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ORIGINAL ARTICLE

Liver stiffness is associated with excess mortality in the general population driven by heart failure: The Rotterdam Study

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Abstract

Background: Elevated liver stiffness reflects hepatic fibrosis but can also be secondary to venous congestion. We aimed to study the association between liver stiffness and mortality in the general population, stratified for heart failure and/or coronary heart disease (CHD).

Methods: We analysed individuals enrolled in the ongoing prospective population-based Rotterdam Study who attended a visit between 2009–2014 that included liver stiffness measurement. Exclusion criteria for the primary analysis were incomplete data on heart failure, unreliable liver stiffness, alcohol abuse and viral hepatitis, leaving 4.153 participants (aged 67.5 ±8.4 years, 44.2% male) for analysis with a median follow-up of 6.0 (interquartile range: 5.1–7.0) years. Secondary analysis included participants with viral hepatitis, alcohol abuse and/or unreliable measurement. The association between liver stiffness and mortality was assessed using Cox regression. Associations between heart failure, CHD, and echocardiographic characteristics and liver stiffness were quantified with linear regression.

Results: Liver stiffness ≥8.0 kPa was associated with mortality (aHR: 1.37, 95%CI: 1.00–1.89). However, this was driven by participants with heart failure (aHR: 2.48, 95%CI: 1.15–5.35), since high liver stiffness was not associated with mortality in participants without heart failure and/or CHD (aHR: 1.07, 95%CI: 0.70–1.64). Results were consistent when individuals with viral hepatitis, alcohol abuse or unreliable liver stiffness measurement were not excluded. Several cardiovascular characteristics were significantly associated with higher liver stiffness, e.g. heart failure, moderate/poor diastolic dysfunction, and right atrium diameter > 4.5 cm.

Conclusion: In our cohort of community-dwelling elderly, high liver stiffness was associated with excess mortality, primarily explained by participants with heart failure. Moreover, heart failure and its indicators were associated with increased liver stiffness.

KEYWORDS
epidemiology, heart failure, liver stiffness, survival

Abbreviations: aHR, adjusted hazard rate; CHD, coronary heart disease; CI, confidence interval; HDL, high-density lipoprotein; HF, heart failure; IVC, inferior vena cava; LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; P25-P75, 25th to 75th percentile.

1 | INTRODUCTION

Liver stiffness assessment is an established non-invasive approach to rule out significant fibrosis among individuals with chronic liver disease.[1,2] However, stiffness of the liver increases not only due to fibrosis but is also affected by inflammation and venous congestion.[3–5] Clinical or subclinical central venous congestion is often present in individuals with cardiovascular disease and has been associated with adverse outcomes.[6–8] Through its association with venous congestion, elevated liver stiffness has been identified as a predictor of short term mortality in patients with acute heart failure.[9,10]

Liver stiffness measurements has been assigned an important role in the early detection of advanced liver disease in at-risk populations, and several groups are currently exploring its use for population-based screening for significant liver disease.[1,11–13] However, as elevated liver stiffness is not a specific tool for fibrosis, it might predominantly reflect central venous congestion, particularly among patients at high cardiovascular risk.[14]

We, therefore, aimed to study (1) the association between liver stiffness and mortality in relation to the presence of (signs) of heart failure and (2) study the association between liver stiffness and indicators of heart failure.

Lay Summary

Liver stiffness, a marker for liver fibrosis, is linked to mortality and liver-related adverse outcomes among patients with chronic liver disease. However, the observed excess mortality among an elderly general population with high liver stiffness was primarily explained by heart failure. This finding was further supported by the observation that heart failure and markers of heart failure were associated with higher liver stiffness.

