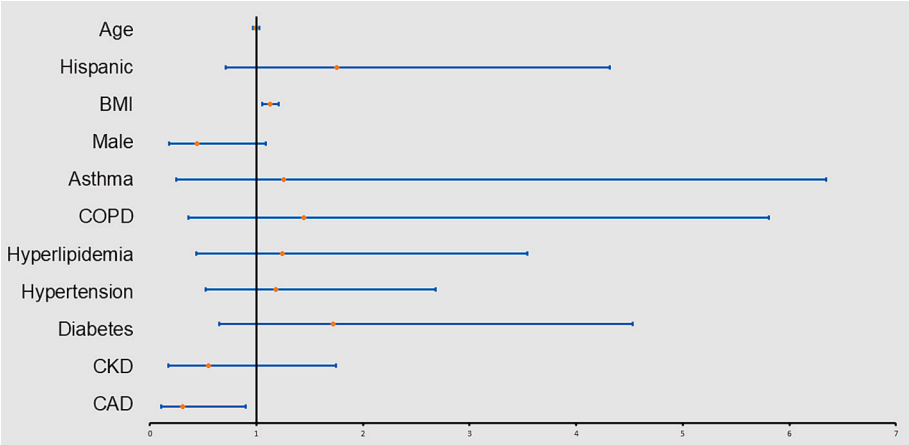

Fig. 4. Forest plot of results of multivariable logistic regression. The logistic regression included co-morbidities, ethnicity, age, sex, and Body mass index (BMI). These variables were included in the logistic regression model as they have been found to be related to steatotic liver disease in prior studies. COPD (Chronic obstructive pulmonary disease). CKD (Chronic kidney disease). CAD (Coronary artery disease).

not feasible.

4.1. Limitations and strengths

There are several limitations of this study that should be considered. First, this study is a large community-based observational analysis; despite utilizing multivariable regression models to reduce confounding bias, residual confounding may persist. Secondly, our cohort was limited to patients who underwent autopsy and may not represent all individuals who suffered SCD. Laboratory and imaging studies were not available across all subjects. Despite these limitations, this study was performed using histology-based diagnosis of SLD, which is the gold standard. Given the low national autopsy rate in the USA, this is the only feasible way to conduct this study.

5. Conclusions

Individuals with SCD and SLD were more likely to be Hispanic and prevalence of CAD was significantly lower. Given the enormous global burden of SLD, these findings highlight the urgent need for further elucidation of specific non-ischemic etiologies and ethnicity-related disparities in SCD associated with SLD.

Funding statement

This work is funded, in part, by National Institutes of Health, National Heart Lung and Blood Institute Grants R01HL145675 and R01HL147358 to SSC. SSC holds the Pauline and Harold Price Chair in Cardiac Electrophysiology at Cedars-Sinai. The funding sources not been involved in the preparation of this work or the decision to submit for publication.

Data availability statement

The data in this manuscript are from an ongoing study, and there is currently no IRB-approved mechanism by which this data will be deposited in a public repository. All analytical methods are included in this published article. De-identified participant data will be made available after publication upon reasonable request to the corresponding author, following approval of a proposal and a signed data use agreement.

CRediT authorship contribution statement

Jonathan Vo: Writing – review & editing, Writing – original draft, Investigation, Formal analysis, Data curation, Conceptualization. **Thien T.T.T. Truyen:** Conceptualization, Data curation, Formal analysis, Writing – original draft, Writing – review & editing, Investigation. **Audrey Uy-Evanado:** Writing – review & editing, Investigation, Data curation. **Arayik Sargsyan:** Investigation, Data curation. **Harpriya Chugh:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology. **Christopher Young:** Investigation, Data curation. **Sean Hurst:** Investigation, Data curation. **Christina Y. Miyake:** Writing – review & editing. **Kyndaron Reinier:** Writing – review & editing, Methodology, Conceptualization. **Sumeet S. Chugh:** Writing – review & editing, Supervision, Project administration, Methodology, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Sumeet S. Chugh reports financial support was provided by National Institutes of Health, National Heart Lung and Blood Institute. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

The authors would like to acknowledge the significant contributions of Ventura, CA area residents, Ventura Medical Examiner Office, Global Medical Response, Ventura fire departments, local area hospital systems (Simi Valley Adventist Medical Center, Community Memorial Hospital, Saint John Medical Center, Pleasant Valley Medical Center, Los Robles Medical Center, Ventura Country Medical Center, and Ojai Hospital).

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