Aus der Klinik mit Schwerpunkt Kardiologie
der Medizinischen Fakultät Charité – Universitätsmedizin Berlin

DISSERTATION

Deformation analysis of the left heart in patients with advanced liver cirrhosis using 2D-speckle tracking echocardiography

Deformationsanalyse des linken Herzens von Patienten mit fortgeschrittener Leberzirrhose mittels 2D- Speckle-Tracking-Echokardiographie

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Table of Content

List of Figures

List of Tables

List of Abbreviations

A	trans-mitral inflow velocity in late/ active diastole
ALAT	alanine aminotransferase
AP	alcalic Phosphatase
ASAT	aspartate aminotransferase
ASE	American Society of Echocardiography
CCC	cirrhotic cardiomyopathy consortium
CCM	cirrhotic cardiomyopathy
DD	diastolic dysfunction
E	trans-mitral inflow velocity in early/ passive diastole
e’	mitral annulus velocities
EACVI	European Association of Cardiovascular Imaging
ECG	Electrocardiogram
γGT	gamma-glutamyltransferase
GCS	global circumferential strain
GLS	global longitudinal strain
GRS	global radial strain
INR	international normalized ratio
LA	left atrium
LAVI	left atrial volume indices
LTX	liver transplantation
LV	left ventricle
LVEF	left ventricular ejection fraction
MELD	model to end-stage liver disease score
RAAS	renin-angiotensin-aldosterone-system
SR	strain rate
STE	speckle-tracking echocardiography
TDI	tissue doppler imaging
TR	tricuspid-regurgitation
TTE	transthoracic echocardiography
VEGF	vascular endothelial growth factor

Abstract (English)

Background. End-stage liver disease patients may develop cirrhotic cardiomyopathy (CCM) – cardiac dysfunction in cirrhosis patients without previous cardiac impairment. The diagnostic challenge lies within the fact that CCM manifests clinically in acute stress conditions yet presents normal cardiac function at rest. Liver transplantation is a curative option regarding liver cirrhosis but causes immense physiological stress on the patient's body. Hence, accurate diagnostic means which enable early diagnosis of cardiac dysfunction in CCM are necessary to allow successful therapy for end-stage liver cirrhosis patients. Speckle tracking Echocardiography (STE) is an advanced deformation imaging technique which enables sensitive detection of impaired cardiac movement. Previous studies have established impaired strain parameters in early stages of various heart conditions, yet strain analysis in cirrhosis patients is limited. **Aim.** We aim to evaluate the function of the left heart in end-stage liver cirrhosis patients by applying advanced 2D-STE analysis. **Methods.** We analysed echocardiographic data of eighty end-stage liver cirrhosis patients waiting for liver transplantation and thirty matched controls in this retrospective, cross sectional study. Severity of liver disease was assessed by collected laboratory markers which allowed calculation of model to end-stage liver disease (MELD-) score. We evaluated grey-scale transthoracic echocardiographic images in regard to the left heart using conventional parameters and advanced 2D-STE analysis, including ventricular and atrial strain analysis. Statistical significance of results was evaluated using Mann-Whitney-U- or T-Test when appropriate. Correlation analyses using Spearman's coefficient were conducted between clinical and echocardiographic variables. Kaplan-Meier curves and cox regression analysis were calculated for different strain parameters in order to assess predictors of mortality. **Results.** Left ventricular global longitudinal strain was significantly increased in cirrhosis patients and correlated with MELD-Score (r = -.361, p <0,01). Left atrial strain in reservoir and conduit function was significantly reduced, along with atrial strain rate in all phasic functions. STE analysis allowed diagnosis of diastolic dysfunction, which was not detected by conventional echocardiographic parameters. **Conclusion.** STE analysis allowed a more detailed evaluation of left ventricular and atrial function than standard echocardiographic parameters and should be further considered for cardiac assessment of liver cirrhosis patients, in example before liver transplantation.

Abstract (German)

Hintergrund. Patienten mit Leberzirrhose im Endstadium können eine zirrhotische Kardiomyopathie (CCM) entwickeln – dies umfasst eine kardiologische Dysfunktion bei Leberzirrhotikern ohne vorherige Herzinsuffizienz. Die diagnostische Herausforderung liegt darin, dass sich die CCM in klinischen Stresssituationen manifestiert, jedoch der Patient in Ruhe eine normale Herzfunktion vorweist. Die Lebertransplantation ist die einzige kausale Therapieoption der Leberzirrhose im Endstadium. Es wurde bereits gezeigt, dass dieser Eingriff das kardiovaskuläre System vor eine erhebliche Stresssituation stellt und eine CCM aufdecken kann. Daher ist eine akkurate kardiale Diagnostik notwendig, damit bereits eine latente Herzinsuffizienz frühzeitig erkannt werden kann, bevor sie in ein manifestes Stadium übergeht. Speckle-tracking-Echokardiographie (STE) ist eine moderne Bildgebung und Deformationsanalyse, welche myokardiale Bewegungsstörungen sensitiv erkennt. Bisherige Studien konnten reduzierte Deformationsparameter in Frühstadien verschiedener kardiologischer Erkrankungen beobachten, jedoch ist die Datenlage bezüglich Deformation bei Leberzirrhose limitiert. **Zielsetzung.** Unser Ziel ist es, die Funktion des linken Herzens bei Patienten mit Leberzirrhose im Endstadium mittels 2D-STE zu evaluieren. **Methoden.** Wir schlossen 80 Patienten mit Leberzirrhose im Endstadium, die auf eine Lebertransplantation warteten, und 30 entsprechende Kontrollprobanden in diese retrospektive Querschnittsstudie mit ein. Der Schweregrad der Leberzirrhose wurde anhand der gesammelten Laborparameter und des daraus berechneten ‚model to end-stage liver disease' (MELD-) Scores bewertet. Wir evaluierten transthorakale echokardiographische Graustufenbilder in Bezug auf das linke Herz mittels konventioneller Parameter und moderner 2D-STE, einschließlich ventrikulärer und atrialer Deformationsanalyse. Statistische Signifikanz wurde anhand Mann-Whitney-U- oder T-Test berechnet. Mittels Korrelationsanalysen (Spearman's Koeffizienten) untersuchten wir Zusammenhänge zwischen klinischen und echokardiographischen Variablen. Kaplan-Meier-Kurven und Cox-Regressionsanalysen wurden für Deformationsparameter berechnet, um Prädiktoren für die Mortalität zu bewerten. **Ergebnisse.** Patienten mit Leberzirrhose erwiesen eine statistisch signifikant erhöhte links-ventrikuläre longitudinale Deformation, welche mit dem errechneten MELD-Score korrelierte (r = -.361, p <0,01). Die links-atriale Deformation und/oder Deformationsrate zeigten sich signifikant reduziert in allen funktionellen Phasen des linken Vorhofs. STE-

Analysen ermöglichten die Diagnose einer diastolischen Dysfunktion, welche durch konventionelle Parameter nicht erkannt wurde. **Fazit.** Die STE-Analyse ermöglichte eine detailliertere Beurteilung der links-ventrikulären und -atrialen Funktion und sollte für die kardiale Beurteilung von Patienten mit Leberzirrhose, beispielsweise vor einer Lebertransplantation, grundsätzlich in Betracht gezogen werden.

1. Introduction

1.1. Liver Cirrhosis

Liver cirrhosis and hepatic cancer account for up to 3.5% of all deaths globally, demonstrating an increasing tendency worldwide since 2000 (1). However, aetiological trends have been observed in the more recent years: While prevalence of alcoholic liver cirrhosis remains at a high with over 50% of mortality related to cirrhosis being attributed to alcohol (1), medical advancements in antiviral therapy and preventative vaccinations have led to a decreasing prevalence of Hepatitis B and C in countries such as Germany (2). Additionally, demographic changes including rising metabolic risk factors and an ageing population affect the rising numbers of NAFLD (1-4).

Advances in diagnosis and preventative measures including vaccinations and implemented policies to limit alcohol consumption have been made, yet therapeutic measures for long term treatment remain limited, with liver transplantation (LTX) representing the last resort (4). While liver transplantation is the second most common after kidney transplantation, only fewer than 10% of global needs are met at current transplantation rates (3). The mismatch between demand and availability highlights the importance of careful patient evaluation including preoperative cardiac diagnostics in cirrhosis patients, as cardiovascular complications are a major cause of perioperative morbidity and mortality (5).

1.2. Cardiac Function and Imaging in Patients with Liver cirrhosis

Cardiac function in cirrhosis patients has been subject to previous clinical inquiries. In liver cirrhosis intrahepatic resistance increases, causing portal hypertension (6). For compensation an increase in portal inflow is achieved by re-perfusing pre-existing portal systemic collateral vessels and generating new collaterals by expressing vascular endothelial growth factor (VEGF) (6). VEGF also induces further signalling cascades, which lead to increased bioavailability of vasodilatory factors nitric oxide and prostacyclin (6-8). Nitric oxide- and prostacyclin-induced splanchnic arterial vasodilation – specifically in mesenteric and splenic vascular beds – increases portal inflow in cirrhosis patients (6, 7). This reduces effective arterial blood volume and blood pressure and thus activates renin-angiotensin-aldosterone-system (RAAS) (6, 7, 9). Splanchnic vasodilation itself results in reduced cardiac afterload, while RAAS-activation raises effective atrial volume through water and Na^{2+} retention; both resulting in state of high

cardiac output (6, 7). Hyperdynamic circulatory syndrome is thus defined by high cardiac output and low systemic vascular resistance (6) and can result in cardiac remodelling and dysfunction in cirrhosis patients (**Figure 1**) (6, 7, 10).

