Clinical Biochemistry 123 (2024) 110688

Contents lists available at ScienceDirect

Clinical Biochemistry

journal homepage: www.elsevier.com/locate/clinbiochem

# The liver-heart axis in patients with severe obesity: The association between liver fibrosis and chronic myocardial injury may be explained by shared risk factors of cardiovascular disease

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ARTICLE INFO

*Keywords:*
Severe obesity
Liver fibrosis
Cardiac fibrosis
Enhanced Liver Fibrosis test
Cardiac troponin
Myocardial injury
NT-proBNP

ABSTRACT

*Background:* Severe obesity is associated with increased risk of non-alcoholic fatty liver disease and cardiovascular disease. We hypothesized that liver fibrosis as quantified by the Enhanced Liver Fibrosis (ELF) test would be predictive of myocardial injury and fibrosis, expressed by higher concentrations of cardiac troponin T and I measured by high-sensitivity assays (hs-cTnT and hs-cTnI, respectively).

*Material and methods:* We performed cross-sectional analyses of baseline data from 136 patients (mean age 45 years, 38 % male) with severe obesity participating in the non-randomized clinical trial *Prevention of Coronary Heart Disease in Morbidly Obese* Patients (ClinicalTrials.gov NCT00626964). Associations between ELF scores, hs-cTnT, and hs-cTnI concentrations were assessed using linear regression analysis.

*Results:* ELF scores were associated with hs-cTnT in the unadjusted model (B 0.381, 95 % Confidence Interval [CI] 0.247, 0.514), but the association was attenuated upon adjustment for potential confounders (B −0.031, 95 % CI −0.155, 0.093). Similarly, for hs-cTnI, an observed association with ELF scores in the unadjusted model was attenuated upon adjustment for potential confounders ((B 0.432, 95 % CI 0.179, 0.685) and (B 0.069, 95 % CI −0.230, 0.367), respectively). Age, sex, hypertension, and estimated glomerular filtration rate were amongst the shared predictors of ELF score, hs-cTnT, and hs-cTnI that provided the univariable models with the highest R-squared and lowest Akaike Information Criterion values.

*Conclusions:* Contrary to our hypothesis, ELF score did not predict myocardial injury and fibrosis, but we rather demonstrated an association between liver fibrosis and myocardial injury and fibrosis may be explained by shared risk factors of cardiovascular disease.

## 1. Introduction

Cardiometabolic risk factors such as adiposity, insulin resistance, dysglycemia, dyslipidemia and hypertension frequently cluster and are major risk factors for diseases such as type 2 diabetes mellitus (T2DM), non-alcoholic fatty liver disease (NAFLD) and cardiovascular disease (CVD) [1]. The impact of these risk factors is amplified by lifestyle (physical inactivity, smoking, and diet) as well as by genetics, sex, age and systemic inflammation; the latter potentially representing a common pathophysiological pathway [1,2]. With the relentless rise in

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https://doi.org/10.1016/j.clinbiochem.2023.110688
Received 6 July 2023; Received in revised form 13 November 2023; Accepted 20 November 2023
Available online 22 November 2023

overweight and obesity worldwide, NAFLD has become one of the most common forms of chronic liver disease [3,4]. Patients with NAFLD may develop complications such as liver fibrosis and cirrhosis, though the leading cause of mortality among these patients is CVD [5,6].

The Enhanced Liver Fibrosis (ELF) test is a non-invasive blood test that measures three direct but organ unspecific markers of fibrosis: hyaluronic acid (HA), procollagen III amino-terminal peptide (PIIINP), and tissue inhibitor of matrix metalloproteinase 1 (TIMP-1). In patients with liver disease, the ELF test, in conjunction with other laboratory and clinical findings, can be used to assess the risk of progression to cirrhosis and liver-related events [7,8]. Though the ELF test is used for the assessment of liver fibrosis, its constituents have shown to associate with disease in other organs and predict mortality, such as in systemic sclerosis [9,10] and in heart failure (HF) [11–13].

Cardiac troponins are sensitive and specific biomarkers of acute and chronic myocardial injury [14–16]. Whereas cardiac troponins are universally used for diagnosing acute myocardial infarction, chronic myocardial injury, expressed as stable, mild increase in cardiac troponin concentrations, has been associated with markedly increased risk of HF and cardiovascular death [15,17]. Moreover, cardiac troponins have been shown to associate with replacement and interstitial cardiac fibrosis assessed by cardiac magnetic resonance, using measurements of late gadolinium enhancement and increased myocardial extracellular volume, respectively [18–20]. Pathophysiologically, it is therefore conceivable that chronic myocardial injury, reflected in chronic release of cardiac troponins, contributes to the development of myocardial fibrosis, an important intermediary in the evolution of cardiac impairment. Accordingly, chronic elevations in cardiac troponins may be considered a surrogate marker for cardiac fibrosis [18–22].

Another cardiac biomarker that has been shown to associate with interstitial cardiac fibrosis is N-terminal pro-B-type natriuretic peptide (NT-proBNP) [23,24]. The biologically active hormone B-type natriuretic peptide (BNP) is upregulated to protect the heart during myocardial strain and hemodynamic stress, and BNP and the amino terminal fragment of its prohormone, NT-proBNP, are released into circulation upon cardiomyocyte stretch [25,26]. Clinically, NT-proBNP is used for the diagnostic and prognostic assessment of patients with suspected HF [27,28]. Moreover, BNP and NT-proBNP are also strongly associated with risk of HF and CVD death [29,30]. Of note, body mass index (BMI) inversely correlates with BNP and NT-proBNP [31,32].

