Digestive Diseases and Sciences (2018) 63:1355–1362
https://doi.org/10.1007/s10620-018-5006-7

ORIGINAL ARTICLE

Pronounced Coronary Arteriosclerosis in Cirrhosis: Influence on Cardiac Function and Survival?

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Received: 13 December 2017 / Accepted: 28 February 2018 / Published online: 8 March 2018

Abstract

Background The relation between excessive alcohol consumption and coronary arteriosclerosis has remained controversial. The etiology of cirrhosis has been considered a substantial risk factor for development of arteriosclerotic lesions. The coronary artery calcium-score derived from coronary CT angiography is a robust marker of coronary arteriosclerosis.

Aims To study the burden of coronary arteriosclerosis in cirrhotic patients of various etiologies and association to cardiac dysfunction and survival.

Methods Fifty-seven patients with cirrhosis without cardiovascular disease underwent coronary CT angiography, tissue Doppler echocardiography, electrocardiogram and registration of clinical and biochemical characteristics.

Results In patients with cirrhosis the median coronary artery calcium-score was increased in comparison with age and race-adjusted healthy reference values (men: 328 vs. 9 HU and women: 136 vs. 0 HU; $p<0.001$). Moreover, the coronary artery calcium-score in alcohol-related cirrhosis was significantly higher than in nonalcohol-related cirrhosis (362 vs. 46 HU, $p<0.001$). Coronary artery calcium-score correlated with age ($p=0.002$) but not with established cardiovascular risk factors including smoking, type 2 diabetes, hypertension, gender, or hypercholesterolemia. Coronary artery calcium-score was associated with diastolic dysfunction, lateral e´ ($p=0.025$), but not with other markers of cardiac dysfunction. During a median follow-up of 25 months 12 patients (21%) died but coronary artery calcium-score was not associated with survival.

Conclusions Coronary arteriosclerosis was particular extensive in patients with alcoholic cirrhosis. However, the current results suggest that coronary arteriosclerosis only have limited influence on cardiac function and survival. Surprisingly, no other established risk factors apart from age seemed to interfere with coronary arteriosclerosis in cirrhotic patients.

Keywords Alcoholic cirrhosis · Portal hypertension · Coronary artery calcium · Coronary angiography · Cardiomyopathies

Introduction

Coronary arteriosclerosis (CA) is a major cause of morbidity and mortality of coronary artery disease (CAD) world wide [1, 2]. Population-based studies have shown that the major risk factors for the development of CA include arterial hypertension, smoking, obesity, hyperlipidaemia, and diabetes mellitus [3]. In patients with cirrhosis evidence regarding CA risk factors is only sparsely studied. In particular, the relation between excessive alcohol consumption and CA is controversial and it has been debated whether the etiology of cirrhosis per se is a determinant of developing CA [4–6]. Furthermore, in patients with stable cirrhosis evidence regarding the impact of arteriosclerosis on cardiac function and survival are scarce. An increasing amount of evidence of cardiovascular changes in cirrhosis has led to the definition of cirrhotic cardiomyopathy [7]. Cirrhotic cardiomyopathy is seen in 40–45% of the patients with cirrhosis and includes systolic and diastolic dysfunction and electro-mechanical abnormalities [8]. Whether CA and cirrhotic cardiomyopathy mutually interact or are two distinct manifestations of heart abnormalities is still unclear.

Noninvasive coronary computed tomography angiography (CT-A) allows assessment of the coronary plaque

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composition and the arteriosclerotic burden [9]. The extent of CA can be quantified using the Agaston score method defined as Coronary artery calcium (CAC)-score [10]. CAC-score is a robust marker of the coronary atherosclerotic burden and it also predicts risk of CAD-related events and all-cause mortality with an approximately linear dose–response relationship, even after adjusting for established risk factors in noncirrhotic patients [9, 11, 12].

Since the extent of CA in cirrhotic patients and its relation to etiology and cardiac function are unknown we aimed at determining the burden of CA in relation to patient characteristics, cardiac function, and mortality.