It has been established that patients with cirrhosis may develop cirrhotic cardiomyopathy (CCM); a condition broadly defined as cardiac dysfunction in cirrhosis patients with no previously known heart condition, which presents itself in acute stress conditions (6, 7, 9-11). Official criteria for systematic diagnosis were first established in 2005 at the World congress of Gastroenterology (7). As CCM entails impaired systolic and/ or diastolic functions, these criteria were based on standard echocardiographic parameters – including left ventricular ejection fraction (LVEF) at rest, early diastolic filling ratio, deceleration time, and isovolumetric relaxation time (10-14). Additional supportive criteria such as electrophysiological abnormalities, increased cardiac biomarkers, or altered cardiac anatomy were also included (10-14).

However, as cardiac dysfunction manifests in stress conditions, diagnosis of CCM is often missed and its true prevalence is unknown (11). Patients remain asymptomatic at rest with a seemingly normal cardiac function due to the state of low peripheral resistance with subsequent low left ventricular (LV) afterload and thus cardiac work (7, 11). This highlights the importance for an effective diagnostic approach and revised criteria have been proposed by the Cirrhotic Cardiomyopathy Consortium (CCC) in 2020 (13). These new and updated CCM-defining criteria focussed on modern understanding of heart failure, clinical applicability, and advanced diagnostic techniques – including strain analysis for diagnosis of systolic dysfunction (13).

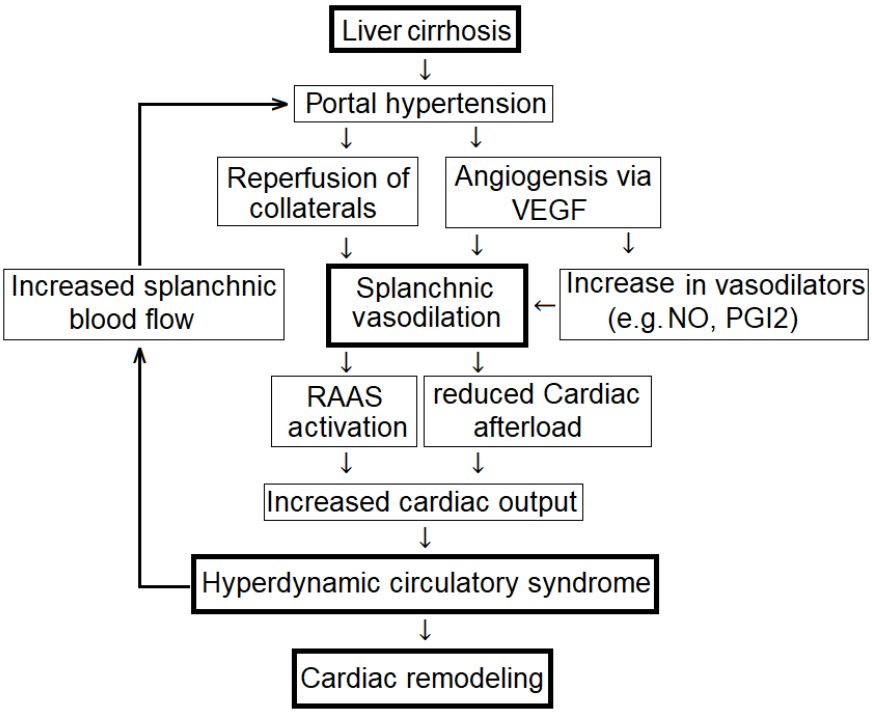

Figure 1 *– Pathogenesis of hyperdynamic circulatory syndrome present in cirrhotic cardiomyopathy. VEGF – vascular endothelial growth factor, NO – nitric oxide, PGI2 – Prostacyclin, RAAS – renin-angiotensin-aldosterone-system. Original Figure: Franzisca von Köckritz.*

1.3. Echocardiography – first line imaging diagnostic

Many people think of the heart as the core organ in our body, associating its pumping action directly to the idea of living. Its function revolves around supplying the entire body with oxygen and nutrients, according to the current metabolic requirements. Thus, evaluating cardiac function is an important process prior to any medical adjustment influencing metabolic conditions – ranging from administering new medication to invasive operative procedures.

Various non-invasive imaging techniques have been established to supplement basic assessments through physical examinations, laboratory biomarkers and electrocardiographic analysis. These include echocardiography, cardiac magnetic resonance, computer tomography, and more. All imaging modalities allow unique visual assessments of anatomy, movement and thus functionality. However, echocardiography is usually the first to be used and allows patient assessment directly at the bedside (15).

Echocardiography has become more relevant since its first diagnostic use in the 1950s (15). Continuous innovation including the development of various echocardiographic

techniques has contributed to the exponential increase in use, with more specific medical information provided (16). Different modes assess cardiac anatomy and function in specific detail, which in combination provides a thorough evaluation of a patients' cardiac condition (15, 17, 18). This wide range of application combined with quick, low-cost, and risk-free technology explains how echocardiography has established itself as first-line imaging diagnostic of cardiac diseases (15).

1.4. Strain Imaging with Speckle Tracking Echocardiography

Myocardial Strain Imaging defines a technique to evaluate regional and global cardiac function, relying on the orientation and deformation – or 'strain' – of individual myocardial fibres (18-21). First strain data were obtained by processing cardiac wall motion velocity and displacement, measured by Tissue Doppler Imaging (TDI) (20, 22). In the last two decades tissue tracking technology emerged as a direct method to assess cardiac strain, using either cardiac magnetic resonance imaging or echocardiography; the latter however has proven advantageous in clinical routines through easier accessibility, no contraindications for patients, higher temporal resolution, and lower cost (18, 19).

Tissue tracking works by identifying a detected pattern within a region of interest in a sequence of images (19). In echocardiography this is achieved by speckle tracking (STE). Speckles are stable acoustic artifacts from ultrasound-myocardial interactions (18, 19, 21-23). Statistically these speckles are distributed equally throughout the visualized tissue (20), yet the random arrangement ensures a unique pattern for each region of the myocardium (18). These 'myocardial fingerprints' are tracked frame to frame by speckle-tracking software to determine the spatiotemporal shift representing regional tissue movement and allowing calculations for strain and strain rate (18-22). In general, these are computed using Lagrangian strain S_L and natural strain rate SR_N calculations (19).

Normal strain – occurring perpendicular or orthogonally to the surface – of the LV can be measured in three directions: longitudinal (GLS), radial (GRS), and circumferential (GCS) (18, 21). While it is dimensionless, it is frequently given in % (18, 24). An increase in myocardial dimension is reflected by positive, while a decrease is reflected by negative strain and strain rate values. The LV undergoes thickening in radial, while shortening in longitudinal and circumferential axes during ventricular systole – thus measuring positive and negative strain and strain rate respectively (18-20). 2D-STE

analysis of the left atrium (LA) only allows measuring of longitudinal strain and strain rate; radial strain cannot be obtained due to the thin walls of the atrium (25). Strain rate (SR) provides the amount of strain over time and is given in s^{-1}.

STE offers certain technical advantages. While TDI only allows strain measurements in reference to the external probe, STE overcomes this angle dependency by measuring between two points within the region of interest (19); this enables calculations of circumferential and radial strain (19, 21). As STE discriminates between active and passive deformation of cardiac fibres it is far less affected by tethering or general cardiac motion (18, 21). However, as always in image processing, the quality of images is a major limitation (18, 20, 21, 24). While STE is more advanced than TDI it is still affected by frame rate (i.e., temporal resolution) and image foreshortening (18, 19, 24). 'Through the plane motion' phenomenon further limits STE as speckles moving along their 3D-plane may move beyond the visualized 2D-plane image and cannot be tracked (18, 19, 24). This could be overcome by 3D-Speckle tracking (18, 19, 24). Lastly, soft- and hardware inter-vendor differences cause high variability of strain measurements, which need to be considered when analysing different studies (20, 22).

1.5. Project aim

STE is an advanced technique which has been established to certain extent for cardiac assessment. Throughout the years it has demonstrated its capabilities allowing its use to progress from purely scientifical to clinical application. STE thus has been involved in cardiac assessment in various medical conditions (21, 26). However, only a manageable number of studies revolve around incorporating STE in cardiac evaluation in liver cirrhosis patients. While the importance of advanced and accurate cardiac evaluation in cirrhosis is evident, conflicting results must be assessed in further context. This dissertation aims to retrospectively evaluate left cardiac function in end-stage liver cirrhosis patients. We focus especially on cardiac evaluation using STE aiming to detect previously described cardiac dysfunction. Our investigation will compare STE assessment with standard echocardiography as we assess left ventricular and additionally left atrial function. In order to understand the importance of applying these advanced cardiac imaging techniques we aim to investigate correlations of strain assessment with advancement of liver cirrhosis. Lastly, we want to establish if strain analysis allows for predictions about mortality.

Corresponding publication:

von Köckritz, F.; Braun, A.; Schmuck, R. B.; Dobrindt, E. M.; Eurich, D.; Heinzel, F. R.; Pieske, B.; Escher, F.; Zhang, K., Speckle Tracking Analysis Reveals Altered Left Atrial and Ventricular Myocardial Deformation in Patients with End-Stage Liver Disease, J Clin Med, 2021 Feb 24;10(5):897. DOI: 10.3390/jcm10050897.