2 | PARTICIPANTS AND METHODS

2.1 | Study population

This study was performed within the Rotterdam Study, a large ongoing cohort established in 1989. Individuals aged ≥45 years old living in Ommoord, a suburb of Rotterdam, the Netherlands, were eligible to participate, regardless of their health. However, participants with poor health may be less willing or unable to attend the research visits. Since 2009, the hepatology department has introduced abdominal ultrasound and transient elastography in the regular visits. The rationale and details of the Rotterdam Study have been extensively described recently.[15] For the current analyses, we enrolled participants who visited the research center between 2009 and 2014 with liver stiffness data (Figure 1). Exclusion criteria were lack of data on heart failure, unreliable liver stiffness measurement and known liver disease (alcohol abuse [≥60 gram per day] and viral hepatitis). Alcohol abuse and viral hepatitis were considered exclusion criteria to simulate a screening setting for advanced fatty liver disease and investigate the potential benefit. Of note, we repeated our primary analysis, including patients with viral hepatitis and/or alcohol abuse to validate our findings.

2.2 | Hepatology assessment

Participants underwent abdominal ultrasound to assess hepatic steatosis based on hyper-echogenicity of the liver parenchyma. At the same visit, a liver stiffness measurement was performed (FibroScan®, EchoSens, France). Measurements not meeting the reliability criteria of Boursier et al., were discarded.[16] Liver stiffness was considered high when ≥8.0 kPa according to cut-offs provided for research among the general population.[17]

2.3 | Cardiovascular assessment

Data on cardiovascular diseases, including heart failure and coronary heart disease (CHD), were obtained during the study visits and from treating medical professionals. Diagnoses were verified by research physicians according to the definitions as outlined in the ESC guidelines.[18] Briefly, heart failure was defined as a combination of the presence of typical symptoms or signs of heart failure, such as breathlessness at rest or during exertion, ankle edema and pulmonary crepitations, confirmed by objective evidence of cardiac dysfunction or when two typical symptoms suggestive of heart failure were present and at least one of the following: history of cardiovascular disease, positive response to initiated treatment for heart failure or objective evidence of cardiac dysfunction. CHD was defined as myocardial infarction or revascularisation (e.g. percutaneous coronary intervention or coronary artery bypass grafting). Detailed methodological information on the data collection and definitions used for cardiovascular diseases have been published previously.[19]

By transthoracic echocardiograms, systolic and diastolic function was assessed in several ways. For systolic function, we used fractional shortening, which was based on the left ventricular end-diastolic dimension (LVEDD) and left ventricular end-systolic dimension (LVESD) and defined as: (LVEDD − LVESD)/LVEDD × 100%. Additionally, the sonographers made a qualitative global assessment of systolic function based on the 2D echocardiogram. Diastolic function was assessed using the E/A ratio and mitral valve deceleration time. The peak E velocity was the early filling velocity occurring with mitral valve opening and the peak A velocity was the velocity occurring with contraction of the atrium.[20] The average of three cycles have been used to calculate the E/A ratio. The mitral valve deceleration time was the time between peak E and crossing of the wave when extrapolated with the baseline. The E/A ratio and mitral valve deceleration time were then combined for a qualitative assessment of diastolic dysfunction. Specifically, normal (E/A ratio