Patients and Methods

Study Design

We performed a prospective, observational pathophysiological study in a cohort of stable patients with cirrhosis hospitalized at Hvidovre Hospital or Rigshospitalet. All included patients gave their written informed consent before participation and the study protocol was approved by the Ethics Committee for Medical Research in Copenhagen (H-4-2013-045), and performed in accordance with the guidelines established in the Helsinki Declaration.

Patient Population

A total of 104 patients with cirrhosis attending the Hepatology outpatient clinics at Hvidovre Hospital and Rigshospitalet in the period from September 2014 to July 2016 were evaluated for inclusion. Inclusion criteria: age 18–75 years and a diagnosis of cirrhosis based on either histology or clinical, biochemical and ultrasonography findings. Exclusion criteria: preexisting cardiac or respiratory disease ($n=9$), type 1 diabetes ($n=3$), ongoing infections ($n=3$), impaired renal function (estimated glomerular filtration rate < 45 ml/min/1,73 m [2]) ($n=6$), previous TIPS or liver transplantation ($n=2$), malignancy ($n=2$), anti-HCV medication ($n=5$), refused participation ($n=7$) or considered incapable to adhere to the study protocol due to heavy drinking ($n=10$).

All patients underwent clinical evaluation, blood sample collection, 12-lead ECG, tissue Doppler echocardiography, and coronary CT imaging in the same day. In order to reduce confounding factors diuretics and beta-blockers were withdrawn 48 h prior to the investigations.

Clinical Characteristics

Demographic characteristics, smoking habits, prescribed medication and alcohol consumption were collected through medical records in combination with standardized questionnaires. Habits of smoking were registered as smoker if current or previously smoking. Moreover, smoking pack years were calculated.

The severity of the liver disease was assessed according to the Child–Pugh (CP) classification and the model for end-stage liver disease (MELD) score. Data from liver vein catheterization were obtained from medical records if available. The hepatic venous pressure gradient (HVPG) was measured in 44 patients (77%) and serves as a proxy marker of portal hypertension.

For registration of risk factors, arterial hypertension was defined by previously diagnose of hypertension or current use of antihypertensive medication. Hypercholesterolemia was defined as total cholesterol > 5 mmol/l and hypertriglyceridemia if triglycerides > 2.0 mmol/L.

Coronary CT

Coronary CT scans were acquired using a 320-slice MDCT scanner (Aquillion One Vision Edition, Toshiba Medical Systems, Nasu, Japan). CAC-score calculation is based on the method developed by Agaston and in brief it is derived by a weighted density score given to the highest attenuation value multiplied by the area of the calcification [10, 13].

CT data are analyzed in VitreaCore version 6.5 (Vital Images Inc., USA). The analysis followed the recommendations of the Society of Cardiac CT and was performed by a level-3 certified specialist in cardiac CT who was blinded to patient data.

Echocardiography

Transthoracic echocardiography was performed by two experienced echocardiographers using a commercially available system (Epiq 7G, Phillips, Andover, MA, USA), and images were digitally stored for later off-line analysis. Cardiac chamber dimensions and volumes and left ventricular (LV) mass were measured according to the current recommendations [14]. LV ejection fraction (LVEF) was measured by the Teicholz method. Left ventricular inflow velocities were determined using pulsed-wave Doppler with a 4-mm sample placed between the tips of the mitral leaflets during diastole at end-expiration. The following parameters were measured: isovolumetric relaxation time (IVRT); peak early filling (E) and its deceleration time; atrial filling peak (A); and E/A ratio. Mitral annulus velocities (e') were acquired by pulse-wave tissue Doppler imaging with the sample volume placed at the septal and lateral mitral annulus. The left atrial volume was determined by area-length method from end-systolic apical four-chamber and two-chamber views. LA maximum volume indexed (LAVI) was then averaged from both views and corrected for BSA. Tricuspid

regurgitation peak velocity (TR) was determined using a continuous-wave Doppler with the sample placed between the tricuspid valves in the regurgitation jet. Cardiac output (CO) was calculated using the LVOT VTI method. Analysis was performed off-line with dedicated software (Q-lab vs. 10.1.1., Phillips, Andover, MA, USA).