2. Methodology

2.1. Study Design

For this retrospective cross-sectional study, we analysed clinical data collected solely for the purpose of guideline-compliant medical treatment. The study was approved by the local ethics committee (Reference number: EA4/065/19) and fulfilled requirements of the Berlin Act for Protection of Data Privacy (BlnDSG) and the State Hospital Act for Data Protection for Research (LKG, §25). The study manuscript has previously been published in 2021 in the *Journal of Clinical Medicine* including the methodology and results discussed in this dissertation (27).

A G*Power analysis can be used to quantify how big the study population needs to be for an assumed effect size. Due to the prior known discrepancy of available data in our systems for possible patients and controls an allocation ratio of the study groups was set at 2. The calculated total study population, for a medium effect size of 0,5, was given as n=198 with the two individual examined groups being n=132 and n=66. However, due to the retrospective nature of this study acquired patient and control cohorts were limited to the number of suitable data points available.

An archive of 290 liver cirrhosis patients, who had been transplanted from 03.01.2013 until the 29.12.2016, was provided by the Liver transplantation centre of the Charité Virchow Clinic. Of these, 157 patients had transthoracic echocardiographic (TTE) images available in our system and were individually assessed. Patients were excluded when any of the following applied: no strain imaging analysis possible from TTE, poor TTE image quality (E.g.: ECG not recognized by software for analysis, image framerate too low, greyscale too low, unstable image views, missing TTE chamber views), medical history of cardiovascular disease or reduced LVEF. In order to compare patients' data, a control group was put together from preexisting data within our system. To do so we included people without history of hepatic or cardiac disease who received laboratory

and TTE examinations (usually as part of an evaluation for possible live organ donation at our campus). TTE images of controls were also individually assessed for the above-mentioned criteria. Since data were analysed retrospectively for this study the number of possible controls was limited to available data.

Finally, we recruited 80 liver cirrhosis patients and 30 healthy controls for our retrospective analysis (**Figure 2**).

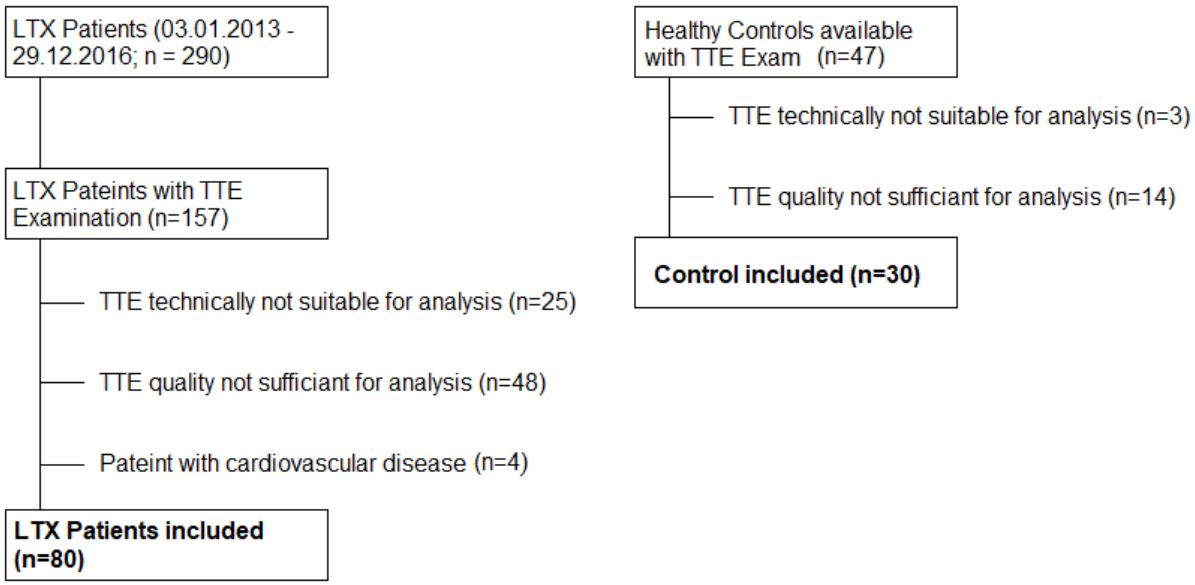

Figure 2 *– Consort Flow chart of study population.*

2.2. Non-Echocardiographic Variables

Non-echocardiographic information was collected using the clinics digital patient file system SAP (by F.V.K. and A.B.). Baseline demographics including age, sex, height, and weight were collected to compare the two groups and to allow calculations of body mass index and body surface area. Laboratory biomarkers were recorded to allow separate assessment of cirrhosis – including alanine and aspartate aminotransferases (ALAT, ASAT), alcalic Phosphatase (AP), gamma-glutamyltransferase (γGT), creatinine, international normalized Ratio (INR), and total serum bilirubin. Subsequently the 'Model to End-stage Liver Disease Score' (MELD) was calculated (by FVK) according to the accepted formula *(28)*: $MELD = 10 \times (0.957 \times ln(Creatinine) + 0.378 \times ln(Bilirubin) + 1.12 \times ln(INR) + 0.643)$. By proposed standards, values < 1 were corrected to 1.0 to allow correct calculation (28). We aimed to compile anthropometric measures and laboratory markers collected closest to the date of Echocardiography, to evaluate the patients' health condition at that precise moment.

2.3. Echocardiographic Variables

Patients received TTE examinations during evaluation for organ transplantation. Controls received TTE examinations for check-up purposes or during organ/ tissue donation evaluation. Due to the retrospective nature of the study, examinations were conducted with no other specific focus than indicated. Exams were performed by cardiologists using a Vivid 7 (GE Vingmed, Horton, Norway) Ultrasound machine and adhered to standardized, routine 2D-echocardiography (16, 29). This included images taken in parasternal long-axis, parasternal short-axis at level of papillary muscle, apical two-chamber and four-chamber and apical long axis views. Additionally, examiners were able to apply Tissue Doppler when TTE images were recorded.

Images taken were stored within the clinics data centre and were run with the EchoPAC Software Only (Version 201; GE-Healthcare, Horton, Norway) for all echocardiographic analysis (by F.V.K.). For simplicity, values for tricuspid-regurgitation (TR) and LVEF were obtained from the corresponding examination report. All other measurements were taken de novo from the corresponding TTE visuals. Measurements from the original analysis saved along with the images were ignored. If more than one image was stored for a required view, all were subjectively evaluated, and the most suitable concerning image quality and complete depiction of anatomy was picked for analysis.

Standardized measurements were taken in appropriate TTE views (16, 30): LV end-diastolic and end-systolic diameters, as well as intraventricular septum and LV posterior wall thicknesses were recorded from parasternal long-axis view; maximum, pre-atrial contraction, and minimum LA volumes and lengths were recorded in apical four- and two chamber views; trans-mitral inflow velocity in early/ passive (E) and late/ active (A) diastole, septal and lateral mitral annulus velocities (e'), and deceleration time were taken in apical four-chamber views assessed with pulse-waved doppler. Data collected allowed for further calculations regarding the left heart including ventricular relative wall thickness, mass and mass index, and atrial volume indices (LAVI), ejection volumes and ejection fractions for reservoir, conduit, and contractile phasic functions (31). Furthermore, E/A and E/e' ratios were assessed. To compute E/e' ratio, an average of both mitral annular velocities (septal and lateral) had initially been calculated (30).

For 2D-STE analysis we required three consecutive cardiac cycles recorded in apical long axis, two- and four chamber and, if available, parasternal short axis views. The

software required manual tracing of each region of interest (i.e., left ventricle or atrium in described views) and checked if segments were recognized for analysis, as illustrated by **Figure 2**. If the software was unable to recognize regions of interest, or if tracking was perceived as insufficient, we adjusted our manual input. We accepted a maximum of one unrecognized segment of the region of interest. LV GLS was recorded for epi-, endo-, and mid-myocardial layers from which an average GLS for each view was calculated. Subsequently an overall average GLS was computed. LV GRS and GCS were analysed if parasternal short axis views were available. LA strain and strain rate analysis from two- and four chamber views applied systolic gating processing (start of analysis with onset of QRS-complex) (25, 32) and were expressed graphically by the software. As demonstrated in **Figure 3**, manual readings recorded from graph peaks express strain/ strain rate for different phasic functions. Conduit strain was calculated as the difference between peak longitudinal and peak contractile strain (32).