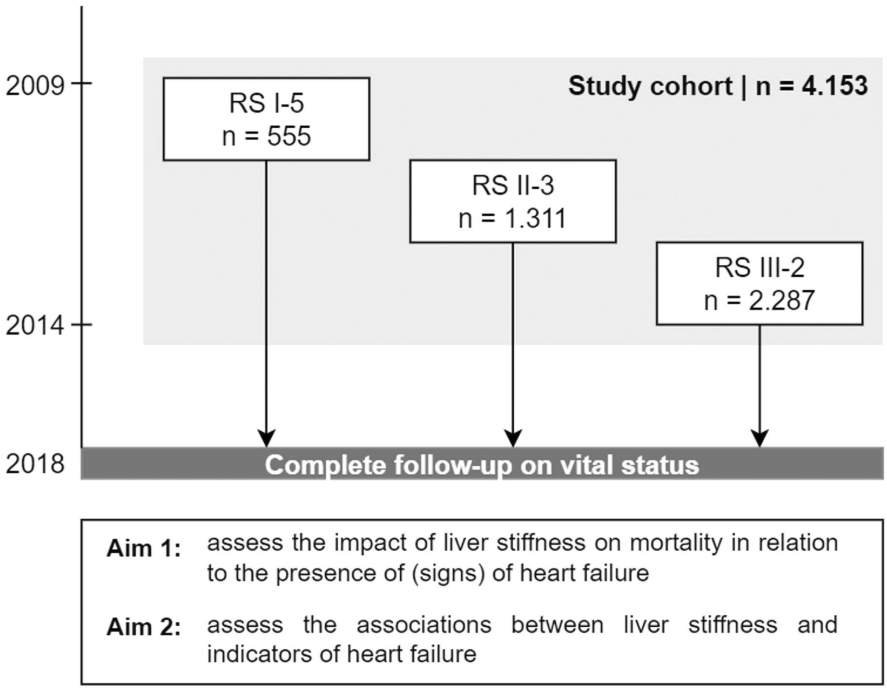

FIGURE 1 Overview of the aims and Rotterdam Study subsets included in our study. Three different Rotterdam Study cohorts that attended a visit between 2009 and 2014 were used for our aims and follow-up on vital status was complete until May 2018. *n*, number; RS, Rotterdam Study.

0.75–1.50 and deceleration time 150–280 ms), impaired relaxation (E/A ratio < 0.75 and deceleration time > 280 ms) and restrictive (E/A ratio > 1.50 and deceleration time <150 ms).[20] Diastolic dysfunction was considered indeterminate if only one of the two criteria for dysfunction was met.

2.4 | Follow-up and mortality data

All-cause mortality data were obtained from local registries and clinical follow-up data. Verified information on all-cause mortality was available until May 2018. Cause of death data was complete until the 1st of January 2015.

2.5 | Covariates

Prior to the study visit, a home interview was scheduled in which, among others, data on alcohol intake and smoking were collected. Blood samples were taken during each study visit and subsequent laboratory tests included liver biochemistry, serum glucose, serum lipids. Anthropometric measurements included length, weight and waist circumference. Medication data were obtained during the interview and linkage with electronic systems of pharmacies. Last, the metabolic syndrome was defined according to the ATP-III criteria,[21] and was present if at least three of the following components were present: (1) (pre)diabetes, defined as fasting glucose >5.6 mmol/L, anti-diabetic drug use or diagnosis of diabetes by health care professionals; (2) High waist circumference, defined as >102 cm in males or > 88 cm in females; (3) Hypertriglyceridemia, defined as triglycerides ≥1.7 mmol/L and/or lipid-lowering drug use; (4) Hypo-HDL, defined as high density lipoprotein (HDL) < 1.04 mmol/L in male or <1.30 in female and/or lipid-lowering drug use; and (5) hypertension, defined as either a systolic blood pressure ≥ 130 mmHg, diastolic blood pressure ≥ 85 mmHg and/or antihypertensive drug use.

2.6 | Statistical analysis

First, we assessed the associations between liver stiffness at baseline and all-cause mortality using Cox proportional hazard regression. Participants were censored at the end of the follow-up. Associations were explored in the entire cohort and in subgroups with (1) no CHD nor heart failure, (2) heart failure (3) CHD without heart failure at time of the study visit. Liver stiffness has been assessed dichotomously and on a continuous log-transformed scale. Covariates were selected upfront based on findings reported in previous studies and based on clinical relevance.[22,23] In model 1, analyses were adjusted for age and sex, in model 2 also for smoking, alcohol consumption and steatosis, and in model 3 also for the individual components of the metabolic syndrome (hypertension, (pre)diabetes, high waist-circumference, hypo-HDL, hypertriglyceridemia, [model 3]). In sensitivity analysis, we added excluded individuals for viral hepatitis or alcohol abuse and liver stiffness measurements regardless of their IQR. Missing data on covariates used in the models were not imputed since the rate of missing data did not exceed 2%.