The heart and the liver display multifaceted interactions [2], and in clinical practice it is common to observe heart diseases affecting the liver and vice-versa [33]. As prior studies have suggested a link between NAFLD and the risk of HF [1,11,12], we hypothesized that liver fibrosis as quantified by the ELF test would be predictive of myocardial injury and fibrosis, expressed by higher concentrations of cardiac troponin T and I measured by high-sensitivity assays (hs-cTnT and hs-cTnI, respectively). To enhance our understanding of underlying mechanisms, we furthermore sought to test the alternative hypothesis that a potential association between liver fibrosis and cardiac injury and fibrosis could be explained by shared risk factors. We additionally assessed potential associations between ELF scores and NT-proBNP concentrations.

## 2. Material and methods

### 2.1. Study design and participants

This is a cross-sectional study using baseline data from a controlled clinical trial including patients with severe obesity designed to compare the 1-year effects on aortic stiffness of Roux-en-Y Gastric Bypass (RYGB) with intensive lifestyle intervention. The study was conducted at Vestfold Hospital Trust in Norway, and patients were assigned to a comprehensive lifestyle modification program at the Clinic of Medicine and Rehabilitation or referred to bariatric surgery at the Department of Endocrinology, Obesity and Nutrition, between February 2008 and February 2011. Inclusion criteria were BMI $\geq$ 40 kg/m$^2$, or $\geq$ 35 kg/m$^2$ accompanied with at least one obesity-related comorbidity. The study design, the primary outcome (aortic stiffness) and data on weight-loss and changes in metabolic biomarkers have previously been published [34–37]. Patients with one of the following conditions or diseases were excluded: unstable angina, cardiac arrhythmias, uncompensated HF, cardiac pacemakers, intra-cardiac devices, end-stage renal disease, known bleeding disturbances, serious psychiatric disorders, serious eating disorders, or myocardial infarction or a cerebrovascular event (within the past 6 months).

### 2.2. Variables and data measurement

The number of participants eligible for inclusion in the original study was 239. Of these, 39 patients declined to participate, leaving 200 patients to be enrolled in the study. Biomarkers relevant for the current analysis were available from 136 patients (please find a schematic overview of patient inclusion for the current study, Fig. 1, in the Supplementary Material). Detailed descriptions of data sources and measurements have previously been published [34–37]. The participants underwent medical examinations which included measurement of body weight and height. Blood samples were collected after an overnight fast and patients were advised to abstain from medication and smoking prior to the tests on the day of examination.

The diagnosis of T2DM was defined as either a prior history of T2DM or a fasting serum glucose level $\geq$ 7.0 mmol/L [38]. The Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) was calculated as [fasting serum glucose (mmol/L) x fasting serum insulin (pmol/L)]/135 [39]. Dyslipidemia was defined as use of lipid lowering medication or elevated low-density lipoprotein (LDL) cholesterol, or raised triglycerides and lowered high-density lipoprotein (HDL) cholesterol; with cut-offs LDL $\geq$ 3.0 mmol/L for men and women, triglycerides $\geq$ 1.7 mmol/L for men and women, or HDL cholesterol $<$ 1.0 mmol/L for men or $<$ 1.3 mmol/L for women [40,41]. The patients' smoking status was self-reported and defined as current smoking or not.

### 2.3. Biochemical analyses

Standard laboratory analyses were performed at the Central Laboratory, Vestfold Hospital Trust, which is accredited according to NS-EN ISO 15189 and serves as the main analytical facility in the hospital. In brief, analyses of serum glucose, creatinine and blood lipids were performed using dry reagent slide technology on the Vitros FS 5.1 (Ortho-Clinical Diagnostics, NY, USA). LDL cholesterol concentrations were estimated using the Friedewald equation and estimated glomerular filtration rate (eGFR) was calculated by the applicable CKD-EPI equation for a creatinine method traceable to isotope-dilution mass spectrometry. Hemoglobin A1c (HbA1c) was analyzed using high performance liquid chromatography on Tosoh HLC-723 G7 (Tosoh Corporation, Tokyo, Japan) and insulin was analyzed using an immunoassay from Linco Research Inc. (St. Charles, MO) [35,42]. Measurements of alanine aminotransferase (ALT) was performed on Cobas 8000, module c702 (Roche Diagnostics, Basel, Switzerland).

Serum samples were stored at −80° Celsius pending analysis of the ELF$^{TM}$ test [7,8]. As mentioned above, the ELF$^{TM}$ test encompasses three different biomarkers, HA, PIIINP and TIMP-1, that were measured on an ADVIA Centaur® XP Immunoassay System (Siemens Healthineers, Erlangen, Germany). The HA has an analytical variation ($CV_A$) $<$ 8 % (concentration range 11–966 ng/mL), PIIINP has a $CV_A$ $<$ 7 % (concentration range 1.9–124 ng/mL) and TIMP-1 has a $CV_A$ of $\leq$ 6 % (concentration range 73–1050 ng/mL). The ELF score was automatically computed using the ADVIA Centaur® XP Immunoassay System. A higher concentration of individual biomarkers entails a higher ELF score, which indicates a greater likelihood of more severe fibrosis. The ELF score is calculated by a specific formula: $2.278 + 0.851 \times \ln(HA) + 0.751 \times \ln(PIIINP) + 0.394 \times \ln(TIMP\text{-}1)$, all expressed in ng/mL [43]. An ELF

score of 7.7 or lower indicates no/mild fibrosis, whereas ELF scores between 7.7 and 9.8 indicate moderate fibrosis, and ELF scores of 9.8 and above indicate severe fibrosis [7,44].