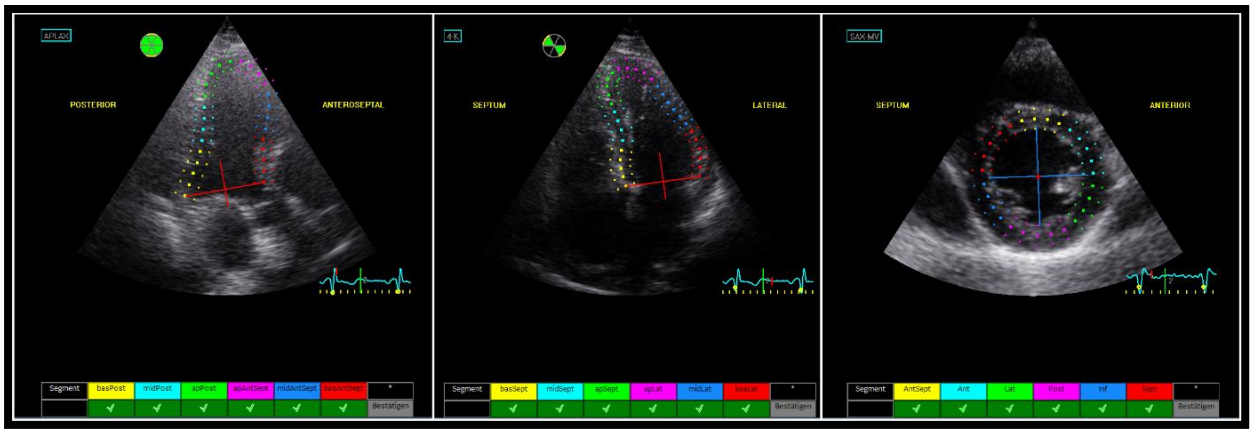

Figure 3 *– Example of automated recognition of Region of Interest for Speckle tracking analysis in apical long-axis, four-chamber and parasternal short axis views using EchoPAC Only Software Version 201. Original Figure: Franzisca von Köckritz.*

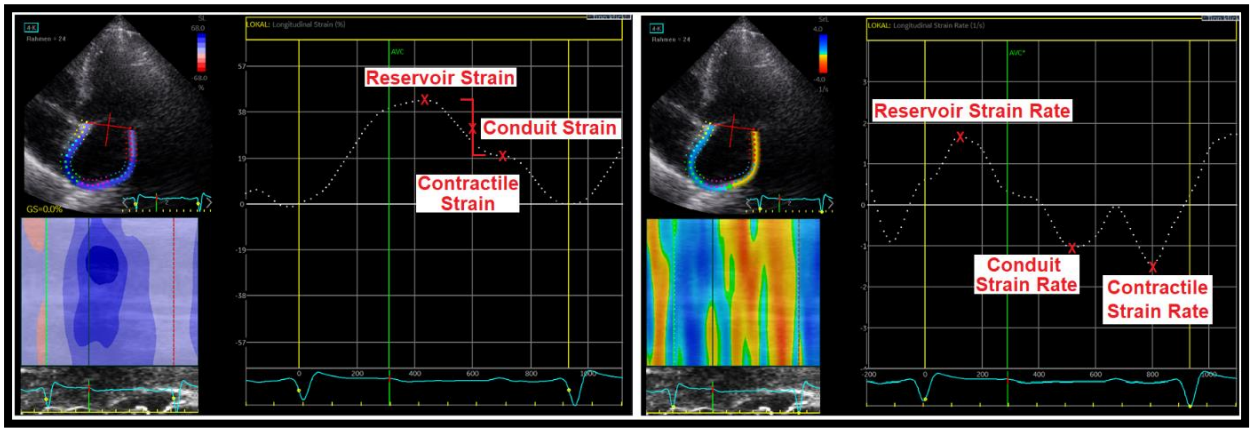

Figure 4 *– Example of graphical assessment of left atrial strain and strain rate using EchoPAC Only Software Version 201. Labels show where manual readings were taken for which variable. Original Figure: Franzisca von Köckritz.*

2.4. Statistics

Statistics were computed utilizing IBM SPSS® (Version 25; SPSS Inc., Chicago, II, USA) for Windows (by F.V.K.). To apply appropriate significance tests, variables were initially tested for normal distribution for patient and control groups. Normal distribution was evaluated graphically and by applying the Kolmogorov-Smirnov-Test. Latter indicated normal distribution when $p > 0.05$. When both tests indicated normal distribution for the two groups, statistical significance of observed differences was calculated applying the T-Test– if not, the Mann-Whitney-U Test was applied. The Kruskal-Wallis Test was applied to compare strain results within the patient group according to aetiology of cirrhosis.

Furthermore, we analysed existing relationships in the data (including normal and non-normal distributed Variables) using the Spearman's correlation (r). We focused specifically on data of patients, comparing established biomarkers and echocardiography with the newly applied speckle tracking analysis of LV and LA.

Mortality analyses were computed if data was available. Kaplan Meier functions were computed to evaluate mortality in patients according to strain values. Cox regression analysis assessed predictors for mortality from the data at hand.

Numeric results of each assessed group are presented as average mean ± standard deviation and the corresponding statistical significance value p. We agreed upon a level of significance when $p < 0.05$. Presentation and visualisation of data including tables and non-image figures are computed with Microsoft Excel® for Microsoft 365 (V. 2111).

3. Results

Results presented in Tables 1-3 have been published in 2021 in the *Journal of Clinical Medicine* (27). Modifications are indicated accordingly.

3.1. Baseline Characteristics

We retrospectively evaluated laboratory markers and TTE images of 80 cirrhosis patients. Patients suffered cirrhosis of different aetiologies (**Figure 4**) and had

undergone TTE within the evaluation process for liver transplantation (LTX). To compare patients to the public we added a control group of 30 individuals, who had TTE images taken for general check-ups or within the process of organ and tissue donation. Detailed demographic data and laboratory markers for both groups are found in the above-mentioned publication (27). Biomarkers were primarily collected from lab work done either exactly on the day of echocardiography or ± 10 days; only one patient had lab work records from 33 days before TTE. Patients showed significantly elevated liver enzymes (including transaminases and alcalic phosphatase), creatinine, bilirubin, and INR. The subsequently calculated MELD-Score mirrored this increase likewise (17 vs. 7).

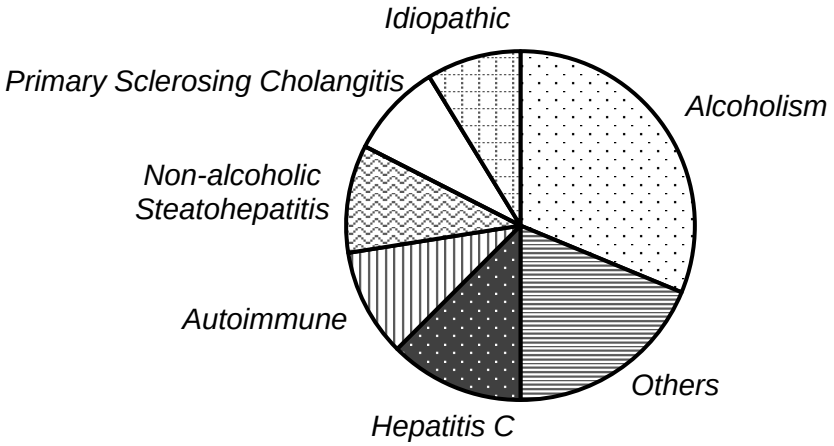

Figure 5 *– Aetiology of Cirrhosis of Patients. Reasons for Cirrhosis which occurred twice or less were grouped within "Others". Original Figure: Franzisca von Köckritz.*

3.2. Echocardiographic and Speckle-Tracking Evaluation

Various standard echocardiography measurements were taken, and speckle tracking analysis was performed for the left ventricle when appropriate TTE images were available for evaluation. **Table 1** summarizes the significantly changed values concerning the left ventricle. None of the other investigated data showed significant changes – including ratio of diastolic transmitral inflow velocity, deceleration time, septal and lateral mitral annular velocities, and Tricuspid regurgitation. Patient and control groups displayed preserved LVEF (>50%) (33). Concerning speckle tracking analysis, GLS was significantly elevated throughout the entirety of cardiac layer, while GCS and

GRS remained unaltered. GLS analysis for aetiologies as listed in Figure 1 resulted in no significant difference between subgroups (p = 0.143).

We assessed the left atrium through volumetric echocardiographic measurements and subsequently calculated LAVI, emptying volumes and ejection fraction as presented in **Table 2**. Left atrial volume and emptying volume increased significantly in patients, yet no change in ejecting fraction was established. Speckle tracking analysis was additionally preformed and presented significantly reduced strain and strain rate within reservoir and conduit phasic functions. Contractile function was only reduced concerning strain rate. ECG quality limited data points available.

Table 1 *– Echocardiographic parameters and Strain Analysis of the Left Ventricle. Modified from von Köckritz et al., 2021 (27)*

	Controls			**ESLD Patients**			**Test**	***p***
Aorta Sinus (mm)	29.53	±	3.60	30.56	±	3.49	T	*0.176*
LVEDD (mm)	44.80	±	5.74	47.59	±	6.63	T	*0.045*
LVESD (mm)	34.20	±	4.47	35.75	±	9.22	U	*0.416*
IVS (mm)	9.50	±	1.59	11.12	±	1.84	U	*<0.001*
PW (mm)	9.77	±	1.52	11.05	±	1.89	U	*0.001*
RWT	0.44	±	0.07	0.47	±	0.10	U	*0.121*
LVM (g)	149.27	±	51.96	199.11	±	62.34	U	*<0.001*
LVMI (g/m^2)	79.87	±	21.99	102.49	±	28.50	U	*<0.001*
LV $Volume_{max}$	107,43	±	31,03	118,50	±	38,52	T	*0,161*
LV $Volume_{min}$	59,20	±	22,73	57,11	±	20,24	T	*0,642*
E (m/sec)	0.71	±	0.16	0.80	±	0.22	U	*0.058*
A (m/sec)	0.59	±	0.17	0.70	±	0.23	U	*0.035*
E/A ratio	1.25	±	0.36	1.23	±	0.41	T	*0.828*
DT (ms)	214.10	±	50.59	236.43	±	56.92	T	*0.068*
e' septal (m/sec)	0.13	±	0.20	0.08	±	0.02	U	*0.188*
e' lateral (m/sec)	0.10	±	0.03	0.10	±	0.02	U	*0.984*
E/e' ratio	7.57	±	2.88	9.42	±	2.88	T	*0.005*
TR (m/sec)	2,41	±	0,33	2,53	±	0,38	T	*0,232*
LVEF (%)	60.90	±	4.70	60.00	±	5.17	U	*0.274*
GLS Average	-18.73	±	2.95	-21.39	±	4.06	T	*<0.001*
GLS Mid-myocardial	-18.56	±	2.63	-21.26	±	4.05	T	*<0.001*
GLS Endocardial	-21.34	±	3.00	-24.16	±	4.58	T	*<0.001*
GLS Epicardial	-16.28	±	2.39	-18.75	±	3.62	U	*<0.001*
GCS	-17.16	±	5.06	-19.85	±	6.69	T	*0.093*
GRS	30.77	±	21.22	35.92	±	18.79	U	*0.298*

