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ORIGINAL ARTICLE

Independent Associations of Aortic Calcification with Cirrhosis and Liver Related Mortality in Veterans with Chronic Liver Disease

Steven R. Horbal[1,2] · Patrick X. Belancourt[3] · Peng Zhang[1,2] · Sven A. Holcombe[1,2] · Sameer Saini[4] · Stewart C. Wang[1] · Anne E. Sales[3,5] · Grace L. Su[4,6]

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Abstract

Introduction Abdominal aortic calcifications (AAC) are incidentally found on medical imaging and useful cardiovascular burden approximations. The Morphomic Aortic Calcification Score (MAC) leverages automated deep learning methods to quantify and score AACs. While associations of AAC and non-alcoholic fatty liver disease (NAFLD) have been described, relationships of AAC with other liver diseases and clinical outcome are sparse. This study's purpose was to evaluate AAC and liver-related death in a cohort of Veterans with chronic liver disease (CLD).

Methods We utilized the VISN 10 CLD cohort, a regional cohort of Veterans with the three forms of CLD: NAFLD, hepatitis C (HCV), alcohol-associated (ETOH), seen between 2008 and 2014, with abdominal CT scans ($n = 3604$). Associations between MAC and cirrhosis development, liver decompensation, liver-related death, and overall death were evaluated with Cox proportional hazard models.

Results The full cohort demonstrated strong associations of MAC and cirrhosis after adjustment: HR 2.13 (95% CI 1.63, 2.78), decompensation HR 2.19 (95% CI 1.60, 3.02), liver-related death HR 2.13 (95% CI 1.46, 3.11), and overall death HR 1.47 (95% CI 1.27, 1.71). These associations seemed to be driven by the non-NAFLD groups for decompensation and liver-related death [HR 2.80 (95% CI 1.52, 5.17; HR 2.34 (95% CI 1.14, 4.83), respectively].

Discussion MAC was strongly and independently associated with cirrhosis, liver decompensation, liver-related death, and overall death. Surprisingly, stratification results demonstrated comparable or stronger associations among those with non-NAFLD etiology. These findings suggest abdominal aortic calcification may predict liver disease severity and clinical outcomes in patients with CLD.

Keywords Non-alcoholic fatty liver disease · Hepatitis C · Alcohol-associated liver disease · Abdominal aortic calcification · Body composition biomarkers

Abbreviations

AAC	Abdominal aortic calcification
AUDIT-C	Alcohol use disorders identification test
CLD	Chronic liver disease
CT	Computed tomography
CVD	Cardiovascular disease
HCV	Hepatitis C Virus
ICD	International Statistical Classification of Disease and Related Health Problem
MAC	Morphomic Aortic Calcification Score
NAFLD	Non-alcoholic fatty liver disease
VISN	Veterans Integrated Services Network

✉ Steven R. Horbal
shorbal@med.umich.edu

1 Department of Surgery, University of Michigan, Ann Arbor, MI, USA

2 Morphomics Analysis Group, University of Michigan, Ann Arbor, MI, USA

3 VA Ann Arbor Healthcare System, Ann Arbor, MI, USA

4 Division of Gastroenterology and Hepatology, University of Michigan, Ann Arbor, MI, USA

5 Sinclair School of Nursing and Department of Family and Community Medicine, University of Missouri, Colombia, MO, USA

6 Gastroenterology Section, Ann Arbor VA Healthcare System, Ann Arbor, MI, USA

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Introduction

Chronic liver diseases (CLD) are estimated to affect 1.5 billion people worldwide [1, 2]. Causally, 59% of CLDs are attributed to non-alcoholic fatty liver disease (NAFLD), 9% to hepatitis C virus (HCV), and 2% to alcohol-related liver disease (ETOH) [2–4]. Comorbid occurrences of hepatic manifestation and cardiovascular conditions are prevalent; those with CLD have higher cardiovascular disease (CVD) burden than the general population [5, 6]. The strongest risk factors for NAFLD and CVD include insulin resistance, diabetes, obesity, and metabolic syndrome [7–11].

Abdominal aortic calcifications (AAC) were previously considered incidental findings from medical imaging. AAC has recently gained clinical interest as a strong independent predictor of incident CVD and related events [12–16]. Previous research has demonstrated strong associations of AAC with standard cardiovascular risk scores, stronger predictive ability of AAC for cardiovascular events than Framingham Risk Scores, evidence supporting the approximation of coronary calcification scores from AAC, and demonstration of AAC additively improving cardiovascular risk classification [15, 17–21]. Computer tomography (CT) scans can be opportunistically leveraged for surveillance purposes, capturing calcification measurements in anyone who already has a scan and contextualizing calcification burden among the general population [22, 23]. The Morphomics Analysis Group has developed the Morphomic Aortic Calcification Score (MAC) to identify those with elevated AAC [18, 21].