Measurements of hs-cTnT, NT-proBNP, and C-reactive protein (CRP) were performed on biobanked samples (stored at −80° Celsius) using Cobas 602 (Roche Diagnostics, Rotkreuz, Switzerland), while hs-cTnI was analyzed on an ADVIA Centaur® XPT Immunoassay System (Siemens Healthineers, Erlangen, Germany). The hs-cTnT assay reported quantitative results down to 3 ng/L (limit of blank) and had a 99th percentile of 9 ng/L for females and 16 ng/L for males [45]. The hs-cTnI assay reported quantitative concentrations down to 2.5 ng/L (limit of quantification), and had a 99th percentile of 39.6 ng/L for females and 58.0 ng/L for males [45]. In patients with suspected acute coronary syndrome, the 99th percentile is the clinical decisional level of hs-cTnT and hs-cTnI with a characteristic rise and/or fall of cardiac troponin levels [46,47]. The NT-proBNP assay reported quantitative concentrations down to 5 ng/L (limit of detection) and had a 97.5th percentile of 254 ng/L for females and 169 ng/L for males [48]. In patients with suspected HF, elevated concentrations of NT-proBNP support a diagnosis of HF, whereas NT-proBNP concentrations below 125 ng/L make a diagnosis of HF unlikely [27]. Values below the lowest reported concentrations of hs-cTnT, hs-cTnI, and NT-proBNP were assigned a value corresponding to 50 %, i.e. 1.5 ng/L, 1.25 ng/L, and 2.5 ng/L respectively.

### 2.4. Statistical analyses

Baseline data were stratified according to tertiles of ELF scores. Values are reported as means [standard deviation (SD)] or medians [interquartile range (IQR)] for continuous data and as number, n (percentage) for categorical data. Between-group comparisons of continuous data were performed using one-way ANOVA for normally distributed data and Kruskal-Wallis test for continuous variables with skewed distribution. Between-group comparisons for categorical data were performed using the Chi-Square or Fisher's exact test, as appropriate.

Correlations between ELF score, hs-cTnT, hs-cTnI, and NT-proBNP were assessed using Spearman's rank correlation. We furthermore used linear and logistic regression analyses to assess associations between ELF score and the outcome variables hs-cTnT, hs-cTnI, and NT-proBNP. Due to non-normal distributions of hs-cTnT, hs-cTnI, and NT-proBNP concentrations, their concentrations were transformed with the natural logarithm prior to linear regression analyses. In the logistic regression analyses, we dichotomized hs-cTnT, hs-cTnI, and NT-proBNP at their respective median concentrations.

To further assess predictors of ELF score, hs-cTnT, hs-cTnI, and NT-proBNP, we performed univariable linear regression analyses each with ELF score, hs-cTnT, hs-cTnI, and NT-proBNP as respective outcome variables. From the linear regression models, we reported coefficients (unstandardized betas, *B*), 95 % confidence intervals, and p-values. The level of statistical significance was defined as $p < 0.05$ (two-sided). The univariable models were furthermore evaluated using Akaike Information Criterion (AIC) and R-squared ($R^2$): AIC is a method to compare the relative quality of different models for a given dataset, to determine which model best fits the data; the model with the lowest AIC value, is the best model to fit the data [49,50]. R-squared is a measure of the proportion of the variance for a dependent variable that is explained by the independent variable [51], such that the higher the R-squared, the greater the proportion of the variance of the dependent variable is explained, and the better the model. We thus considered the best univariable models as the models with the lowest AIC values and highest R-squared values. All statistical analyses were conducted using Stata Statistical Software: Releases 16 and 17. (College Station, TX: StataCorp LLC.).

### 2.5. Ethics

The study was registered at Clinical Trials.gov (NCT00626964) and conducted according to the principles in the Declaration of Helsinki. The protocol was approved by the Regional Committees for Medical and Health Research Ethics in Norway (REK S-05175), and written informed consent was provided by all the participants.

## 3. Results

### 3.1. Baseline characteristics

The mean age of the 136 participants included in the current analysis was 44.9 years (SD 10.3), and 38.2 % were male. The mean ELF score was 8.5 (SD 0.8), and the median concentrations of hs-cTnT and hs-cTnI were 4.7 (25-75th percentile 3.3 to 7.7) ng/L and 2.9 (25-75th percentile 1.0 to 6.7) ng/L, respectively. The median concentration of NT-proBNP was 31.1 (25-75th percentile 17.1 to 65.5) ng/L. Clinical baseline characteristics stratified according to tertiles of ELF scores are shown in Table 1. Patients with higher ELF scores demonstrated higher concentrations of hs-cTnT and hs-cTnI. Furthermore, patients with higher ELF scores tended to be older, male, more frequently have hypertension and T2DM, have greater waist circumference, and lower kidney function, but lower concentrations of CRP.