To explore how cardiovascular health relates to liver stiffness, we assessed the associations between cardiovascular characteristics and liver stiffness cross-sectionally using linear regression among all included participants, adjusted for the covariates in model 3. Investigated parameters reflected several domains of cardiovascular disease and comprised systolic function (fractional shortening

and qualitative assessment), diastolic function (E/A ratio and qualitative assessment) and markers of systemic venous congestion (right atrium diameter). Among the included participants, missing data on these investigated parameters (the exposure variables), were not imputed.

Analyses were performed in R version 4.0.4 (Foundation for Statistical Computing), using the *survival* package 3.2–10. *p*-values <0.05 were considered statistically significant.

2.7 | Ethics

The Rotterdam Study has been approved by the Medical Ethics Committee of Erasmus MC (registration number MEC 02.1015) and by the Dutch Ministry of Health, Welfare and Sport (Population Screening Act WBO, licence number 1071272-159521-PG). The Rotterdam Study Personal Registration Data collection is filed with the Erasmus MC Data Protection Officer under registration number EMC1712001. The Rotterdam Study has been entered into the Netherlands National Trial Register (NTR; www.trialregister.nl) and into the WHO International Clinical Trials Registry Platform (ICTRP; www.who.int/ictrp/network/primary/en/) under shared catalogue number NTR6831. All participants provided written informed consent to participate in the study and to have their information obtained from treating physicians. All authors had access to the study data and reviewed and approved the final manuscript.

3 | RESULTS

3.1 | General characteristics

Between 2009 and 2014, liver stiffness was part of standard examination and measured in 4.573 participants. After excluding 215 participants for unreliable measurements, 113 for incomplete data on heart failure, 57 for alcohol abuse (≥60 grams per day) and 35 for viral hepatitis, 4.153 participants remained for analysis. The mean age was 67.5 ± 8.4 years, 44.2% was male and metabolic comorbidity was highly prevalent (46.7% metabolic syndrome, 13.8% diabetes). The median liver stiffness was 4.8 kPa [3.9–5.9] and was 8.0 kPa or higher in 6.2% ($n = 256$). Liver stiffness distribution according to the rule of five was as follows: 57% < 5 kPa, 41% between 5 and 10 kPa, 1.7% between 10 and 15 kPa and 0.3% ≥ 15 kPa. Participants with self-reported liver disease ($n = 124$) had higher liver stiffness than those without (6.5 kPa vs. 5.1 kPa). CHD was present in 321 (7.7%) participants and heart failure in 97 (2.3%). Additional characteristics are available in Table 1. During the median follow-up of 6.0 [5.1–7.0] years, 373 deaths were recorded, resulting in an overall mortality rate of 15.1 per 1.000 person-years. Among those with data on cause-specific mortality data, 30% died due to cerebro-cardiovascular causes and 48% due to malignancy. Of note, no liver related mortality was reported.

TABLE 1 Participants' characteristics.

	Study population $n = 4.153$
General	
Age (years)	67.5 (8.4)
Male	1834 (44.2)
Current/former smoking	2759 (66.6)
Comorbidity	
Hypertension	2880 (69.4)
Diabetes	568 (13.8)
Metabolic syndrome	1909 (46.7)
Cardiovascular disease	
CHD −, HF −	3769 (90.8)
CHD +, HF +	34 (0.8)
CHD +, HF −	287 (6.9)
CHD −, HF +	63 (1.5)
Cardiovascular assessment	
Fractional shortening (%)	42.3 (5.0)
Qualitative systolic function	
Normal	3598 (87.1)
Fair	462 (11.2)
Moderate/poor	73 (1.8)
E/A ratio	0.95 (0.29)
Qualitative diastolic dysfunction	
Normal	2662 (65.8)
Impaired relaxation	71 (1.8)
Restrictive pattern	29 (0.7)
Indeterminate	1283 (31.7)
Right atrium diameter (cm)	3.4 (0.5)
Hepatic assessment	
Steatosis	1379 (33.2)
Liver stiffness (kPa)	4.8 [3.9, 5.9]
Liver stiffness ≥8.0 kPa	256 (6.2)

Note: Data is presented as mean (SD), median [P25-P75] or *n* and percentage.