While the relationship of AAC and NAFLD has been described, evidence supporting the associations of AAC with other liver diseases and clinical outcomes is relatively sparse and may be overlooked [6]. The liver is a central organ supporting homeostasis, metabolism, immunity, digestion, and detoxification [24, 25]. Modification of lipid and glucose metabolism are common factors of both cardiovascular disease and liver disease [26–29]. While similar, the causal direction of effect of CLD and other metabolic diseases is difficult to discern and likely bidirectional [30–33]. While the pathogenic mechanism is not well understood, the associations between CLD and CVD are of clinical importance: for example, the treatment of HCV results in improved all-cause mortality including CVD-related outcomes [33–35].

The purpose of this study was to evaluate the association of AAC and liver-related clinical outcomes in a large cohort of Veterans with CLD. We sought to evaluate the effects of elevated aortic calcification and clinically relevant events when stratified by NAFLD classifications. Understanding the clinical effects of AAC and NAFLD may further assist clinicians in identifying those who may benefit from intervention or treatment.

Methods

Study Cohort

This study retrospectively utilizes the Veterans Integrated Services Network (VISN) 10 liver disease cohort [36]. Encounters occurred within the VISN 10 regional Veterans Health Administration network and the Danville, Illinois facility. Participants had an inpatient or outpatient encounter and a liver disease diagnosis between 1/1/2008 and 12/31/2014 and had an abdominal CT within 90 days of the diagnosis code. The cohort was restricted to include those with the three main liver disease diagnoses (HCV, NAFLD, and ETOH). HCV was defined as any positive HCV viral load during the study period. Patients with alcoholic liver disease were identified using ICD-9 codes for alcohol-related diseases or positive AUDIT-C scores (3 for female and 4 for male) in the absence HCV virus or ICD codes for other liver diseases (see supplementary tables). NAFLD was defined based on the absence of HCV virus, ETOH codes or positive alcohol use disorders identification test (AUDIT-C) and International Statistical Classification of Disease and Related Health Problem (ICD) codes for other liver diseases. Participants were excluded if mortality occurred within 180 days of the CT, had liver transplant or hepatocellular carcinoma at entry to cohort. Due to MAC score depending on the presence of abdominal CT scans, participants without observable imaging at the L3 and L4 vertebral level were removed from the analysis ($N = 4616$, $n = 3604$, removed 1008). See Fig. 1 for a flowchart describing the selection procedure and study design.

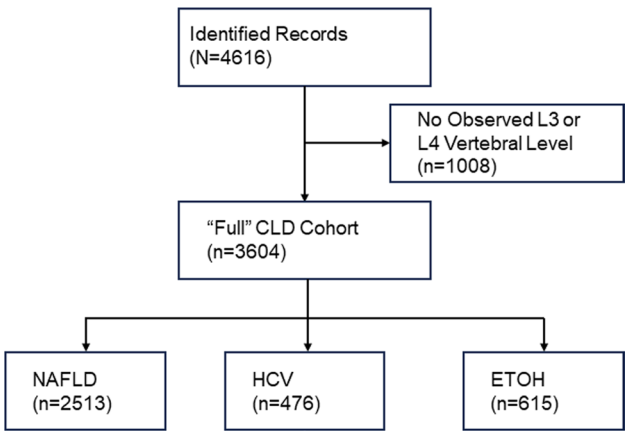

Fig. 1 Flow chart for study design and stratification

Study Measures

Cirrhosis, decompensated cirrhosis, diabetes mellitus, hypertension, and peripheral vascular disease was defined based off ICD-9 or ICD-10 codes (provided in supplemental information). Death was obtained from SPatient table found in the Veterans Affairs' Corporate Data Warehouse (VA CDA) [37]. The "Vital Status" file was used for verification and validation. Outcomes were conditionally dependent on ICD-9 or ICD-10 codes and accumulated time after the CT date [38]. For the outcome of hepatic decompensation, we utilized the codes previously described and validated in the VA CDA with the exclusion of the codes for esophageal varices without bleed (ICD 9- 456.21) [38]. Survival time was based on introduction to study or first diagnosed outcome or censoring. Accumulated time was calculated for each specific outcome (accumulated days-to-death, hepatic decompensation days, cirrhosis days). Death hazard was modeled as presence of death outcome, and time-to-death. Hepatic decompensation (outcome) was defined as presence of decompensation and time-to-hepatic decompensation development. Cirrhosis (outcome) was defined as presence of cirrhosis and time-to-cirrhotic development. Liver-related death was defined as the presence of decompensated outcome prior to time-to-death. Those with baseline cirrhosis or decompensation were excluded from the development of cirrhosis or decompensation.