LVEDD – LV end-diastolic diameter, LVESD – LV end-systolic diameter, IVS – interventricular septum, PW – posterior wall thickness, RWT – relative wall thickness, LVM – LV mass, LVMI – LV mass index, TR – Tricuspid regurgitation velocity, LVEF – LV ejection fraction, DT – deceleration time, GLS – global longitudinal strain, GCS – global circumferential strain, GRS – global radial strain

Table 2 *– Echocardiographic parameters of Left Atrium. Modified from von Köckritz et al., 2021 (27)*

	Controls			**Cirrhosis Patients**			**Test**	***p***
LA $Volume_{max}$ (ml)	28.85	±	17.21	75.13	±	49.52	T	*<0.001*
LA $Volume_{pre\text{-}a}$ (ml)	16.65	±	8.64	40.68	±	28.90	T	*<0.001*
LA $Volume_{min}$ (ml)	9.00	±	6.11	21.27	±	14.95	T	*<0.001*
$LAVI_{max}$ (ml/m²)	15.37	±	8.65	38.73	±	24.04	T	*<0.001*
$LAVI_{pre\text{-}a}$(ml/m²)	8.90	±	4.23	21.24	±	15.04	T	*<0.001*
$LAVI_{min}$ (ml/m²)	4.83	±	3.27	10.90	±	7.11	T	*<0.001*
LA TotEV (ml)	19.85	±	13.15	53.86	±	38.48	T	*<0.001*
LA PassEV (ml)	9.96	±	6.14	35.71	±	32.13	T	*<0.001*
LA ActEV (ml)	8.45	±	5.45	19.81	±	18.61	T	*0.001*
LA TotEF (%)	68	±	17	71	±	11	T	*0.872*
LA PassEF (%)	39	±	13	45	±	16	T	*0.052*
LA ActEF (%)	51	±	18	48	±	16	T	*0.213*
Reservoir strain	39.97	±	9.74	32.86	±	10.65	T	*0.002*
Conduit strain	21.12	±	7.40	15.38	±	6.94	T	*<0.001*
Contractile strain	18.85	±	5.08	17.48	±	7.37	T	*0.352*
Reservoir SR	1.66	±	0.44	1.39	±	0.40	T	*0.003*
Conduit SR	-1.92	±	0.72	-1.23	±	0.47	T	*<0.001*
Contractile SR	-2.43	±	0.68	-1.87	±	0.64	T	*<0.001*

pre-a – pre atrial contraction, LAVI – left atrium volume index, TotEV – total emptying volume, PassEV – passive emptying volume, ActEV – active emptying volume, TotEF – total emptying fraction, PassEF – passive emptying volume, ActEF – active emptying volume, SR – strain rate

Table 3 *– Correlation Analysis within the Cirrhosis Cohort. Significant correlations are marked with an asterisk: * marks p < 0,05, ** marks p < 0,01. Modified from von Köckritz et al., 2021 (27)*

	ALAT (U/L)	**ASAT (U/L)**	**Creatinine (mg/dl)**	**Bilirubin**	**INR**	**MELD**
LV Average GLS	-.306**	-.297**	-0.084	-.328**	-.324**	-.361**
LV Myocardial GLS	-.304**	-.294**	-0.09	-.325**	-.325**	-.360**
LV Endocardial GLS	-.302**	-.300**	-0.063	-.313**	-.338**	-.346**
LV Epicardial GLS	-.306**	-.296**	-0.114	-.349**	-.293**	-.379**
LA Reservoir Strain	.275*	.301**	-.271*	.228*	0.162	0.111
LA Contractile Strain	.223*	.316**	-.239*	.228*	0.119	0.127
LA Conduit Strain	0.186	0.191	-0.155	0.16	0.107	0.058
LA Reservoir SR	.249*	.234*	-.246*	0.198	0.179	0.144
LA Conduit SR	-.273*	-0.217	.250*	-.272*	-0.014	-0.102
LA Contractile SR	-.315**	-.274*	.288**	-0.105	0.055	0.068
LA TotEV	0.01	-0.022	.296**	0.076	.324**	.273*
LA PassEV	-0.04	-0.076	.323*	0.085	0.227	0.227
LA ActEV	-0.087	-0.147	0.155	-0.126	.345**	0.058
LA TotEF	.282*	0.158	-0.145	0.102	-0.041	0.012
LA PassEF	0.209	0.195	0.09	.281*	-0.038	0.226
LA ActEF	.317*	0.156	-0.233	-0.029	0.111	-0.046

SR – strain rate, TotEV – total emptying volume, PassEV – passive emptying volume, ActEV – active emptying volume, TotEF – total emptying fraction, PassEF – passive emptying volume, ActEF – active emptying volume, ALAT – alanine aminotransferase, ASAT – aspartate aminotransferase.

Correlation analyses were preformed and summarized in **Table 3**. We found that left ventricular GLS correlates with transaminases, bilirubin, INR, and hence MELD- score throughout all cardiac layers. This suggests that advanced liver cirrhosis is associated with increased left ventricular GLS. Left atrial strain and strain rate correlated with liver enzymes and creatinine relatively consistently; a correlation with MELD could not be established. Left atrial volumetric echocardiography in contrast provided varying correlations with all investigated laboratory markers.

At the time of data collection 13 liver cirrhosis patients had passed away after LTX. We were unable to identify a predictor of mortality using cox regression analysis. Kaplan Meier curves merely demonstrated a visual trend of higher mortality in patients with pathological left atrial reservoir and conduit strain – however, level of significance was not reached (**Figure 6**).

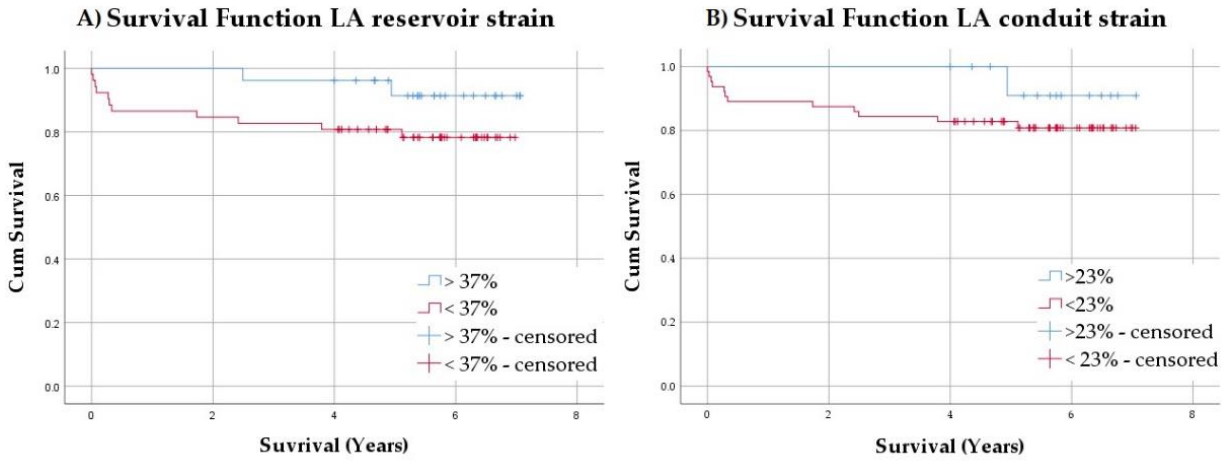

Figure 6 *– Kaplan Meier Curves for left atrial reservoir and conduit strain.*

4. Discussion

4.1. Clinical Relevance

Cardiological diagnostics have been developed throughout the last decades, allowing for more detailed evaluations of various heart conditions. Our investigation aimed to apply advanced STE in end-stage liver disease patients, to assess the benefits it may provide in cardiac evaluation prior to LTX. The main results presented in this dissertation and the corresponding publication (27) show that: 1) while LVEF was unaltered LV GLS was significantly elevated in all cardiac layers in cirrhosis patients compared to controls;

2) elevated GLS values correlated with severity of liver disease calculated by MELD-Score; 3) LA strain and strain rate are significantly decreased in cirrhosis patients.

While the effects of liver cirrhosis on the heart have been established and summarized under the term ‘cirrhotic cardiomyopathy’, advanced cardiac diagnostics have yet to be fully incorporated into the procedure of diagnosis of the condition. This is especially relevant when considering end-stage liver cirrhosis patients for LTX. Estimates for patients undergoing LTX with undiagnosed heart disease are as high as 50% (5, 7, 10, 12, 34), which is especially concerning considering cardiovascular complications are a major cause of perioperative morbidity and mortality, with up to 21% of post-transplantation deaths due to cardiovascular events (5, 7, 14).

While the European Association for the study of the Liver endorses standard and stress TTE evaluations according to patients’ cardiovascular risk profiles to expose cardiac dysfunction preceding LTX (35), advanced evaluation of images is yet to be endorsed. Jansen et al. were able to demonstrate a correlation between STE parameters at time of listing and TTE evaluation and the patients time of undergone LTX (36). Results suggested a possible prognostic value as LV GLS was a predictor of time to LTX (36). This might suggest that STE parameters gained from simple TTE evaluations as part of the evaluation process are useful to estimate the urgency of LTX (36). In another study Jansen et al observed a correlation between LV GLS and development of acute on chronic liver failure and overall survival after transjugular intrahepatic portosystemic shunt procedure (37), again suggesting prognostic use of STE parameters. While our study was unable to identify a significant predictor of mortality using STE parameters, further investigations assessing a possible prognostic value should be considered.