Abbreviations: CHD, coronary heart disease; HF, heart failure.

3.2 | Liver stiffness is associated with mortality in individuals with heart failure but not in those without

In the overall study population, liver stiffness ≥8.0 kPa was associated with excess mortality in fully adjusted models (adjusted hazard ratio[aHR] 1.37, 95%CI 1.00–1.89) Table 2. Interestingly, this association was driven by participants with heart failure (aHR 2.48, 95%CI 1.15–5.35), since it disappeared after excluding participants with heart failure and/or CHD (aHR 1.07, 95%CI 0.70–1.64). Liver stiffness ≥8.0 kPa in participants with CHD alone was not significantly associated with increased mortality risk despite a modest effect (aHR 1.43, 95%CI 0.58–3.49). Importantly, results were consistent when

TABLE 2 Mortality risk for the presence of liver stiffness ≥8.0 kPa.

	Events/*n*	HR	95% CI	*p*
Entire population	373/4153			
Model 1		1.44	1.06–1.96	**0.018**
Model 2		1.45	1.06–1.98	**0.020**
Model 3		1.37	1.00–1.89	0.054
Subgroup analysis				
CHD −, HF −	280/3769			
Model 1		1.18	0.80–1.76	0.405
Model 2		1.19	0.79–1.79	0.394
Model 3		1.07	0.70–1.64	0.755
HF +	42/97			
Model 1		2.09	1.08–4.06	**0.030**
Model 2		2.35	1.13–4.89	**0.023**
Model 3		2.48	1.15–5.35	**0.021**
CHD +, HF −	51/287			
Model 1		1.25	0.53–2.93	0.615
Model 2		1.19	0.50–2.84	0.690
Model 3		1.43	0.58–3.49	0.437

Note: Results were obtained with Cox regression analysis. Model 1 was adjusted for age and sex, model 2 also for smoking, alcohol consumption and steatosis and model 3 also for the individual components of the metabolic syndrome (hypertension, (pre)diabetes, high waist circumference, hypo-HDL, and hypertriglyceridemia). *P*-values indicated in bold reflect statistically significant findings as defined by a *P*-value < 0.05.

Abbreviations: CHD, coronary heart disease; CI, confidence interval; HF, heart failure; HR, hazard rate.

individuals with viral hepatitis or alcohol abuse were not excluded (Table S1). Similar results were obtained when liver stiffness was assessed on a continuous log-transformed scale (aHR 2.20 per log(kPa) 95%CI 1.04–4.67) among participants with heart failure (Table S2). Similarly, among those without heart failure and/or CHD, high liver stiffness categories (5–10 kPa, 10–15 kPa and ≥ 15 kPa) were not associated with excess mortality compared to liver stiffness <5 kPa.

3.3 | Cardiovascular disease and function was associated with liver stiffness

There were clear associations between a range of cardiovascular characteristics and higher liver stiffness in our cohort Table 3. For example, the presence of heart failure with CHD (+1.9 kPa, $p < 0.001$) or without CHD (+1.7 kPa, $p < 0.001$), moderate to poor diastolic dysfunction (+0.7 kPa, $p = 0.004$) and right atrium diameter over 4.5 cm (+0.7 kPa, $p = 0.001$) were associated with significantly higher liver stiffness levels. Interestingly, presence of CHD in the absence of heart failure was not associated with liver stiffness (+0.0 kPa, $p = 0.81$). Similar patterns were observed when liver stiffness was assessed as a categorical variable using 8.0 kPa as cut-off Table S3.

TABLE 3 Associations between cardiovascular characteristics and liver stiffness.