Biomarkers

Blood samples were obtained from the cubital vein, and plasma was stored at − 80 °C until analyses. High-sensitivity troponin T (hs-TnT) and probrain natriuretic peptide (proBNP) were measured on an automated Modular E platform (Roche, Mannheim, Germany). The lower limit of quantification was 13 ng/L and 5.9 pmol/L, respectively. Samples with values below LLQ were given the LLQ values. Intra-assay imprecisions of hs-TnT were < 7.8% for concentrations < 6.5 ng/L and < 1.4% for concentrations > 23.4 ng/L. Intra-assay imprecisions of proBNP were < 1.9% for concentrations < 7.55 pmol/L and < 1.3% for concentrations > 1669 pmol/L.

Follow-up Registration and Poor Outcome

All patients were prospectively followed up at 6-month intervals by ambulatory visits, telephone calls or review of the medical files. Poor outcome was defined as death.

Statistics

Data were stored and analyzed using IBM SPSS Statistics 22. The results are reported as median and IQR (25th–75th percentile) or as *n* (%) as appropriate. The primary outcome for this analysis was CAC-score. CAC-score was registered as a continuous variable, and correlations were performed by the nonparametric method of Kendall´s tau-b to investigate possible interrelation with continuous variables. The Mann–Whitney or Chi-square tests were used to compare continuous or categorical variables.

All reported *p* values are two-tailed with values less than 0.05 considered statistically significant.

Results

The study included a total of 57 patients. Baseline patient characteristics are shown in Table 1. The median age of the patients was 58 years, 67% being men. 81% of the patients had alcohol-related cirrhosis ($n = 46$), 9% had cryptogenic cirrhosis ($n = 5$), 5% had posthepatitic cirrhosis ($n = 3$), and 5% had cirrhosis from other etiologies ($n = 3$). According to the Child–Pugh classification, 13% belonged to Child–Pugh (CP) class A, 74% to class B, and 13% to class C. With respect to patient risk factors for arteriosclerosis, 63% of the patients were smokers, 21% had type 2 diabetes mellitus, 21% had hypercholesterolemia with a cholesterol level > 5 mmol/l, 11% previous had arterial hypertension diagnose, and 8% had hypertriglyceridemia (> 2.0 mmol/L). Only 3.5% of the patients (two patients) were treated with statins at baseline.

Table 1 Clinical and biochemical characteristics of 57 patients with cirrhosis

	Median ($n = 57$)	Total range IQR	Percentages (%)
Age (years)	58	52; 63.5	
Sex (n = male)	38		67
Child–Pugh	7	7; 8.75	
MELD	10	8; 12	
HVPG (mmHg)	16.5	11.25; 20	
Smoking pack years	12.5	0; 20	
Smoking (= n)	36		63
HsCRP (mg/L)	4	2; 9.5	
Cholesterol (mmol/l)	4.1	3.5; 5	
Hypercholesterolemia[a]	12		21
Triglycerides (mmol/l)	1.06	0.77; 1.51	
Hypertriglyceridemia[b]	4		7
Diabetes mellitus (= n)	12		21
Hypertension (= n)	6		11
Etiology (= n)			
Alcohol	46		81
Nonalcohol	11		19

Results are presented as median and IQR 25%; 75% or *n* (%)

[a]Hypercholesterolemia defined as cholesterol > 5 mmol/L

[b]Hypertriglyceridemia defined as triglycerides > 2 mmol/L

Coronary Arteriosclerosis

The median CAC-score for men with cirrhosis was 328 HU compared to a normal age-adjusted reference median value of 9 in the control population ($p < 0.001$) [15]. Among the female cirrhotic patients, the median CAC-score was 136 versus 0 in the control population ($p = 0.001$) [15]. Association between CAC-score and clinical and biochemical characteristics is showed in Table 2.