### 3.2. Cross-sectional association between ELF score, hs-cTnT, hs-cTnI, and NT-proBNP

ELF score correlated significantly with both hs-cTnT ($r = 0.498$; $p < 0.001$) and hs-cTnI ($r = 0.367$; $p < 0.001$) concentrations, but not with NT-proBNP concentrations ($r = 0.020$; $p = 0.814$). In the unadjusted linear regression model, ELF score was associated with hs-cTnT concentrations and hs-cTnI concentrations; B 0.381 (95 % confidence interval [CI] 0.247 to 0.514) and 0.432 (95 % CI 0.179 to 0.685), respectively. Upon adjustment for sex and age, the associations were attenuated and were not statistically significant in the fully adjusted models; B −0.031 (95 % CI −0.155 to 0.093) and B 0.069 (95 % CI −0.230 to 0.367), respectively (Tables 2A and 2B). The logistic regression analyses portrayed similar results; the ELF score was associated with hs-cTnT and hs-cTnI concentrations above the respective median concentrations of hs-cTnT and hs-cTnI in the unadjusted models (Odds Ratio [OR] 3.63 (95 % CI 2.04 to 6.46) for supramedian hs-cTnT concentrations, and OR 2.60 (95 % CI 1.53 to 4.40) for supramedian hs-cTnI concentrations), yet, no significant associations were observed in the fully adjusted logistic regression models; OR 0.64 (95 % CI 0.25 to 1.64) and OR 1.19 (95 % CI 0.60 to 2.36), respectively (Tables 3A and 3B).

ELF scores did not associate with NT-proBNP concentrations in the linear nor logistic regression models, neither in the unadjusted models or adjusted models; B −0.196 (95 % CI −0.491 to 0.098) in the fully adjusted linear regression model, and OR 0.551 (95 % CI 0.294 to 1.032) in the fully adjusted logistic regression model (Tables 2C and 3C).

### 3.3. Assessing predictors of ELF score, hs-cTnT, hs-cTnI, and NT-proBNP

We assessed which exposure variables most accurately predicted each of the outcome variables; ELF score, hs-cTnT and hs-cTnI, by comparing R-squared and AIC values from univariable analyses of each given outcome variable (Table 4). For hs-cTnT, the predictors age, sex and eGFR (all $p < 0.001$) provided the highest R-squared and lowest AIC values in the univariable analyses (besides hs-cTnI which is closely related to hs-cTnT as they are both markers of myocardial injury). eGFR inversely associated with hs-cTnT concentrations. For hs-cTnI, the predictor sex provided the highest R-squared and lowest AIC values (besides hs-cTnT), followed by age and ELF score with the subsequently highest R-squared values and hypertension with the subsequently lowest AIC value (all $p < 0.010$). With ELF score as the dependent variable, age, hs-

**Table 1**
Baseline characteristics stratified according to tertiles of Enhanced Liver Fibrosis scores.

| Variable | All participants | ELF score < 8.2 | ELF score ≥ 8.2 to ≤ 8.9 | ELF score > 8.9 | P-value |
|---|---|---|---|---|---|
| N | 136 | 46 | 45 | 45 | |
| Enhanced Liver Fibrosis (ELF) score | 8.5 (0.8) | 7.7 (0.3) | 8.5 (0.2) | 9.4 (0.5) | NA‡ |
| High-sensitivity cardiac Troponin T, ng/L | 4.7 (3.3, 7.7) | 3.5 (3.0, 5.3) | 4.6 (3.2, 6.8) | 8.3 (5.0, 12.7) | <0.0001 |
| High-sensitivity cardiac Troponin I, ng/L* | 2.9 (1.0, 6.7) | 1.0 (1.0, 4.1) | 2.8 (1.0, 5.3) | 5.2 (1.0, 8.9) | 0.003 |
| NT-proBNP†, ng/L | 31.1 (17.1, 65.5) | 31.9 (19.5, 61.7) | 24.5 (11.9, 47.0) | 38.9 (19.6, 154.4) | 0.081 |
| Male sex, n (%) | 52 (38.2) | 9 (19.5) | 16 (35.6) | 27 (60) | <0.0001 |
| Age, years | 44.9 (10.3) | 38.0 (7.2) | 45.5 (9.9) | 51.2 (9.1) | <0.0001 |
| White race, n (%) | 133 (97.8) | 46 (100) | 42 (93.3) | 45 (100) | 0.82 |
| Ischemic heart disease, n (%) | 14 (10.3) | 2 (4.4) | 2 (4.4) | 10 (22.2) | 0.24 |
| Hypertension, n (%)* | 99 (73.3) | 25 (54.4) | 32 (72.7) | 42 (93.3) | <0.0001 |
| Dyslipidemia, n (%) | 118 (86.8) | 38 (82.6) | 41 (91.1) | 39 (86.7) | 0.49 |
| T2DM§, n (%) | 38 (27.9) | 6 (13.0) | 10 (22.2) | 22(48.9) | <0.0001 |
| Current smoker, n (%) | 19 (14) | 9 (19.6) | 7 (15.6) | 3 (6.7) | 0.19 |
| Weight, kg | 131.5 (22.5) | 130.8 (17.9) | 127.4 (20.9) | 136.2 (27.6) | 0.18 |
| Body mass index, kg/m$^2$ | 43.8 (5.8) | 44.1 (4.8) | 43.4 (5.1) | 44.0 (7.2) | 0.85 |
| Fat mass, kg* | 61.9 (13.6) | 64.0 (11.6) | 60.0 (12.7) | 61.6 (16.2) | 0.38 |
| Waist circumference, cm | 129.8 (13.1) | 127.8 (11.9) | 127.7 (13.5) | 133.9 (13.3) | 0.036 |
| Skeletal muscle mass, kg* | 38.9 (7.9) | 37.5 (6.3) | 37.8 (7.6) | 41.4 (9.1) | 0.035 |
| Systolic blood pressure, mmHg | 142 (20) | 137 (20) | 143 (19) | 148 (19) | 0.042 |
| Diastolic blood pressure, mmHg | 80 (12) | 79 (12) | 80 (9) | 81 (13) | 0.73 |
| Pulse Pressure, mmHg* | 62 (19) | 56 (16) | 63 (20) | 67 (19) | 0.024 |
| Mean arterial pressure, mmHg | 101 (12) | 99 (14) | 101 (10) | 103 (13) | 0.19 |
| Carotid-femoral pulse wave velocity, m/s | 8.7 (1.9) | 7.9 (1.6) | 8.4 (1.2) | 9.8 (2.1) | <0.0001 |
| Heart rate, beats/min* | 77 (13) | 73 (12) | 80 (15) | 78 (12) | 0.045 |
| Glucose, mmol/L | 5.4 (4.9, 6.5) | 5.1 (4.6, 5.6) | 5.3 (4.9, 5.8) | 6.1 (5.3, 7.4) | <0.0001 |
| HbA1c, mmol/mol | 39.5 (34, 44) | 37 (32, 40) | 39 (33, 42) | 43 (39, 60) | <0.0001 |
| Insulin, pmol/L* | 88 (55, 132) | 79 (55, 124) | 86 (53, 112) | 101 (61, 154) | 0.91 |
| HOMA-IR* | 3.7 (2.1, 6.3) | 3.1 (2.0, 5.4) | 3.4 (2.0, 5.4) | 4.5 (2.7, 8.2) | 0.037 |
| ALAT, U/L | 27 (19, 38) | 22 (15, 28) | 26 (20, 37) | 35 (24, 44) | <0.0001 |
| Total cholesterol, mmol/L | 5.0 (1.0) | 5.0 (1.0) | 5.2 (0.9) | 4.8 (1.0) | 0.12 |
| Low-density lipoprotein cholesterol, mmol/L* | 3.1 (0.9) | 3.1 (0.9) | 3.2 (1.0) | 2.9 (0.9) | 0.32 |
| High-density lipoprotein cholesterol, mmol/L | 1.2 (0.3) | 1.2 (0.3) | 1.2 (0.2) | 1.2 (0.4) | 0.78 |
| Triglycerides, mmol/L | 1.5 (1.0, 2.0) | 1.3 (1.0, 2.1) | 1.7 (1.2, 2.0) | 1.4 (1.1, 2.0) | 0.23 |
| Estimated glomerular filtration rate (CKD-EPI ||), ml/min/1.73 m2 | 104 (92, 111) | 108.3 (102.4, 114.6) | 103.7 (96.3, 110.5) | 95.6 (77.9, 104.9) | <0.0001 |
| C-reactive protein, mg/L | 5.8 (3.0, 9.5) | 8.7 (4.6, 11.2) | 4.7 (2.5, 8.4) | 4.4 (3.1, 7.8) | 0.014 |