Aortic calcification biomarkers were measured using Analytic Morphomics [21, 22, 39]. MAC score conceptualization and operationalization are described elsewhere [18, 21–23]. Briefly, the central aortic lumen zone was identified on each CT slice between the L1 and L4 vertebral levels. Dynamic thresholding was used to identify calcification regions and to control for measurement confounding created by contrast phase [22]. Morphological regions with pixel values five standard deviations above the reference were classified as calcification [21, 22]. AAC was conceptualized as the percentage of the aortic wall obfuscated by calcification. A binary MAC score is useful to identify those with clinically elevated calcification levels: those with calcification greater than 4.21% of the aortic wall relative to the L3 and L4 levels were considered elevated [18]. The threshold of 4.21% was chosen to maximize the sensitivity and probability of discovering those with elevated calcium burden [21, 23].

Descriptive statistics were performed to report differences among cohort participants with the three different CLD diagnoses. Logistic regression was used to evaluate the odds of clinical comorbidities among all cohort participants with elevated and normal MAC scores. Logistic regression was also performed to establish an association of aortic calcification with clinical comorbidities for adjustment in the Cox proportional hazard models. Cox proportional hazard was used to estimate the hazard of each clinical outcome among participants with elevated and normal MAC scores. Proportional hazards assumptions were verified through graphical inspection Figs. 2 and 3 displays Kaplan-Meier curves reflecting survival probability for each clinical outcome. Hazard ratios for all participants are reported, as well as stratification by NAFLD ($n = 2513$) and non-NAFLD ($n = 1091$). Logistic regression models were adjusted for age and sex. Cox proportional hazard ratios were adjusted for age, sex, body mass index (BMI), peripheral vascular disease, congestive heart failure, hypertension, and diabetes.

A sensitivity analysis was performed to evaluate the relationship of hepatic steatosis severity on aortic calcification

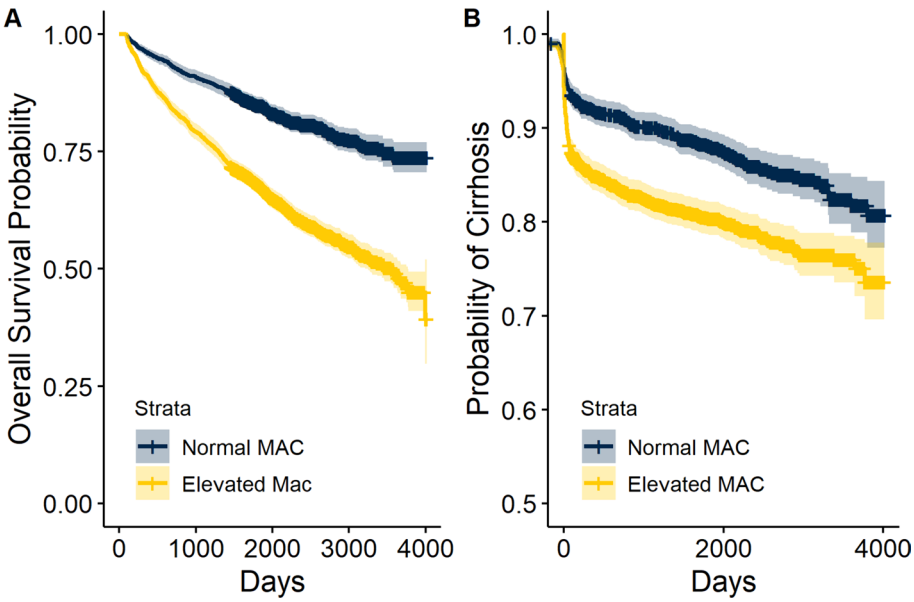

Fig. 2 Kaplan–Meier curves for aortic calcification and **A** overall death, **B** cirrhosis