4.2. Assessment of Systolic Function using Left ventricular Strain

It has been established that LVEF only allows limited conclusions to be drawn about the cardiac condition in patients with cirrhosis, as it is affected by the splanchnic vasodilatory state causing normal or even increased values (13). Speckle tracking echocardiography has previously given further and more detailed information on cardiac function in various conditions, yet studies applying STE in cirrhosis patients have presented conflicting results – reporting reduced and/or increased global longitudinal strain in patients (38-40) when compared to controls. In this retrospective analysis we were able to demonstrate that GLS in patients with cirrhosis and normal LVEF was significantly

elevated (i.e., more negative). The increase in strain was observed throughout all cardiac layers (endo-, mid-, and epi-myocardial), which illustrates increased myocardial stress in respect to hyperdynamic circulatory syndrome and supplements the previous findings (39).

Higher GLS values have previously been described in cirrhosis patients with clinically significant portal hypertension and decompensated advanced liver disease (40). In agreement to this, our correlation analysis correlated increased GLS to increased liver-specific markers (ASAT, ALAT, bilirubin, INR) and hence MELD-scores. This further suggests that GLS increases with severity of liver cirrhosis. However, various authors have additionally described subclinical systolic impairment with reduced GLS (i.e., less negative) in cirrhosis patients with preserved LVEF (38, 40, 41) and additionally described a correlation between reduced GLS and higher MELD-score (41). Confirming these opposing results, *Mechelink et al.* established a non-linear relationship between survival and GLS, concluding both are negative prognostic factors (40). In our study we were unable to determine a predictor of mortality after LTX using Kaplan Meier Curves. While several studies have analysed cardiac function post-LTX using standard echocardiographic measurements (42), only very few have done so using GLS. These were able to demonstrate normalization of pathological strain (38, 39).

Until now GLS of the left ventricle is the most investigated parameter in STE. This is partly because GLS is determined by subendocardial fibres orientated parallel to the long-axis of the heart, which are compromised earliest in cardiac dysfunction (22). GCS and GRS, determined by mid-myocardial and epicardial fibres, are affected as impairment reaches a more transmural state (22). This process of deterioration can be observed in our results: while all layers are affected the endocardial layer showed the overall highest strain. Subsequently GLS is significantly increased in cirrhosis patients while GCS and GRS showed a trend towards increased strain – yet statistically insignificant. The robustness and reproducibility of GLS (21-23) further adds to its interest among physicians. It is averaged from measurements taken in three separate TTE views (apical long axis, two- and four chamber). In contrast, GCS and GRS are exclusively recorded in parasternal short axis view, thus affecting reducibility and variability of measurements. Interpretation of GCS and GRS is further limited by the transmural non-uniformity during contraction (26). This stability is reflected by our

results considering calculated standard deviation. Standard deviation is slightly increased for GCS and strongly increased for GRS when compared the GLS values, suggesting higher variability.

Along with strain imaging, standard echocardiographic parameters were measured. We were able to observe a significant increase in the following measurements in the cirrhosis group: LV end-diastolic diameter, intraventricular septum thicknesses, LV posterior wall thicknesses, LV mass and mass index. LV mass index was within normal ranges for both groups, however cirrhosis patients presented with significantly higher index than controls (79.9 g/m² < 102.5 g/m²). Calculated relative wall thickness showed no statistical difference between the two groups. This constellation suggests concentric cardiac remodelling in cirrhosis patients (43).

4.3. Assessment of Diastolic Dysfunction using Left Atrial Strain

While CCM is most often defined by the systolic dysfunction and impaired cardiac response in stress, it may also entail LV diastolic dysfunction (DD). DD is considered an early marker of CCM and can be assessed non-invasively through echocardiography (9). The original criteria for DD in CCM agreed upon at the World congress of Gastroenterology in 2005, have been superseded by the new guidelines set by the American Society of Echocardiography & European Association of Cardiovascular Imaging (ASE/EACVI) in 2016. According to these four conventional echocardiographic parameters should be used to diagnose DD and assess severity, including the following: mitral annular velocities (e' septal <7cm/s or e' lateral <10cm/s), early trans-mitral inflow velocity to average mitral annular velocity ratio (E/e' >14), LA volume index (LAVI >34ml/m²), and tricuspid regurgitation velocity (TR >2.8m/s) (30).

Our assessment concerning DD in cirrhosis patients remained inconclusive when considering our results of the above-mentioned parameters. Of the four parameters our cirrhosis group solely presented with significantly increased and pathological LAVI values, suggesting pathological dilation of the LA. While E/e' ratio also showed a significant increase in patients, the obtained average presented "grey zone" results allowing indeterminate interpretation (30, 44). TR values and both mitral annular velocities were all within normal range and no significant difference was observed for either between the two groups. Our patients thus present normal diastolic function,

according to ASE/EACVI guidelines based upon conventional echocardiographic parameters.

However, modern cardiac diagnostic methods should be considered for a more detailed evaluation. The interest in STE has expanded in consequence to the established diagnostic relevance of LV strain, sparking the evaluation of the LA using strain imaging (45, 46). LA strain analysis offers an alternate approach in evaluating LV filling pressures and diastolic function (25, 33, 47), and allows differentiation between active and passive myocardial movement and between the different atrial phasic functions (reservoir, conduit, and contractile function) (45, 48). Normal ranges have been established for LA strain and strain rate by a systematic review and meta-analysis (49, 50). While studies have been conducted utilizing LA strain in cardiac conditions such as heart failure, valvular heart disease, atrial fibrillation and coronary heart disease (46), data on LA strain in end-stage liver disease is scarce.

To the best of our knowledge this is the first study to assess LA strain including strain rate in patients with cirrhosis. The results of this study demonstrate a significant difference in LA strain and strain rate between healthy controls and cirrhosis patients; values for LA reservoir strain, conduit strain, and strain rates in all phasic functions were significantly reduced. These findings expand those of *Sampaio et al.*, who likewise described reduced reservoir strain and unaltered LA contractile strain in cirrhotic patients (51). Reduced LA strain and strain rate have been associated with various cardiac pathologies and increased LV filling pressure (52). It has been suggested that LA strain acts as an early marker of heart failure with preserved ejection, as LA reservoir and conduit strain have been observed to decline prior to DD diagnosis using conventional echocardiographic parameters (33). LA strain additionally allows accurate grading of DD, as it continues to decline with progressing severity (46). In agreement with the previously stated, the results presented suggest increased sensitivity of STE parameters concerning left atrial function and DD compared to conventional echocardiographic parameters. This supports conclusions drawn by previous studies (33, 50, 53) and extends clinical applicability of LA strain and strain rate.

4.4. Outlook on newly proposed CCM Criteria

Due to the increasing focus on strain analysis in modern cardiac evaluation, new CCM criteria have been proposed in 2020 by the CCC and include advanced speckle tracking

analysis (13). These criteria included adjustments of previously established parameters for systolic dysfunction in CCM (i.e., LVEF) and included LV GLS as an additional diagnostic criterion. While the CCC have agreed upon a lower limit for GLS (set at -18%), an upper limit is not regarded to diagnose systolic dysfunction. CCM Criteria regarding conventional echocardiographic parameters for DD have been revised according to the 2016 ASE/EACVI guidelines. LA strain was additionally endorsed to allow classification of patients with initial 'indeterminate' diastolic function.

When applying these new criteria to our cohort of 80 cirrhosis patients the prevalence of CCM was 27.5%. Systolic disfunction was assessed using LV GLS, as all our patients required normal LVEF to be included in this study. Reduced GLS was present in 17.5% of our patients, suggesting systolic dysfunction according to the newly proposed criteria. However, elevated GLS values are not regarded. Considering the previously established association of increased GLS with hyperdynamic circulatory syndrome in cirrhosis and as a negatively prognostic factor for survival, we believe that an upper reference limit for GLS needs to be considered in the diagnosis of early CCM.

After initial evaluation using conventional echocardiographic parameters, diastolic function was evaluated precisely in all but nine cases. LA strain was considered for further evaluation of patients who presented with indeterminate function, as recommended by the CCC. Four additional patients were consequently diagnosed with DD, leaving the following results concerning diastolic function: 58 patients presented with normal diastolic function, 12 patients presented with DD grade I, 7 patients presented with DD grade II, and 3 patients presented with DD grade III. While these results appear to demonstrate a limited effect of LA strain concerning DD diagnosis and classification, we were able to observe that of the cirrhosis patients with normal diastolic function 62% demonstrated reduced LA strain. Considering the suggested increased sensitivity of STE analysis to conventional parameters, reduced LA strain should be further evaluated as an early marker in diastolic assessment and should not exclusively be referred to in indeterminate cases.

4.5. Our limitations and future inquiries for speckle tracking technology

This study was able to demonstrate the potential of strain analysis in CCM diagnosis. However, various limitations must be acknowledged for accurate interpretation of these results. The retrospective nature of this study has limited the data and cardiac imaging

available for evaluation, as images were taken for clinical purposes and without the investigative focus of this study (27), especially considering the mentioned G*Power calculations. Previous studies were able to demonstrate changes in cardiac function of CCM patients post-LTX using conventional and strain imaging techniques (39, 42). Our study was unable to find a predictor for mortality, which have been described previously. Kaplan-Meier curves merely demonstrated a visual trend towards reduced post-transplant survival in patients with impaired LA reservoir and conduit strain (27). Relevance of the discussed findings is limited when considering the small sample size of our single-centre study and results should be expanded upon with a larger study cohort (27).