Risk Factors for Arteriosclerosis

Age correlated with CAC-score ($r = 0.294$, $p = 0.002$) but smoking or not ($p = 0.58$) or smoking pack years ($p = 0.67$) were not associated with CAC-score. Neither, did we find any other significant association between CAC-score and established risk factors such as type 2 diabetes mellitus,

Table 2 Kendall´s tau-b correlations between CAC-score and clinical and biochemical characteristics in patients with cirrhosis

	Coefficient	*p* value
Age (years)	0.294	0.002
Sex	–	0.22
Child–Pugh	−0.066	0.52
MELD	− 0.083	0.40
HVPG (mmHg)	−0.008	0.94
Smoking pack years	−0.043	0.67
Smoking (yes/no)	–	0.58
Cholesterol (mmol/l)	0.025	0.79
Hypercholesterolemia[a]	–	0.36
Triglycerides (mmol/l)	0.134	0.17
Hypertriglyceridemia[b]	–	0.12
HsCRP (mg/L)	0.025	0.80
Diabetes mellitus	–	0.45
Hypertension	–	0.15
Etiology	–	0.012

Results are presented as Kendall´s tau-b correlations for interval parameters. Mann–Whitney U test for bivariate parameters

[a]Hypercholesterolemia defined as cholesterol > 5 mmol/L

[b]Hypertriglyceridemia defined as triglycerides > 2 mmol/L

arterial hypertension, male, sex, hypertriglyceridemia, or hypercholesterolemia (p = NS). Moreover, no correlation was seen between CAC-score and high sensitive CRP (HsCRP) ($p = 0.80$). Finally, we did not find significant correlations between CAC-score and severity of the liver disease or degree of portal hypertension as reflected by the Child–Pugh score ($p = 0.519$), MELD score ($p = 0.397$) or HVPG ($p = 0.943$).

Etiology of the Liver Disease

Patients with alcohol-related cirrhosis had a significantly higher median CAC-score of 362 versus 46 in the nonalcoholic cirrhotic patients ($p < 0.012$). Smoking habits and smoking pack years seemed more pronounced in patients with alcohol-related cirrhosis, but this difference was not significantly different from that in the nonalcoholic cirrhotic patients ($p = 0.30$ and $p = 0.23$, respectively). There were no other significant differences with respect to age or other risk factors between patients with alcohol-related cirrhosis and nonalcohol-related cirrhosis. Clinical and biochemical characteristics of patients with alcohol-related and nonalcohol-related cirrhosis are showed Table 3.

Cardiac Function

CAC-score was associated with a decrease in diastolic function (lateral e': $r = -0.218$, $p = 0.025$), but it was not significantly associated with other variables of diastolic or systolic function (Table 4). Neither did we find any relations to electrophysiological abnormalities including the QTc interval.

Mortality

During a median follow-up of 25 months 12 patients died (21%). Patients who died had a higher CAC-score (median 391 (IQR 52; 719)) than surviving patients within the follow-up period (median 232 (IQR 0;727)). Despite this trend, we found no significant association between CAC-score and mortality ($p = 0.30$). Neither did we find any significant association between mortality and cardiac systolic function or diastolic function or cardiac electrophysiological changes.

Table 3 Clinical and biochemical characteristics of cirrhotic patients with alcohol versus nonalcohol etiology