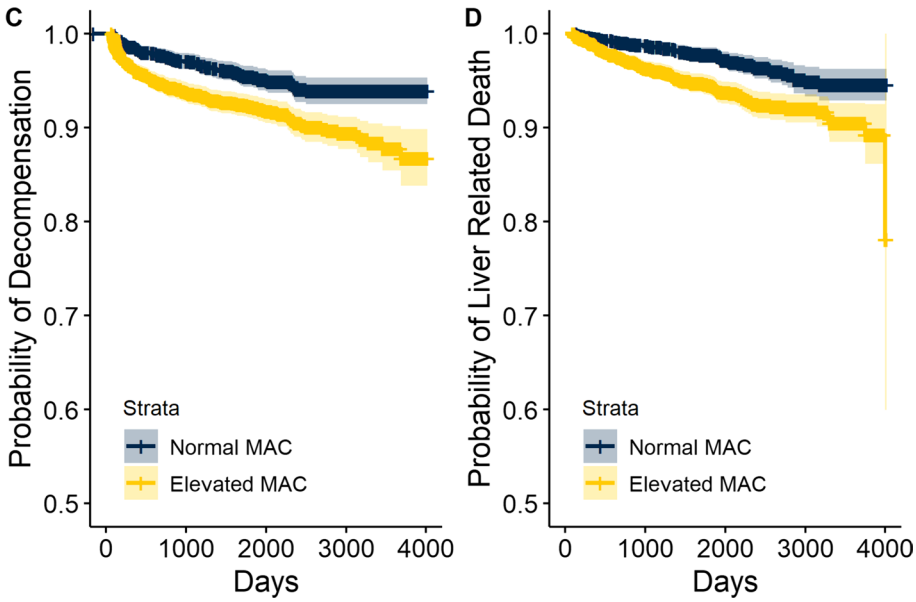

Fig. 3 Kaplan–Meier curves for aortic calcification and **A** decompensation, **B** liver-related death

and the clinical outcomes investigated in this study. Participants with ETOH liver disease were removed from consideration as ETOH would have a different causal mechanism of hepatic steatosis. Severity of hepatic steatosis was classified based on prior classification determined using MRI PDFF [40]. Those with a median value below 57 HU were categorized as normal levels ($n = 234$), a median 42–57 HU were mildly elevated levels ($n = 618$), a median 18–42 were moderately elevated levels ($n = 378$), and those under 18 HU were severely elevated levels ($n = 52$) Due to sample size and prevalence of outcomes steatosis factors were condensed into those of lower ($n = 852$) and higher ($n = 430$) steatosis severity.

Analysis was performed with R version 4.12 [41]. Figures were generated with ggplot2 [42]. Where appropriate, statistical significance was set to $\alpha = 0.05$.

Results

Table 1 reports baseline descriptive statistics for the three groups used in the analysis (NAFLD, HCV, ETOH). Mean patient age at CT was 62.70 (SD 12.64) for NAFLD, 57.04 (SD 7.02) for HCV, and 57.45 (SD 11.22) for ETOH. The cohort was mostly white (76%) and male (93%). Mean BMI was 30.81 (SD 6.65) for NAFLD, 27.32 (SD 5.77) for HCV, and 28.38 (SD 6.48) for ETOH. Most groups were significantly different regarding clinical comorbidities and outcomes.

Mean and median aortic attenuation were not significantly different among the three groups. Mean total abdominal calcium volume at the L3 vertebral level was 633.59 mm^3 (SD 965.16) for NAFLD participants, 691 mm^3 (SD 979.12) for HCV, and 468.82 mm^3 (SD 730) for ETOH participants. Mean wall percent calcification was 16.71 (SD 21.34) for NAFL, 13.38 (SD 17.87) for HCV, and 18.19 (SD 18.19), and 18.19 (SD 21.18) for ETOH participants. Elevated MAC scores were most prevalent in the ETOH group (~ 63%), followed by the NAFLD group (~ 58%) and the HCV group (~ 55%).

Table 2 reports odds ratios between the MAC scores and presence of clinical comorbidities in the full cohort. Significant unadjusted associations were observed for all clinical comorbidities (Cirrhosis, Decompensated Cirrhosis, Diabetes Mellitus, Hypertension, Congestive Heart Failure). After adjustment for age, significant associations were observed between MAC and the clinical comorbidities in all instances. After adjustment for age and sex, significant associations were observed between MAC and cirrhosis [OR 2.34 (95% CI 1.79, 3.08)], decompensated cirrhosis [OR 3.04 (1.93, 4.94)], diabetes mellitus [OR 1.23 (95% CI 1.05, 2.14)], hypertension [OR 1.47 (1.03, 2.14)], peripheral vascular disease [OR 1.92 (95% CI 1.54, 2.52)], and congestive heart failure [OR 1.39 (95% CI 1.07, 1.83)].