Categorical variables are reported as number, n (%) (using Pearson's chi-squared test). Normally distributed continuous variables are reported as mean (standard deviation) (using one-way ANOVA), whereas continuous variables with a skewed distribution are reported as median (interquartile range) (using Kruskal-Wallis test).
*For high-sensitivity cardiac troponin I n = 133; Hypertension n = 135; Fat mass n = 135; Skeletal muscle mass n = 135; Pulse Pressure n = 134; Heart rate n = 132; Insulin n = 134; HOMA-IR n = 133; Low-density lipoprotein cholesterol n = 135.
† NT-proBNP = N-terminal pro-B type natriuretic peptide ‡ NA = Not applicable §T2DM = Type 2 diabetes mellitus; CKD-EPI || = Chronic Kidney Disease Epidemiology Collaboration.
Additional description of the analysis is reported in the Supplemental Material, page 4.

cTnT, and sex were the variables that most accurately predicted ELF score, all $p < 0.001$. Common for ELF score, hs-cTnT and hs-cTnI as outcome variables, was that age and sex were amongst the predictors providing the best models (low AIC value and high R-squared) for hs-cTnT, hs-cTnI and ELF score, followed by other risk factors of CVD.

We also assessed which exposure variables that would predict NT-proBNP concentrations in univariable linear regression analyses: besides hs-cTnT and hs-cTnI, lower eGFR and higher age were the only predictors of NT-proBNP concentrations in the univariable models ($p < 0.05$) and provided the highest R-squared and lowest AIC values (see Supplemental Material, Table S1).

## 4. Discussion

In the current study, we hypothesized that liver fibrosis as quantified by the ELF test would be predictive of chronic myocardial injury and fibrosis, expressed by hs-cTnT and hs-cTnI concentrations. Contrary to our expectations, we observed that the significant univariable associations between the ELF scores and hs-cTnT and hs-cTnI concentrations were attenuated and no longer significant after adjustment for potential confounders. This might suggest that the association could be explained by shared risk factors for hepatic and cardiac injury and fibrosis, rather than an independent and potentially causal pathway.

### 4.1. The liver-heart axis

Cardiac disease and liver disease are prevalent causes of mortality and morbidity and commonly coexist. Cardiac dysfunction, and congestive HF in particular, are often associated with hepatic injury reflected in elevated concentrations of liver transaminases, and impaired liver synthetic function reflected in increased international normalized ratio (INR) and decreased albumin levels. Conversely, the liver processes blood lipids, produces coagulation factors and inflammatory mediators, and hepatic disease may promote and aggravate cardiac dysfunction. Taken together, these observations may suggest an interplay and pathophysiological communication between the heart and the liver. For instance, recent experimental data in mice suggested that the coagulation factor XI, which is exclusively synthesized in the liver, may play a protective role against pathological remodeling of the heart [52]. Still, the knowledge concerning how these organs may

**Table 2A**
Cross-sectional association between the Enhanced Liver Fibrosis (ELF) score and the outcome high-sensitivity cardiac troponin T concentrations, using linear regression.

| | ELF score Beta Coefficient (95 % Confidence Interval) | | | | | |
|---|---|---|---|---|---|---|
| | **Model 1** | **p-value** | **Model 2** | **p-value** | **Model 3** | **p-value** |
| ELF score | 0.381 (0.247, 0.514) | <0.001 | 0.041 (-0.096, 0.179) | 0.551 | −0.031 (-0.155, 0.093) | 0.623 |

Model 1 unadjusted,
Model 2 adjusted for sex and age,
Model 3 adjusted for model 2, body mass index, dyslipidemia, T2DM, hypertension, smoking and estimated Glomerular Filtration Rate.
Additional description of the analysis is reported in the Supplemental Material, page 4.