STE has proven advantageous, and several studies have concluded significant clinical relevance. Progress has been made to overcome limitations such as standardisation of measurements by implementing deformation imaging guidelines, allowing increasingly comparative results to be obtained (32). However, studies have shown that inter-vendor variability of the equipment still significantly impacts results. Without normal ranges for individual vendors, comparisons of studies are still limited, and vendors need to be considered in future discussions. Until recently, strain software verified for LV STE has commonly been used to evaluate other cardiac chambers. While results have been prospective and encouraging, chamber-specific software is still necessary, due to anatomical and functional differences impacting automated image analysis (32). Technological progress has also been made to allow more accurate STE investigations, such as the development of chamber specific software, however its use is not yet widespread. A recent study evaluated dedicated versus non-dedicated strain software for LA measurements and concluded that LA-dedicated software reached similar strain values as non-dedicated software yet proved higher reproducibility of those (54). These results suggest that future LA assessment should be computed using dedicated software.

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Eidesstattliche Versicherung

„Ich, Franzisca Vivien Victoria von Köckritz, versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema: Deformation analysis of the left heart in patients with advanced liver cirrhosis using 2D-speckle tracking echocardiography – Deformationsanalyse des linken Herzens von Patienten mit fortgeschrittener Leberzirrhose mittels 2D- Speckle-Tracking-Echokardiographie selbstständig und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe.

Alle Stellen, die wörtlich oder dem Sinne nach auf Publikationen oder Vorträgen anderer Autoren/innen beruhen, sind als solche in korrekter Zitierung kenntlich gemacht. Die Abschnitte zu Methodik (insbesondere praktische Arbeiten, Laborbestimmungen, statistische Aufarbeitung) und Resultaten (insbesondere Abbildungen, Graphiken und Tabellen) werden von mir verantwortet.

Ich versichere ferner, dass ich die in Zusammenarbeit mit anderen Personen generierten Daten, Datenauswertungen und Schlussfolgerungen korrekt gekennzeichnet und meinen eigenen Beitrag sowie die Beiträge anderer Personen korrekt kenntlich gemacht habe (siehe Anteilserklärung). Texte oder Textteile, die gemeinsam mit anderen erstellt oder verwendet wurden, habe ich korrekt kenntlich gemacht.

Meine Anteile an etwaigen Publikationen zu dieser Dissertation entsprechen denen, die in der untenstehenden gemeinsamen Erklärung mit dem/der Erstbetreuer/in, angegeben sind. Für sämtliche im Rahmen der Dissertation entstandenen Publikationen wurden die Richtlinien des ICMJE (International Committee of Medical Journal Editors; www.icmje.og) zur Autorenschaft eingehalten. Ich erkläre ferner, dass ich mich zur Einhaltung der Satzung der Charité – Universitätsmedizin Berlin zur Sicherung Guter Wissenschaftlicher Praxis verpflichte.

Weiterhin versichere ich, dass ich diese Dissertation weder in gleicher noch in ähnlicher Form bereits an einer anderen Fakultät eingereicht habe.

Die Bedeutung dieser eidesstattlichen Versicherung und die strafrechtlichen Folgen einer unwahren eidesstattlichen Versicherung (§§156, 161 des Strafgesetzbuches) sind mir bekannt und bewusst.“

Datum Unterschrift

Anteilserklärung an den erfolgten Publikationen

Franzisca Vivien Victoria von Köckritz hatte folgenden Anteil an den folgenden Publikationen:

Publikation:

von Köckritz, F.; Braun, A.; Schmuck, R. B.; Dobrindt, E. M.; Eurich, D.; Heinzel, F. R.; Pieske, B.; Escher, F.; Zhang, K., Speckle Tracking Analysis Reveals Altered Left Atrial and Ventricular Myocardial Deformation in Patients with End-Stage Liver Disease, J Clin Med, 2021 Feb 24;10(5):897. DOI: 10.3390/jcm10050897.

Beitrag von Franzisca von Köckritz im Einzelnen:

1. Erfassung der Laborparameter, anthropometrischen Angaben, Mortalitätsdaten und spezifischen echokardiographischen Messungen (LVEF und TR) aus OP-Berichten, Arztbriefen, TTE-Berichten oder ähnlichem hinterlegt in der digitalen Patientenakte im SAP (mit Hilfe von A.B.).

2. Selektion der geeigneten Patienten und gesunden Kontrollprobanden.

3. Evaluation und Selektion geeigneter TTE-Bilder der ausgewählten Patienten und Kontrollprobanden für die weitere Analysen.

4. Analyse der TTE-Bilder bezügliche aller konventionellen-, Doppler- und STE-Parametern mittels EchoPAC Software und Erfassung dieser für die statistische Auswertung.

5. Berechnung aller Variablen (z.B. MELD, RWT, LVMI, LAVI, LA EF und EV, LA conduit strain).

6. Durchführung der gesamten statistischen Analysen mittels SPSS.

7. Verfassung und Formatierung des Manuskripts der Publikation, inklusive Visualisierung der Daten. Alle Tabellen, Abbildungen, und graphische Darstellungen wurden eigens erstellt.

8. Bearbeitung der Revisionen im Peer-Review Prozess (mit Hilfe von K.Z.)

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Unterschrift, Datum und Stempel der erstbetreuenden Hochschullehrerin

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Unterschrift der Doktorandin

Auszug aus ‚Journal Summary List 2020'

Journal Data Filtered By: **Selected JCR Year: 2019** Selected Editions: SCIE,SSCI
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Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
1	NEW ENGLAND JOURNAL OF MEDICINE	347,451	74.699	0.660800
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3	JAMA-JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION	158,632	45.540	0.290050
4	Nature Reviews Disease Primers	7,567	40.689	0.032310
5	BMJ-British Medical Journal	118,586	30.223	0.145170
6	ANNALS OF INTERNAL MEDICINE	58,033	21.317	0.091210
7	JAMA Internal Medicine	17,260	18.652	0.086180
8	PLOS MEDICINE	32,312	10.500	0.065990
9	Journal of Cachexia Sarcopenia and Muscle	3,553	9.802	0.007860
10	Cochrane Database of Systematic Reviews	67,763	7.890	0.134360
11	CANADIAN MEDICAL ASSOCIATION JOURNAL	15,212	7.744	0.016160
12	JOURNAL OF TRAVEL MEDICINE	2,659	7.089	0.006360
13	MAYO CLINIC PROCEEDINGS	15,627	6.942	0.024990
14	JOURNAL OF INTERNAL MEDICINE	10,912	6.871	0.014180
15	BMC Medicine	15,204	6.782	0.042500
16	MEDICAL JOURNAL OF AUSTRALIA	11,075	6.112	0.011070
17	Translational Research	4,043	5.411	0.008350
18	JOURNAL OF THE ROYAL SOCIETY OF MEDICINE	4,214	5.238	0.002580
19	JAMA Network Open	2,239	5.032	0.007660

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Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
20	Deutsches Arzteblatt International	4,817	4.796	0.007380
21	ANNALS OF FAMILY MEDICINE	5,567	4.686	0.010880
22	JOURNAL OF GENERAL INTERNAL MEDICINE	20,229	4.597	0.026960
23	AMERICAN JOURNAL OF MEDICINE	24,975	4.529	0.024230
24	Journal of Personalized Medicine	617	4.433	0.001950
25	AMERICAN JOURNAL OF PREVENTIVE MEDICINE	23,547	4.420	0.040180
26	European Journal of Internal Medicine	4,933	4.329	0.010280
27	AMYLOID-JOURNAL OF PROTEIN FOLDING DISORDERS	1,486	4.323	0.002920
28	BRITISH JOURNAL OF GENERAL PRACTICE	6,669	4.190	0.008670
29	Frontiers in Medicine	3,034	3.900	0.009870
30	PREVENTIVE MEDICINE	17,316	3.788	0.030080
31	PALLIATIVE MEDICINE	5,413	3.739	0.008460
32	AMERICAN JOURNAL OF CHINESE MEDICINE	3,531	3.682	0.002970
33	MEDICAL CLINICS OF NORTH AMERICA	3,161	3.529	0.004080
34	EUROPEAN JOURNAL OF CLINICAL INVESTIGATION	6,344	3.481	0.006590
35	PANMINERVA MEDICA	806	3.467	0.000660
36	Journal of Clinical Medicine	5,214	3.303	0.010940
37	ANNALS OF MEDICINE	4,510	3.243	0.005190
38	CANADIAN FAMILY PHYSICIAN	3,833	3.112	0.005150

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Dazugehörige Publikation

Journal of *Clinical Medicine*

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Article

Speckle Tracking Analysis Reveals Altered Left Atrial and Ventricular Myocardial Deformation in Patients with End-Stage Liver Disease

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Abstract: Background: Cardiac function can be influenced by liver cirrhosis and should be thoroughly evaluated before liver transplantation. We investigated left ventricular (LV) and, for the first time, left atrial (LA) strain and strain rate in end-stage liver cirrhosis patients of different etiologies. Methods: This retrospective, cross-sectional study evaluated left heart function in 80 cirrhosis patients and 30 controls using standardized echocardiographic techniques and speckle tracking technology (STE) analysis. Serum markers of liver function were used for correlation analysis. Results: While conventional parameters demonstrated no alteration in systolic function, speckle tracking analysis showed a significant increase in LV longitudinal strain throughout all cardiac layers, with significant correlation to model of end-stage liver disease (MELD) score. LA reservoir and conduit strain as well as LA strain rate in all phases were significantly reduced in end-stage liver disease (ESLD) patients compared to control. STE for the evaluation of LA phasic function seemed to be more sensitive than volumetric methods. Kaplan-Meier curves showed a trend towards reduced post-transplant survival in patients with a reduced LA reservoir and conduit strain. Conclusion: STE analysis detected increased LV and decreased LA deformation in cirrhosis patients, thus proving to be highly sensitive to cardiac changes and useful for more precise cardiac evaluation.