Table 3 reports the relevant clinical events and contributed days for each CLD group observed during the study period. Significant differences were observed for all groups across observed events and contributed time. The maximum contributed study days for any participant was 4015. Overall death was observed at the highest proportion for the ETOH group (37.9%) and the least for the NAFLD group (29.6%). Decompensation was the most prevalent in the HCV group (16.4%) and least prevalent in the NAFLD group (3.5%). Cirrhosis was the most prevalent in the HCV group (43.1%) and lowest in the NAFLD group (9.8%). Liver-related death was most prevalent in the HCV group (13.2%) and lowest

Table 1 Descriptive statistics for CLD cohort at baseline

	NAFLD	HCV	ETOH	*p*
n	2513	476	615	–
Age (mean (SD))	62.70 (12.64)	57.04 (7.02)	57.45 (11.07)	< 0.001
Male (%)	2331 (92.8)	466 (97.9)	597 (97.1)	< 0.001
Race (%)				< 0.001
Black	371 (14.8)	187 (39.3)	107 (17.4)	
White	1908 (75.9)	242 (50.8)	454 (73.8)	
Other	36 (1.4)	4 (0.8)	17 (2.8)	
Unknown	198 (7.9)	43 (9.0)	37 (6.0)	
Elixhauser Index Score (mean (SD))	3.42 (2.45)	3.13 (1.99)	4.38 (2.34)	< 0.001
BMI (mean (SD))	30.81 (6.65)	27.32 (5.77)	28.38 (6.48)	< 0.001
Cirrhosis (%)	146 (5.8)	83 (17.4)	129 (21.0)	< 0.001
Liver decompensation (%)	35 (1.4)	26 (5.5)	63 (10.2)	< 0.001
Hypertension (%)	1231 (48.6)	271 (56.9)	427 (69.4)	< 0.001
Diabetes (%)	1147 (45.6)	132 (27.7)	181 (29.4)	< 0.001
Peripheral vascular disease (%)	392 (15.6)	28 (5.9)	72 (11.7)	< 0.001
Congestive heart failure (%)	255 (10.1)	20 (4.2)	60 (9.8)	< 0.001
L3 calcification volume (mean (SD))	633.59 (965.16)	468.82 (730.00)	691.62 (979.12)	< 0.001
Aortic mean HU (mean (SD))	97.18 (71.17)	101.54 (81.26)	98.96 (73.72)	0.464
L3 area calcification mm^2 (mean (SD))	341.36 (466.56)	253.37 (343.83)	366.85 (499.62)	< 0.001
L3 wall % calcification (mean (SD))	16.71 (21.34)	13.38 (17.87)	18.19 (21.18)	0.001
Elevated MAC Score (%)"	1454 (57.9)	262 (55.0)	386 (62.8)	0.026

Table 2 Odds ratios of MAC and clinical comorbidities for CLD cohort

	Unadjusted	Age	Age + sex
Cirrhosis	2.11 (1.66, 2.72)	2.41 (1.84, 3.17)	2.34 (1.79, 3.08)
Decompensated cirrhosis	2.19 (1.47, 3.67)	3.19 (2.03, 5.17)	3.04 (1.93, 4.94)
Diabetes mellitus	1.64 (1.42, 1.90)	1.26 (1.08, 1.42)	1.23 (1.05, 1.45)
Hypertension	2.27 (1.98, 2.61)	1.54 (1.32, 1.80)	1.47 (1.03, 2.14)
Peripheral vascular disease	3.35 (2.67, 4.25)	2.00 (1.57, 2.57)	1.92 (1.54, 2.52)
Congestive heart failure	2.21 (1.72, 2.87)	1.42 (1.09, 1.87)	1.39 (1.07, 1.83)

Table 3 Clinical events and contributed days for CLD cohort

	NAFLD	HCV	ETOH	*p*
n	2513	476	615	
Death (%)	744 (29.6)	169 (35.5)	233 (37.9)	< 0.001
Days (median [IQR]	1979 [1537, 2686]	2232 [1583, 3220]	1938 [1348, 2794]	< 0.001
Hepatic decompensation (%)	88 (3.5)	78 (16.4)	80 (13.0)	< 0.001
Days (median [IQR]	1958 [1516, 2666]	2160 [1526, 3183]	1879 [988, 2727	< 0.001
Cirrhosis (%)	247 (9.8)	205 (43.1)	175 (28.5)	< 0.001
Days (median [IQR]	1922 [1367, 2617]	1782 [436, 2824]	1664 [202, 2472]	< 0.001
Liver-related death (%)	60 (2.4)	63 (13.2)	53 (8.6)	< 0.001
Days (median [IQR]	1250 [448, 1945]	1195 [777, 1865]	639 [290, 1488]	< 0.001

in the NAFLD group (2.4%). Median contribution days were highest for the HCV group for death [median 2232 IQR (1583, 3320)] and hepatic decompensation [median 2160 IQR (1526, 3183)], while the NAFLD group had the most contributed days the cirrhosis [median 1922 IQR (1367, 2617)] and liver-related death [median 1250 IQR (448,1945)].