**Table 2B**
Cross-sectional association between the Enhanced Liver Fibrosis (ELF) score and the outcome high-sensitivity cardiac troponin I concentrations, using linear regression.

| | ELF score Beta Coefficient (95 % Confidence Interval) | | | | | |
|---|---|---|---|---|---|---|
| | **Model 1** | **p-value** | **Model 2** | **p-value** | **Model 3** | **p-value** |
| ELF score | 0.432 (0.179, 0.685) | 0.001 | 0.060 (-0.234, 0.355) | 0.686 | 0.069 (-0.230, 0.367) | 0.649 |

Model 1 unadjusted,
Model 2 adjusted for sex and age,
Model 3 adjusted for model 2, body mass index, dyslipidemia, T2DM, hypertension, smoking and estimated Glomerular Filtration Rate.
Additional description of the analysis is reported in the Supplemental Material, page 4.

**Table 2C**
Cross-sectional association between the Enhanced Liver Fibrosis (ELF) score and the outcome N-terminal pro-B type natriuretic peptide (NT-proBNP) concentrations, using linear regression.

| | ELF score Beta Coefficient (95 % Confidence Interval) | | | | | |
|---|---|---|---|---|---|---|
| | **Model 1** | **p-value** | **Model 2** | **p-value** | **Model 3** | **p-value** |
| ELF score | 0.098 (-0.144, 0.341) | 0.424 | −0.028 (-0.325, 0.270) | 0.854 | −0.196 (-0.491, 0.098) | 0.190 |

Model 1 unadjusted,
Model 2 adjusted for sex and age,
Model 3 adjusted for model 2, body mass index, dyslipidemia, T2DM, hypertension, smoking and estimated Glomerular Filtration Rate.
Additional description of the analysis is reported in the Supplemental Material, page 4.

**Table 3A**
Cross-sectional association between the Enhanced Liver Fibrosis (ELF) score and the outcome supramedian high-sensitivity cardiac troponin T (hs-cTnT) concentrations, using logistic regression.

| | Odds Ratio (95 % Confidence Interval) | | | | | |
|---|---|---|---|---|---|---|
| | **Model 1** | **p-value** | **Model 2** | **p-value** | **Model 3** | **p-value** |
| ELF score | 3.63 (2.04, 6.46) | <0.001 | 0.80 (0.33, 1.94) | 0.618 | 0.64 (0.25, 1.64) | 0.354 |

Model 1 unadjusted,
Model 2 adjusted for sex and age,
Model 3 adjusted for model 2, body mass index, dyslipidemia, T2DM, hypertension, smoking and estimated Glomerular Filtration Rate.

**Table 3B**
Cross-sectional association between the Enhanced Liver Fibrosis (ELF) score and the outcome supramedian high-sensitivity cardiac troponin I (hs-cTnI) concentrations, using logistic regression.

| | Odds Ratio (95 % Confidence Interval) | | | | | |
|---|---|---|---|---|---|---|
| | **Model 1** | **p-value** | **Model 2** | **p-value** | **Model 3** | **p-value** |
| ELF score | 2.60 (1.53, 4.40) | <0.001 | 1.25 (0.65, 2.40) | 0.509 | 1.19 (0.60, 2.36) | 0.612 |

Model 1 unadjusted,
Model 2 adjusted for sex and age,
Model 3 adjusted for model 2, body mass index, dyslipidemia, T2DM, hypertension, smoking and estimated Glomerular Filtration Rate.
Additional description of the analysis is reported in the Supplemental Material, page 4.

communicate remains incomplete.

### *4.2. Obesity as a risk factor for liver disease and HF*

In accordance with the increasing prevalence of obesity worldwide during the past decades, the incidence of obesity-related co-morbidities such as T2DM, HF with preserved ejection fraction (HFpEF) and NAFLD has surged. Still, whether the presence of NAFLD is associated with subsequent development of HF and in particular HFpEF has not been well established. In a recent study, patients with NAFLD were found to be at increased risk of incident HF, with a higher risk of developing HFpEF than HF with reduced ejection fraction. The authors concluded that the findings suggest an epidemiological link between NAFLD and HF beyond shared risk factors [53]. Potential mediators of this

**Table 3C**
Cross-sectional association between the Enhanced Liver Fibrosis (ELF) score and the outcome supramedian N-terminal pro-B type natriuretic peptide (NT-proBNP) concentrations, using logistic regression.

| | Odds Ratio (95 % Confidence Interval) | | | | | |
|---|---|---|---|---|---|---|
| | **Model 1** | **p-value** | **Model 2** | **p-value** | **Model 3** | **p-value** |
| ELF score | 0.887 (0.574, 1.371) | 0.590 | 0.702 (0.401, 1.231) | 0.217 | 0.551 (0.294, 1.032) | 0.063 |

Model 1 unadjusted,
Model 2 adjusted for sex and age,
Model 3 adjusted for model 2, body mass index, dyslipidemia, T2DM, hypertension, smoking and estimated Glomerular Filtration Rate.
Additional description of the analysis is reported in the Supplemental Material, page 5.