	Total ($n = 57$)	Alcohol etiology ($n = 46$)	Nonalcohol etiology ($n = 11$)	*p* value
CAC-score[a]	289 (16;699)	361.5 (34;840)	46 (0;232)	0.012
Sex (n = male)	38 (67%)	32 (70%)	6 (55%)	0.34
Age	58 (52;63.5)	58.5 (52;63.3)	58 (50;64)	0.98
MELD	10 (8;12)	10 (8;11.5)	13 (8;13)	0.10
Child–Pugh	7 (7; 8.8)	7 (7;8)	8 (5;10)	0.70
HVPG (mmHg)	16.5 (11.3; 20)	16.8 (12.8;20.3)	15.5 (10.8;19.3)	0.45
Smoking (= n)	36 (63%)	31 (67%)	5 (46%)	0.30
Smoking pack years	12.5 (0;20)	15 (0;22.5)	0 (0;20)	0.23
Hypertension (= n)	6 (11%)	5 (11%)	1 (9%)	0.85
Diabetes mellitus (= n)	12 (21%)	9 (20%)	3 (27%)	0.78

Results are presented as median and IQR 25–75% or n (%)

Results are presented as Mann–Whitney U test for interval parameters and Chi-square for bivariate parameters

[a]*CAC-score* coronary artery calcium

Table 4 Kendall´s tau-b correlations between CAC-score and cardiac parameters in patients with cirrhosis

	Median ($n=57$)	Coefficient	p value
Systolic measurements:			
Cardiac output (L/m)	5.0	−0.063	0.51
Left ventricular ejection fraction (LVEF)	66.0	−0.032	0.74
Diastolic measurements:			
E′ lateral (cm/s)	11.3	−0.218	0.025
E′ medial (cm/s)	8.6	−0.144	0.14
TR velocity (cm/s)	258.0	−0.156	0.10
LA volume index (ml/m^2)	32.8	−0.003	0.98
E/A ratio	1.2	0.005	0.62
E/E´ratio	6.8	0.142	0.15
Deceleration	214.0	−0.067	0.48
IVRT	79	0.043	0.65
Other			
QTc	0.427	0.086	0.35
TNT (ng/l)	8.0	0.143	0.13
proBNP (pmol/l)	10.0	0.051	0.59

Results are presented as median (IQR) 25%; 75%

Discussion

To our knowledge this is the first study to describe the arteriosclerotic burden in relation to etiology, cardiac function, and mortality in a stable cohort of patients with cirrhosis.

A main finding of our study is that patients with cirrhosis have significantly more severe CA as compared to a matched reference population from the general population [15]. Previous studies have shown conflicting results. Thus, three studies conclude that the prevalence of CA in cirrhotic patients is high as compared with controls [16–18], whereas 6 other studies report unchanged or reduced prevalence of CA or CAD [2, 5, 19–22]. However, the control cohorts of the individual studies differ substantially and in some studies patients with other diagnoses have served as controls regardless of comorbidities or cardiac history [2, 5, 16, 22]. In the majority of the studies the included patients were candidates for liver transplantation with severe liver failure and very often with more advanced CA [2, 17, 18, 23–30]. An important limitation of these studies is that they use different definitions of CA and CAD, which invalidate a reliable comparison of the findings. Most studies define CA or CAD assessed from obstruction or stenosis on coronary CT angiography [2, 17, 18, 22, 25]. In other studies CA or CAD was based on coronary arteriography performed during a cardiac catheterization [5, 24, 27, 29], reduced ankle/brachial index [19, 21], intima-media thickness [19] or from medical report [16, 23].

Strength of the CAC-score is that it visualizes both obstructive and nonobstructive plaques, and recent results suggest that overall arteriosclerotic lesion predicts CAD-related events regardless of the presence of obstructive or nonobstructive plaque [9]. Furthermore, several studies have demonstrated that CAC scoring improves prediction of risk beyond that of conventional risk factor-based algorithms [12]. Only four of the studies have used CAC-score to assess CA [17, 18, 22, 25]. Three of these have assessed transplant candidates and only one study has included patients with various degrees of liver dysfunction and has compared the results with a control cohort [22]. None of the studies have related their CAC-findings to both cardiac function and mortality.