Table 4 reports hazards ratios of elevated MAC score and clinical outcomes stratified by chronic liver disease status in the CLD Cohort. Cirrhosis development was significantly

Table 4 Hazard ratios of MAC and outcomes in CLD cohort

Cirrhosis	Full Cohort	NAFLD	HCV	ETOH	HCV + ETOH
Age + sex adjusted	2.15 (1.65, 2.80)	2.32 (1.51, 3.58)	1.38 (0.86, 2.22)	1.99 (1.25, 3.18)	1.68 (1.21, 2.33)
Multiple adjusted	2.13 (1.63, 2.78)	2.19 (1.41, 3.41)	1.39 (0.86, 2.23)	1.69 (1.22, 2.36)	2.05 (1.28, 3.28)
Decompensation					
Age + sex adjusted	2.25 (1.64, 3.07)	1.56 (0.94, 2.59)	2.16 (1.27, 3.65)	2.27 (1.52, 3.37)	2.44 (1.33, 4.45)
Multiple adjusted	2.19 (1.60, 3.02)	1.32 (0.79, 2.20)	2.21 (1.31, 3.76)	2.39 (1.60, 3.56)	2.80 (1.52, 5.17)
Liver-related death					
Age + sex adjusted	2.25 (1.53, 3.23)	1.77 (0.94, 3.34)	1.87 (1.06, 3.31)	2.00 (1.27, 3.13)	2.21 (1.08, 4.53)
Multiple adjusted	2.13 (1.46, 3.11)	1.46 (0.76, 2.78)	1.86 (1.04, 3.31)	2.03 (1.28, 3.20)	2.34 (1.14, 4.83)
Death					
Age + sex adjusted	1.56 (1.35, 1.80)	1.45 (1.22, 1.75)	1.65 (1.16, 2.27)	1.70 (1.34, 2.14)	1.72 (1.23, 2.40)
Multiple adjusted	1.47 (1.27, 1.71)	1.34 (1.11, 1.61)	1.57 (1.11, 2.21)	1.66 (1.30,2.11)	1.67 (1.19, 2.36)

Multiple adjustments include Age, BMI, Sex, PVD, CHF hypertension and diabetes

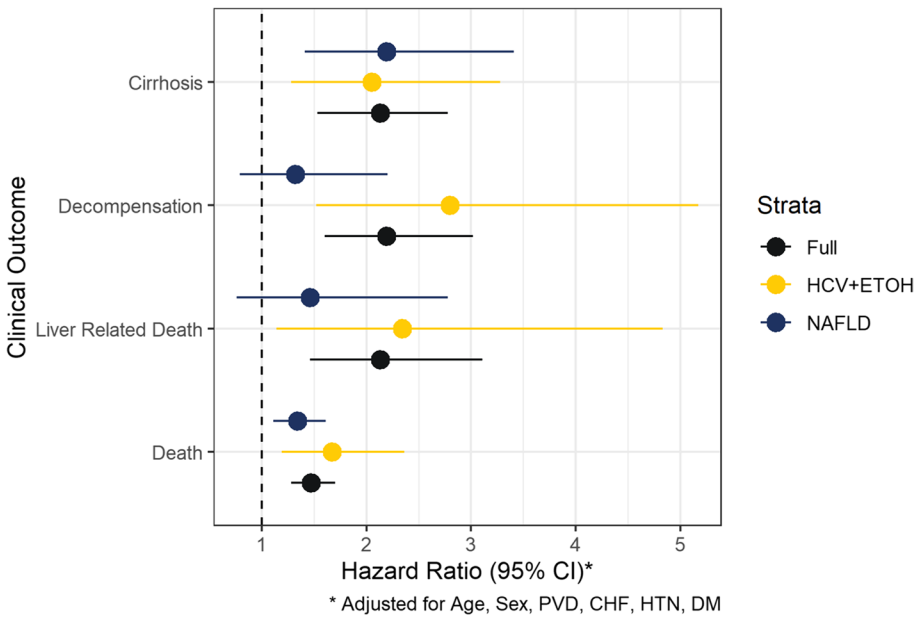

Fig. 4 Hazard ratios of elevated MAC Score and clinical outcomes in the CLD cohort