**Table 4**
Cross-sectional univariable associations with high-sensitivity cardiac troponin T, high-sensitivity cardiac troponin I, and Enhanced Liver Fibrosis (ELF) score as respective outcome variables.

| **Predictor** | **hs-cTnT Beta Coefficient (95 % CI)** | **p-value** | **$R^2$** | **AIC** | **hs-cTnI Beta Coefficient (95 % CI)** | **p-value** | **$R^2$** | **AIC** | **ELF score Beta Coefficient (95 % CI)** | **p-value** | **$R^2$** | **AIC** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Sex | 0.727 (0.525, 0.928) | <0.001 | 0.275 | 238.313 | 0.933 (0.547, 1.319) | <0.001 | 0.149 | 403.217 | 0.633 (0.383, 0.883) | <0.001 | 0.157 | 297.241 |
| Age | 0.035 (0.026, 0.045) | <0.001 | 0.290 | 235.599 | 0.037 (0.018, 0.056) | <0.001 | 0.100 | 410.645 | 0.040 (0.029, 0.051) | <0.001 | 0.284 | 275.141 |
| BMI | −0.012 (-0.032, 0.008) | 0.233 | 0.011 | 280.681 | −0.022 (-0.058, 0.013) | 0.213 | 0.012 | 423.049 | 0.005 (-0.018, 0.028) | 0.679 | 0.001 | 320.366 |
| Dyslipidemia | 0.177 (-0.161, 0.515) | 0.303 | 0.008 | 281.047 | 0.378 (-0.213, 0.969) | 0.208 | 0.012 | 423.01 | 0.057 (-0.333, 0.448) | 0.773 | 0.001 | 320.456 |
| T2DM | 0.726 (0.501, 0.950) | <0.001 | 0.234 | 245.831 | 0.729 (0.297, 1.161) | 0.001 | 0.078 | 413.763 | 0.571 (0.292, 0.849) | <0.001 | 0.109 | 304.795 |
| Hypertension | 0.490 (0.242, 0.738) | <0.001 | 0.103 | 266.309 | 0.597 (0.158, 1.037) | 0.008 | 0.053 | 408.027 | 0.645 (0.364, 0.925) | <0.001 | 0.135 | 299.680 |
| Smoking | −0.168 (-0.499, 0.162) | 0.315 | 0.008 | 281.102 | −0.156 (-0.737, 0.424) | 0.595 | 0.002 | 424.340 | −0.405 (-0.781, −0.030) | 0.035 | 0.033 | 315.994 |
| eGFR | −0.017 (-0.022, −0.012) | <0.001 | 0.256 | 241.926 | −0.010 (-0.020, −0.000) | 0.045 | 0.030 | 420.543 | −0.015 (-0.021, −0.009) | <0.001 | 0.142 | 299.701 |
| hs-cTnT | NA | | | | 1.219 (1.003, 1.434) | <0.001 | 0.489 | 335.338 | 0.505 (0.328, 0.682) | <0.001 | 0.192 | 291.490 |
| hs-cTnI | 0.401 (0.330, 0.472) | <0.001 | 0.489 | 187.591 | NA | | | | 0.185 (0.077, 0.294) | 0.001 | 0.080 | 300.929 |
| ELF score | 0.381 (0.247, 0.514) | <0.001 | 0.192 | 253.077 | 0.432 (0.179, 0.685) | 0.001 | 0.080 | 413.513 | NA | | | |
| NT-proBNP | 0.220 (0.123, 0.318) | <0.001 | 0.130 | 263.189 | 0.248 (0.068, 0.427) | 0.007 | 0.054 | 417.292 | 0.049 (-0.071, 0.169) | 0.424 | 0.005 | 319.888 |

hs-cTnT: high-sensitivity cardiac troponin T; 95 % CI: 95 % Confidence Interval; $R^2$: R-squared; AIC: Akaike Information Criterion; hs-cTnI: high-sensitivity cardiac troponin I; ELF score: Enhanced Liver Fibrosis score; BMI: Body Mass Index; T2DM: Type 2 diabetes mellitus; eGFR: Estimated Glomerular Filtration Rate; NA: not applicable; NT-proBNP: N-terminal pro-B-type natriuretic peptide.
The table shows multiple univariable linear regression models with hs-cTnT, hs-cTnI and ELF score as respective outcome variables. Models with the same outcome variable are evaluated and compared using AIC values for best model to fit the data and $R^2$ as a measure of the proportion of the variance for the outcome variable that is explained by the independent variable. The models with the lowest AIC values and highest R-squared values are considered the best univariable models for a given outcome.
Additional description of the analysis is reported in the Supplemental Material, page 5.

relationship could be hepatokines, i.e. signal substances produced by the liver acting on remote organs [54], however, data on hepatokines contributing to myocardial injury or fibrosis are sparse and not assessed in the current study.