It has been hypothesized, that the structure and localization of the arteriosclerotic plaques are different in cirrhotic patients compared to noncirrhotic individuals [2, 5, 22]. A recent study by Kazankov et al. found no difference in prevalence of nonobstructive and obstructive CAD in cirrhotic patients and controls, but cirrhotic patients had markedly higher number of coronary segments and vessels with atherosclerotic plaques [22]. The length of the plaques was increased and the total plague volume was higher with a higher proportion and volumes of calcified plaque [22]. Conversely, An et al. showed that despite a similar prevalence of CAD in cirrhotic patients and controls, the patients with cirrhosis had significantly more nonobstructive lesions and more extensive involvement of the coronary vessels than controls [2]. Altogether this indicates that the arteriosclerotic process and CAD in patients with cirrhosis differ from CAD in other patients without cirrhosis and hence the risk factors may play a differential role in patients with and without cirrhosis.

Risk Factors

Another important finding of our study is that the cardiovascular risk profile of patients with liver cirrhosis apart from age does not seem to be associated with CAC-score. This is in agreement with findings by Kalaitzakis et al. who observed that alcohol-related cirrhosis and age were the only independent risk factors for CAD [16]. Other studies have, however, shown that risk factors such as age [2, 25, 27, 29], male gender [2, 18, 27], and diabetes [2, 27, 29, 30] are independent determinants of CA in alcohol-related cirrhosis. Since inflammation is believed to play a role in the development of CAD, HsCRP was expected to be elevated as a proxy marker for development of arteriosclerosis. However, HsCRP did not seem to be associated with CAC-score in our study. This could be due to the fact that the cohort consists of stable cirrhotic patient with low hsCRP levels. Furthermore, hsCRP represents multiple aspects of

inflammation processes in liver disease which might blur a possible association.

The disease severity of cirrhosis, as reflected by the Child–Pugh or MELD scores or the degree of portal hypertension, was not associated with the CAC-score. Hence our results are in agreement with several other studies reporting no relationship between severity of cirrhosis and the CA burden [2, 16, 18, 20]. Only in one study by McAvoy et al. a high prevalence of CAD was reported in association to MELD score in patients with end-stage liver disease (ESLD) waiting for a liver transplantation [25] and CAD was one of the leading causes of total mortality following liver transplantation [31, 32].

The effects of cirrhosis per se on risk factors to CAD may be a confounder since the presence of liver dysfunction changes the cholesterol profile, reduce arterial blood pressure, and results in thrombocytopenia. These changes all tend to protect against arteriosclerosis [2, 17]. This would explain why we did not retrieve any associations between the established risk factors and CA in cirrhosis.

Etiology

An important finding from our study suggests that alcohol might be a risk factor for CAD in particular in relation to extensive alcohol consumption in alcoholic related cirrhosis.

Results of earlier postmortem studies led to the assumption that alcohol intake in alcoholic cirrhosis protects against CA since the incidence of myocardial infarction and atherosclerosis were low in autopsy materials [33, 34]. In consistency, later epidemiological and clinical studies have confirmed that a mild to moderate alcohol consumption is associated with a reduced mortality and CAD mortality but there is strong evidence suggesting that the association is J- or U shaped [35–37].

However, the relation of CA and etiology of cirrhosis is still debated since the prevalence of CA disease may differ among patients with an alcoholic etiology and other etiologies of cirrhosis. In some studies the prevalence of CA disease was lower or equally low between different etiologies [18, 22, 23, 25], whereas other studies have found a higher prevalence of CA disease in patients with alcoholic cirrhosis than in those with other etiologies [2, 16].

Our result argues against the prevalent assumption that alcohol and therefore possible alcoholic cirrhosis may protect against CA. In our study alcoholic cirrhosis appeared to be an independent risk factor for CA and this association was not influenced by differences in established risk factors among etiologies. However, the relation of CA and various aetiologies of cirrhosis is complex and results of other studies have demonstrated that, there seems to be a strong overall independent association between cirrhosis itself regardless of etiology on the one hand and known risk factors for CA disease such as type 2 diabetes mellitus, smoking, and truncal obesity on the other [23, 27].