associated with MAC across the different strata, except for HCV status. Associations remained statistically significant after adjustment in the full cohort, the NAFLD and non-NAFLD (HCV+ETOH) groups (See Fig. 4), HRs 2.13 (1.63, 2.78), 2.19 (95% CI 1.41, 3.41), 2.05 (95% CI 1.28, 3.28), respectively. Hepatic decompensation development significantly increased with elevated MAC in the fulld cohort, HR 2.19 (95% CI 1.60, 3.02). This relationship seemed driven by the non-NAFLD group, (HCV + ETOH) HR 2.80 (95% CI 1.52, 5.17), more than the NAFLD group HR 1.32 (95% CI 0.79, 2.20). Similar findings were observed with liver-related death and MAC, HR 2.13 (95% CI 1.46, 3.11) for the full cohort, and for HCV + ETOH, HR 2.34 (95% CI 1.14, 4.83). Overall death was associated with MAC in the full cohort, HR 1.47 (95% CI 1.27, 1.71), for NAFLD HR 1.34 (95% CI 1.11, 1.61) and HCV + ETOH 1.67 (95% CI 1.19, 2.36).

Table 5 Hazard ratios of aortic calcification and clinical outcomes stratified by hepatic steatosis severity

	Lower	Higher
Cirrhosis	2.01 (1.13, 3.53)	3.04 (1.33, 6.93)
Decompensation	1.37 (0.68, 2.78)	3.67 (1.40, 9.61)
Liver-related death	1.71 (0.70, 4.14)	6.88 (1.59, 29.67)
Death	2.41 (1.79, 3.23)	3.28 (1.93, 5.57)

Table 5 reports hazard ratios for MAC score and clinical outcomes stratified by hepatic steatosis severity. Among participants with lower steatosis severity (normal or mild rated liver density) having elevated aortic calcification resulted in increased hazard regarding cirrhosis HR 2.01 (95% CI 1.13, 3.53) and overall death HR 2.41 (95% CI 1.79, 3.23).

Those with higher steatosis severity and elevated aortic calcification had higher hazards for all clinical outcomes: cirrhosis HR 3.04 (95% CI 1.33, 6.93), decompensation HR 3.67 (95% CI 1.40, 9.61), liver-related death HR 6.88 (1.59, 29.67) and HR 3.28 (95% CI 1.93, 5.57).

Discussion

We evaluated the relationship of a novel aortic wall percent calcification score (MAC), with comorbidities and chronic liver disease-related outcomes in a cohort of veterans. MAC was found to be independently associated with cirrhosis, decompensation, liver-related death, and overall death after adjustment for age, sex, and common clinical comorbidities. After stratification by NAFLD status, the relationship of MAC with decompensation and liver-related death in patients with NAFLD was attenuated, while the relationship of MAC with cirrhosis and overall death remained significant. In those with HCV and ETOH, associations of elevated MAC with cirrhosis, decompensation, liver-related death, and overall death remained after multiple adjustment, although this appears to be driven by ETOH. After limiting to those without ETOH, elevated steatosis severity had greater hazard magnitude for cirrhosis, decompensation, liver-related death, and overall death.

The consistent association of NAFLD with subclinical atherosclerosis and prevalent CVD is well established [7, 43–46]. While the findings of this study do support the relationship between NAFLD and atherosclerosis, it is surprising to see stronger hazard ratios among MAC and some clinical outcomes for the HCV and ETOH strata. Liver fibrosis has previously been associated with aortic calcification while cirrhosis has been reported to increase the risk of cardiovascular death regardless of etiology and stage of disease [47–53]. Both aortic calcification and liver fibrosis are causally influenced by inflammation, elevated oxidative stress, and accumulation of pro-inflammatory macrophages [47, 54, 55]. Vascular calcification approximates prolonged disease states of the medial or intimal wall and may explain the overarching relationship [14, 56, 57]. Further, inorganic pyrophosphate deficiencies are associated with pathologic calcification, dysregulation provides a potential encompassing mechanism for arterial calcification promotion [47, 58, 59]. An observational study of hepatic pyrophosphate deficiency reported inorganic pyrophosphate before and after liver transplantation; authors determined that promotion of arterial calcification in several arterial beds were attributed to inorganic pyrophosphate dysregulation via liver disease [47].