	Beta	95% CI	*p*
Clinical assessment			
CHD −, HF −		Reference	
CHD +, HF +	1.89	1.23–2.56	**<0.001**
CHD +, HF −	0.03	−0.22 to 0.28	0.813
CHD −, HF +	1.73	1.23–2.22	**<0.001**
Systolic dysfunction			
Fractional shortening (%)	−0.02	−0.04 to −0.01	**<0.001**
Qualitative systolic function			
Normal		Reference	
Fair	0.34	0.14–0.54	**0.001**
Moderate/poor	0.69	0.22–1.15	**0.004**
Diastolic dysfunction			
E/A ratio	0.45	0.23–0.66	**<0.001**
Qualitative diastolic dysfunction			
Normal		Reference	
Impaired relaxation	−0.08	−0.56 to 0.40	0.734
Restrictive pattern	0.49	−0.22 to 1.20	0.175
Indeterminate	0.09	−0.05 to 0.22	0.199
Systemic venous congestion			
RA diameter (cm)	0.26	0.12–0.39	**<0.001**
RA diameter > 4.5 cm	0.72	0.30–1.15	**0.001**

Note: Results were obtained with linear regression analysis and adjusted for age, sex, smoking, alcohol consumption, steatosis and the individual components of the metabolic syndrome (hypertension, (pre)diabetes, high waist circumference, hypo-HDL and hypertriglyceridemia). Missing data was <2%, except for E/A ratio (3.0%), qualitative diastolic dysfunction (2.6%) and right atrium diameter (10.5%). *P*-values indicated in bold reflect statistically significant findings as defined by a *P*-value < 0.05.

Abbreviations: CHD, coronary heart disease; CI, confidence interval; HF, heart failure; RA, right atrium.

4 | DISCUSSION

In this study, we showed that increased liver stiffness was a predictor of all-cause mortality in the general population. Interestingly, this was primarily accounted for by individuals with heart failure; no association was observed between liver stiffness and mortality among subjects without a history of heart failure or CHD. Last, the presence of heart failure and signs of heart failure were associated with an increase in liver stiffness.

Liver stiffness assessment has become an invaluable tool for stratifying the risk of hepatic fibrosis among patients with established liver disease. Currently, several groups such as LiverScreen are exploring the use of liver stiffness assessment for early detection of significant liver disease in the general population, which prevalence has been estimated to be 1.0%–2.5% using biomarker-based non-invasive tests.[12,24] In this study, high liver stiffness was associated with increased mortality risk. However, the excess mortality

was explained by individuals with heart failure and was independent of the exclusion of patients with viral hepatitis and/or alcohol abuse. In fact, there was no clinically relevant nor statistically significant excess mortality among individuals with high liver stiffness without heart failure or CHD.

Our study may have important consequences for the ongoing liver stiffness-based screening programs and clinical care pathways that aim to detect advanced (fatty) liver disease, because in our cohort of elderly individuals, the 2% of the population with heart failure accounted for 10% of the cases with liver stiffness ≥8.0 kPa. Similarly, the prevalence of liver stiffness ≥10 kPa was 2.0% for the entire population but dropped to 1.6% after focussing on individuals without heart failure and/or CHD. As a result of a high pre-test probability of cardiovascular disease compared to a relatively low pre-test probability of advanced liver disease, elevated liver stiffness in the general population may often be attributed to cardiovascular disease and not reflect liver fibrosis. Especially, since screening programs and/or clinical care pathways for early detection of advanced (fatty) liver disease typically target individuals with metabolic dysfunction who are both at risk for cardiovascular disease and fatty liver disease.[11,13,25] Our findings highlight an important limitation of liver stiffness as a screening tool in the elderly, and suggest that if the goal is to screen for patients at risk for advanced (fatty) liver disease heart failure as a confounder has to be considered. If this cannot be done, referral to a cardiologist appears to be indicated in patients with elevated liver stiffness without other signs of chronic liver disease. The impact of cardiovascular disease on transient-elastography based screening among younger populations is likely to be different than what we demonstrated in this elderly population. Results of ongoing screening studies like LiverScreen are therefore eagerly awaited.