Cardiac Dysfunction

In patients with advanced CA usually both systolic and diastolic function are affected [38, 39]. In our cirrhotic patients, cardiac function was only modestly impaired and only a single cardiac parameter (lateral e') was significantly correlated with CAC-score. This may indicate that CAC in cirrhosis only slightly affects heart function. Accordingly, Kokolis et al. observed that patients with alcohol-related disease (of whom 91% had liver cirrhosis) had a lower degree of CAD but interestingly a more pronounced degree of systolic dysfunction with a higher prevalence of left ventricular dysfunction compared to a control group [5]. This impedes a possible correlation between high CAD prevalence and related cardiac dysfunction. It is, however, an important confounder that patients with cirrhosis may in addition to CA have a cirrhotic cardiomyopathy that affects cardiac function with an increased risk of sudden cardiac death, systolic and diastolic dysfunction, and electrophysiological abnormalities [8, 40–42].

Furthermore, alteration in hemodynamics, inflammation, and structural changes in cirrhosis may also influence cardiac function and blur the presumed association between CA and cardiac dysfunction. Concisely it seems that evidence regarding CA and cardiac dysfunction is absent in our study.

Mortality

Despite the fact that the cirrhotic patients have a high burden of arteriosclerosis, it seems not directly related to death. This may be due to the fact that the arteriosclerotic process among cirrhotic patients probably is different and perhaps less pathogenic than in the general population. Furthermore, patient with cirrhosis often have short lifespan and they might die from other cirrhosis complications before having heart attack due to CA.

Neither was the present study powered to find any association between etiology of cirrhosis and mortality. A Danish nationwide study have among alcohol-related cirrhotic patients reported a higher 10 year-mortality than in patients with other etiologies and they further reported that heart diseases was the most frequent cause of death among cirrhotic patients apart from cirrhotic complication [43]. We were unable to confirm this finding in our study, which could be due to the relatively low mortality (12 patients) and a relatively short follow-up time. It is worth noticing that our study also has some other limitations. Our study was limited by the relative small cohort and that the majority of the cohort consisted of patients with alcohol-related cirrhosis

and only few with viral cirrhosis and none of the patients had NASH (nonalcoholic steatohepatitis).

Currently, we still lack solid data on the prevalence of CAD and its risk factors in patients with cirrhosis of different etiologies. Thus, it is still discussed whether alcohol intake per se, presence of cirrhosis or the combination are the major determinant of arteriosclerosis in alcoholic cirrhosis. However, in the current study we did not included an alcohol-dependent control group without cirrhosis. Such a control group would have enabled us to investigate the pure influence of alcohol on the development of arteriosclerosis and mortality without the confounder of cirrhosis.

Future studies should therefore seek to include individual cohorts and in particular a control group of alcohol-dependent patients without cirrhosis.

Furthermore, evidence regarding relations between cause and severity of cirrhosis, development of CAC and its relation to mortality is scarce and it will need to be investigated in larger, prospective follow-up studies.

In conclusion, our results demonstrate that patients with cirrhosis, especially patients with alcohol-related cirrhosis had more disseminated CA compared to the general population. Besides age, no associations to the established CVD-risk factors were found and CA does not seem to be related to severity of disease or increased mortality. We found only limited evidence of CA and changes in diastolic function and apparently no association to systolic dysfunction or electrophysiological changes. Development of coronary arteriosclerosis in cirrhosis may not share the same pathophysiology as in the background population.

Acknowledgments We sincerely thank the staff at Centre for Functional and Diagnostic Imaging and Research, Hvidovre University Hospital for the effort. We thank Allan Poulsen and Hanne Halgreen for their impressive help with the echocardiography measurements and we also thank laboratory technician Katrine Lyngby for her excellent assistance. This project has received financial support and funds from Novo Nordisk Foundation and Amager Hvidovre University Hospital Research Foundation.

Compliance with ethical standards

Conflict of interest None of the authors had any personal or financial conflicts of interest.

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