### *4.3. The association between hepatic fibrosis and chronic myocardial injury*

We also aimed to address the research question of the potential association between liver disease and HF from an alternative perspective. In the current study we assessed the association between circulating biochemical markers of hepatic fibrosis, a hallmark of NAFLD, quantified by the ELF test, and highly sensitive markers of myocardial injury and subsequent cardiac fibrosis, hs-cTnI and hs-cTnT, as well as NT-proBNP, a biomarker of cardiac strain and hemodynamic stress, in a cohort of patients with severe obesity. No association between ELF score and NT-proBNP concentrations was evident, even in univariable analysis. In contrast, moderately strong correlations between ELF score and cardiac troponin concentrations were observed. These differential patterns between ELF score and cardiac troponins vs. NT-proBNP observation may suggest that despite ongoing chronic myocardial injury, in our study population with mostly mild to moderate degrees of liver fibrosis, cardiac strain and hemodynamic stress were not affected. In other words, cardiac troponins could be a more sensitive marker of the early pathophysiological process than NT-proBNP. However, following adjustment for the demographic variables sex and age in multivariable linear regression models, the associations between ELF [score] and cardiac troponins were attenuated and not statistically significant. Further, in the fully adjusted model, there was no statistically significant association between ELF scores and cardiac troponin concentrations, suggesting that the univariable association could be explained by common risk factors for cardiac injury and hepatic fibrosis. In an attempt to identify the variables most closely associated with liver and myocardial injury and fibrosis, respectively, we observed that age and sex were included among the top three variables for both ELF score, hs-cTnI and hs-cTnT. However, while renal function was identified as a strong predictor of hs-cTnT, hypertension was identified as a strong predictor of hs-cTnI concentrations. The differential effect of renal

function and hypertension on hs-cTnI and hs-cTnT are in line with observations from previous studies [55]. The observation that hs-cTnT was a predictor of ELF scores is novel and in accordance with the theory that subclinical myocardial injury may contribute to liver fibrosis. However, the multivariable modeling suggest that this association may be due to shared risk factors. In addition to hs-cTnT and hs-cTnI, lower eGFR and higher age were identified as univariable predictors of NT-proBNP concentrations. Age and renal function are established predictors of NT-proBNP concentrations, and the associations between cardiac troponins and NT-proBNP are also unsurprising as chronic myocardial injury and fibrosis are intermediaries in the development of HF and NT-proBNP is closely associated with HF risk.

### 4.4. Strengths and limitations

The main strength of the present study is its well-characterized population including important risk factors for CVD and the application of validated diagnostic biomarkers to reflect liver fibrosis and cardiac fibrosis [7,8,19,20]. To our knowledge, there are no comparable studies using the ELF test and high-sensitivity assays for cardiac troponin T and cardiac troponin I to explore the liver-heart axis in patients with severe obesity. The use of these accurate and validated diagnostic biomarkers compared with the use of more invasive and expensive diagnostic modalities such as liver biopsy and cardiac magnetic resonance, enables the exploration of a link between NAFLD and the risk of HF in larger populations.

There are some limitations within the present study that should be acknowledged. Study power was limited by the fact that only a moderate number of patients were eligible for inclusion in the original study, with an even smaller number of participants with measurements of relevant biomarkers available for the current analyses. External validation of our findings in another dataset would therefore be desirable. With larger datasets and further validation in other cohorts, sex stratification and categorization of age might further elucidate potential shared risk factors in the liver-heart axis. The distribution of ELF scores in our sample is relatively narrow, and this may have resulted in weaker associations between ELF scores and cardiac troponins than in a cohort with more extreme ELF score values. This may be considered a limitation. However, we believe that the observed distribution is likely to reflect the distribution of liver fibrosis in individuals with severe obesity. Further, the cross-sectional design is unsuitable for establishing a cause-effect relationship. Follow-up information concerning left ventricular ejection fraction and cardiac biomarker data would have strengthened the manuscript, but unfortunately, such data are not available. All patients in the study were recruited from a tertiary care center for obesity management and the majority of the patients was female and of white ethnicity; hence some selection biases might be present which limit the generalizability of our results.

## 5. Conclusion

Contrary to our main hypothesis, liver fibrosis does not predict cardiac injury and fibrosis. However, univariable and multivariable regression analyses indicate that a potential association between liver fibrosis and cardiac injury and fibrosis may be explained by shared risk factors for CVD. Age and sex were amongst the strongest common predictors, followed by other risk factors of CVD such as hypertension and reduced kidney function expressed by eGFR. Further validation in other cohorts is required to endorse the results. In addition, studies that are more mechanistic are needed to understand the link between NAFLD and CVD.

## Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: T. O. has received honoraria from Roche Diagnostics, Abbott Laboratories, Bayer and CardiNor not related to the current work, and nonfinancial support from Novartis, ChromaDexSomaLogic, Abbott Diagnostics, and Roche Diagnostics via institution. K.M.A. is an Associate Editor of Clinical Biochemistry and Chair of the International Federation of Clinical Chemistry Committee on Clinical Application of Cardiac Bio-Markers, she has served on advisory boards for Roche Diagnostics, Siemens Healthineers and SpinChip, and has received honorarium for consultancy from CardiNor, honorarium for lecturing from Siemens Healthineers and Snibe Diagnostics, and research grants from Siemens Healthineers and Roche Diagnostics. The remaining authors have no conflicts of interest to declare.

## Acknowledgements

This work was supported by Vestfold Hospital Trust, the K.G. Jebsen Center for Cardiac Biomarkers at the Institute of Clinical Medicine, University of Oslo, Norway, Haukeland University Hospital, Akershus University Hospital, and an educational grant (PhD-fellow) from the South-Eastern Norway Regional Health Authority for Dr. Seeberg. We acknowledge generous support by Stiftelsen Kristian Gerhard Jebsen (K. G. Jebsen Center for Cardiac Biomarkers, grant number SKGJ-MED-024).

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinbiochem.2023.110688.

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