While studies examining the relationship of NAFLD and atherosclerosis are prevalent, relatively few studies examine this relationship in those with ETOH-related CLD [60]. A coronary imaging study of patients with end-stage renal disease (due to ETOH) demonstrated higher total prevalence of coronary calcification when compared to the prevalence of a matched cohort without CLD [61]. Further, higher risk of CVD-related mortality has been noted in those with ETOH related CLD than with NAFLD [62]. While stronger risk of atherosclerosis was reported for the ETOH than NAFLD strata, the authors thoughtfully point out that the ETOH group had more advanced states liver disease compared to NAFLD group [60]. Regardless, large cross-sectional study estimated that 10-year Framingham Risk Scores were similar in those with ETOH and NAFLD compared to those without liver disease [63].

Strong associations between HCV and atherosclerosis are reported in all outcomes but cirrhosis, even with adjustment for cardiovascular risk factors [33–35, 64]. Those with chronic HCV infection are susceptible to cardiovascular morbidities through inflammatory and lipid processes [65]. In large cohort studies, those with diagnosed HCV had higher all-cause mortality and diagnostic status was an independently associated with cerebrovascular death [33, 65–68]. However, this could be due to the high co-occurrence of type 2 diabetes, insulin resistance, and steatosis among those with chronic HCV infection and will require further evaluation [69–72].

Consistent associations between vitamin K deficiency and vascular calcification are reported in the literature [73–76]. Vitamin K deficiency is also commonly observed in patients with CLD, and some suggest a protective effect of vitamin K on CLD, particularly metabolic dysfunction-associated fatty liver disease [77–81]. The overlying relationship between vitamin K, atherosclerosis, and CLD may be due to shared risk factors, heterostasis, physical function, or indicative of disease state. Further epidemiologic and causal studies will be necessary to evaluate a common mechanism.

Despite the study population being scanned for indications outside of cardiovascular disease, we detected elevated atherosclerotic burden in more than 55% of the study population. For reference, AAC prevalence has been estimated at 29% in NHANES [82]. Previous studies have associated aortic calcification with cardiovascular disease, overall mortality, incident coronary heart disease, myocardial infarction, diabetes mellitus, and stroke [13, 16, 82, 82–88]. Unsurprisingly, the logistic regression results of this study indicated strong associations of MAC with diabetes mellitus, hypertension, peripheral vascular disease, and congestive heart failure.

This work has limitations. The cohort is limited to veterans, who have been noted to have higher rates of chronic liver disease relative to the general population [1, 89]. There may an additional selection bias as this cohort is limited to those with abdominal CT scan. Therefore, the results may not be generalizable, and magnitude of effect estimates could

be biased away from the null. As the secondary data used in this study leverages patient encounters rather than the recruitment of participants, it is difficult to ascertain whether the patient was lost to follow-up before the study ended. As such, informative biases may exist inflating contribution time in non-censored observations. Finally, as this analysis is cross-sectional, causal inference is limited.

Nevertheless, this work highlights the comorbidity of elevated aortic calcification with NAFLD, HCV, and alcohol-related liver diseases in a large clinically relevant cohort. Future work should validate the direction and magnitude of the relationship between aortic calcification and non-NAFLD liver diseases. Such validation will contextualize comorbidity between atherosclerotic cardiovascular disease and chronic liver diseases and may be useful for the mitigation of cirrhosis, decompensation, liver-related death, and overall death in the clinical setting.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10620-024-08450-5.

Author's contributions Conceptualization SRH, AES, SCW, GLS; Methodology PXB, SRH, PZ, SAH; Formal Analysis and Investigation SRH, PXB, PZ, GLS; Writing—original draft preparation SRH; Writing—review and editing SRH, PXB, PZ, SAH, SS, SCW, AES, SCW, GLS; Resources: PXB, SAH, SS, SCW, GLS. All authors commented, reviewed, and provided impactful edits to the manuscript.

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Data availability Analyses were performed using data from Corporate Data Warehouse domains that are only available within a secure research environment behind the US Department of Veterans Affairs firewall. To comply with VA privacy and data security policies and regulatory constraints, only aggregate summary statistics and results of our analyses are permitted to be shared for publication. Restrictions are in place to maintain Veteran privacy and confidentiality. Access to these data can be granted to persons who are not employees of the VA; however, there is an official protocol that must be followed. Interested researchers can contact the VA Center for Clinical Management Research.

Declarations

Competing interests Authors declare no potential conflicts of interest.

Ethical approval This study was approved by the Institutional Review Boards at VA Ann Arbor Healthcare System Research's (IRB-2018-1136) and the University of Michigan (HUM-0028846).

Consent for publication All authors have read this manuscript and consented for publication.

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