Our study confirms previous reports on higher liver stiffness among patients with cardiovascular disease.[26,27] Although this may partially be attributed to the presence of liver fibrosis due to co-existing fatty liver disease, it is more likely that liver stiffness reflects venous congestion in this specific subgroup for several reasons. First, we have excluded important causes for fibrosis, such as alcohol abuse and viral hepatitis. Second, we addressed several risk factors for fibrosis in multivariable models, such as steatosis and diabetes.[28] Third, there is emerging evidence on the impact of venous congestion on liver stiffness, which in specific subgroups may exceed the impact of fibrogenesis.[3,9] This indicates that liver stiffness may have prognostic value, not only among those with decompensated heart failure,[9,10] but also among non-hospitalized heart failure patients. Now that liver stiffness measurements are becoming readily available by the adoption of elastography on regular ultrasound devices, it would be interesting to see in future studies whether the adoption of liver stiffness in risk prediction models for patients with heart failure leads to improved accuracy and has clinical utility compared to currently available algorithms.

There is plenty of experience with elastography in the liver. However, this technique may also be applied to other structures. Recently, it has even been successfully used to assess the stiffness of inferior vena cava (IVC) in an experimental setting.[29] Using the stiffness of IVC as assessed by transient elastography, one bypasses the impact of fibrosis and hepatic inflammation. The results may then be more specific for venous congestion. However, additional research is required on whether the application of elastography for the IVC is reliable and has value over liver stiffness in cardiovascular disease.

4.1 | Limitations

Although this is one of the first studies assessing the impact of cardiovascular disease on liver stiffness in the general population and the potential consequences for future screening strategies, the following limitations should be considered.

First, this cohort comprised predominantly elderly participants of European ancestry and further research is warranted focusing on multi-ethnic and younger populations. Especially the impact of cardiovascular disease on liver stiffness on a population level might be different from this cohort. Second, this study had a limited median follow-up duration of 6.0 years. Nonetheless, our analyses comprised 24.650 person-years of follow-up given the large sample size. However, due to the slowly progressive nature of liver disease and under the assumption that patients with severe liver disease are less likely to attend our study visit, we may have underestimated the mortality risk for high liver stiffness. Third, cause-specific data was only complete until 1st of January 2015 whereas data on vital status was complete until May 2018. As a result, cause of death was only known in 35% of the participants, hampering additional analysis for cause-specific mortality. Fourth, excluding individuals with alcohol abuse and viral hepatitis could have attributed to liver stiffness not being a risk factor in individuals without heart failure. However, not excluding these individuals in sensitivity analysis did not increase mortality risk in the population without heart failure. Fifth, due to the cross-sectional design of the analysis on the associations of (signs of) cardiovascular disease and liver stiffness, we could not investigate the direction of these associations. However, physiological mechanisms support that cardiovascular disease by venous congestion affects liver stiffness.

5 | CONCLUSION

In this large population-based study, we demonstrated that high liver stiffness was not associated with excess mortality in an elderly population without heart failure and/or CHD. Whereas, among those with heart failure, high liver stiffness was associated with mortality. Furthermore, a range of cardiovascular characteristics and heart failure were associated with an increase in liver stiffness. These findings highlight important limitations of elastography-based (targeted) screening for advanced liver disease in elderly populations with metabolic dysfunction and suggest that cardiovascular disease may need to be considered as cause of high liver stiffness in a population-based screening setting.

AUTHOR CONTRIBUTIONS

Collection of data: LvK, MJS, FZ; Study design, data analysis, writing of the manuscript: LvK, MJS, RdK; Critical review of the manuscript, approval of final version and approval of submission: All authors.

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CONFLICT OF INTEREST STATEMENT

MJS has received speaker's fees and research support from Fujirebio and received grants from Gilead and Fujirebio. RdK is a speaker for Echosens, consultant for AbbVie and received grants from Abbvie, Gilead and Janssen. The other authors had no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data can be obtained upon request. Requests should be directed toward the management team of the Rotterdam Study (secretariat.epi@erasmusmc.nl), which has a protocol for approving data requests. Because of restrictions based on privacy regulations and informed consent of the participants, data cannot be made freely available in a public repository.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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