Keywords: cirrhotic cardiomyopathy; left ventricle; left atrium; speckle tracking; strain

1. Introduction

1.1. Cirrhotic Cardiomyopathy

Cirrhotic cardiomyopathy (CCM) is cardiac dysfunction in patients with end-stage liver disease in the absence of prior heart disease [1–3]. Mild CCM usually remains asymptomatic at rest and most commonly manifests as prolonged QT interval ECG abnormality and sole diastolic dysfunction seen in 2D imaging [2–4]. Diagnosis of CCM is frequently missed or delayed due to its asymptomatic state and seemingly normal cardiac function at rest [2,4–6].

However, acute stress conditions, such as infection, transjugular intrahepatic portosystemic shunt (TIPS) procedure, or liver transplantation (LTx), can lead to extreme forms of CCM with overt heart failure in patients with end-stage liver disease (ESLD) [4,5]. Transthoracic echocardiography (TTE) is required by the European Association for the

Study of the Liver to unmask previously unknown cardiological conditions [5]. More elaborate evaluations (i.e., using dobutamine stress echocardiography) are usually only performed if abnormal TTE results were collected or if the patient's profile presents certain risk factors [4,5]. Estimates of ESLD patients who underwent LTx with an unknown cardiovascular disease are as high as 25–50% [2–6], and cardiovascular events account for approximately 7–21% of the subsequent deaths [5,7]. Thus, other more sensitive diagnostic approaches in cardiac imaging should be considered when evaluating cardiac functions of ESLD patients [5].

1.2. Speckle Tracking Echocardiography

Two-dimensional speckle tracking echocardiography (2D-STE) is a new technique to assess cardiac function, with major focus on the left ventricle (LV) in the clinical setting. It uses grayscale digital images with speckle patterns obtained from sonographic procedures such as TTE and analyzes the relative displacement of individual speckles on a frame-to-frame basis to quantify myocardial deformation, also referred to as "strain" [3,5,8,9]. Strain rate (SR) is the thickening or shortening per time and is yet another tool to assess myocardial function [3,5]. In the updated criteria for diagnosis of cirrhotic cardiomyopathy by the Cirrhotic Cardiomyopathy Consortium (CCC), the evaluation of LV global longitudinal strain (GLS) in addition to left ventricular ejection fraction (LVEF) has been proposed in order to estimate systolic function [1,10].

To date, STE has only been validated for LV assessment [11]. However, in recent years, the established software has also been used for left atrial (LA) evaluation as it allows detailed judgment of LA phasic reservoir, conduit, and contractile functions [11,12]. In comparison to volumetric measurements used conventionally for phasic assessment, LA strain has demonstrated higher sensitivity in early stages of disease, specifically in the assessment of diastolic function [9,12–14].

1.3. Aim

The present retrospective study aims to evaluate left ventricular and atrial myocardial deformation in patients waiting for liver transplantation using speckle tracking technology. The novel aspect of this study is the detailed evaluation of left atrial strain and strain rate in patients with end-stage liver disease.

2. Methodology

2.1. Patients and Control Group

From an archive of 290 LTxs performed in the Charité Campus Virchow center from 2013 until 2016, 80 ELSD patients with normal LVEF were considered for echocardiographic speckle-tracking analysis. Patients with a history of coronary disease, heart failure, congenital heart disease, atrial fibrillation, or moderate-to-severe valvular disease were excluded from the study. Thirty patients matched for age and sex, without liver disease, served as the control group.

Anthropometric measures (height and weight) were recorded for subjects and used to calculate body mass index (BMI) and body surface area (BSA). Laboratory analysis, including liver enzymes aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), alkaline phosphatase (AP), and gamma-glutamyltransferase (γGT); prothrombin time as the international normalized ratio (INR); total serum bilirubin; and creatinine, was performed on blood samples from all subjects on the day of echocardiography $\pm$ 10 days, except for one patient, whose lab results were taken 33 days before. We calculated the model for end-stage liver disease (MELD) score according to conventional formula using creatinine, bilirubin, and the INR. Values less than 1.0 were set to 1.0 for the purposes of calculation. The study was approved by the local ethics committee (#EA4/065/19).

2.2. Echocardiography and STE

TTE examinations were performed in the abovementioned timeframe by specialized cardiologists using Vivid 7 Ultrasound (GE Vingmed, Horton, Norway). Echopac 201 software (GE-Healthcare, Horton, Norway) was used to store TTE images and provided necessary tools for analysis and 2D STE. Standard echocardiographic images were recorded in parasternal short and long axes and apical two, three, and four chamber views using 2D echography. These were used to evaluate LV and LA dimensions and function utilizing established and endorsed techniques (i.e., caliber and volumetric measurements). The collected values permitted further calculations of relative wall thickness (RWT), LV mass (LVM) and mass index (LVMI), and LA volume index (LAVI). Additionally, LA phasic emptying volumes were calculated for the reservoir (TotEV), conduit (PassEV), and contractile (ActEV) phases. All values were then indexed (TotEF, PassEF, and ActEF) according to Andrew et al. [15]. LV ejection fraction (LVEF) data were obtained from statements recorded by examiners.

Furthermore, a pulse-waved (PW) doppler was used during TTE exams, allowing assessment of LV diastolic function through quantification of transmitral inflow velocities during early (E) and late (A) diastole and deceleration time (DT) [16]. The E/A ratio was computed. Septal and lateral mitral annular diastolic velocities (e' septal/lateral) were also collected using the PW doppler. Average e', derived from septal and lateral e´ values, was used to calculate the E/e´ ratio [16].

STE was performed using three consecutive cycles. Total region of interest (ROI) was manually traced for the software to recognize individual regions automatically. If the system did not identify all regions or tracking was visually inadequate, manual adjustments were made to ROI [9]. We accepted a maximum of one region not being identified by the system. LV GLS strain was computed in apical two-, three, and four-chamber (2CH, 3CH, 4CH) views. For LV global circumferential strain (GCS) and global radial strain (GRS) analysis, images in the parasternal short axis at the level of the papillary muscle were used. LA was analyzed in 2CH and 4CH views. LA strain and SR used systolic gating processing, beginning STE measurements with the onset of the QRS complex [11]. LA strain was given graphically by Echopac software. This allowed measuring peak atrial longitudinal strain and peak atrial contraction strain for the reservoir and contractile phasic function accordingly [11,12]. The calculated difference between the two was interpreted as atrial conduit function [11,12]. LA SR was also given graphically, and values for all the previously mentioned phases (SRs—reservoir, SRe—conduit, and SRa—contractile function) were obtained by measuring peak SR at systole and early and late diastole [11].

2.3. Statistical Analysis

Statistical analysis was performed with IBM SPSS Version 25 (SPSS Inc., Chicago, IL, USA) for Windows. All variables were checked for normal distribution graphically and using the Kolmogorov-Smirnov test. Consequently, the Mann-Whitney U or *t*-test were applied when appropriate. The Kruskal-Wallis test was used to compare GLS for different etiologies of cirrhosis. Spearman's correlation coefficient (*r*) was used to analyze any existing relationship between clinical, STE, and LA phasic function parameters in patients. Survival functions (Kaplan-Meier estimator) were computed to show differences in mortality for ESLD patients according to LA strain. Finally, we assessed predictors for mortality using Cox regression analysis.

Results are shown as average mean ± standard deviation and are accepted as statistically significant when $p < 0.05$.

3. Results

3.1. Demographic and Clinical Data

Eighty ESLD patients (47 males and 33 females) and a control group of $n = 30$ (14 males and 16 females) were recruited for this study. Controls had undergone TTE procedures as evaluation for potential organ or tissue donations or as regular checkup.

The basic demographic and clinical parameters are summarized in Table 1. As expected, liver enzymes ALAT, ASAT, and γGT and laboratory markers creatinine, total bilirubin, and INR were all significantly elevated in patients. Hence, the calculated average MELD score was significantly increased ($p < 0.001$).

Table 1. Demographic and clinical data of healthy controls vs. end-stage liver disease (ESLD) patients.

Variables	Controls				ESLD Patients				Statistics
	n				*n*				*p*
Gender (Male %)	30	46.70			80	58.80			0.258
Age (years)	30	48.57	±	12.93	80	52.47	±	10.24	0.145
BMI (kg/m^2)	30	24.43	±	3.40	79	26.30	±	5.11	0.067
ALAT (U/L)	30	23.63	±	10.19	80	58.39	±	48.49	<0.001
ASAT (U/L)	30	27.73	±	21.51	80	81.48	±	73.86	<0.001
AP (U/L)	29	66.34	±	18.01	80	235.91	±	376.25	<0.001
γGT (U/L)	30	21.40	±	11.80	80	159.75	±	212.32	<0.001
Creatinine (mg/dL)	30	1.02	±	0.06	80	1.16	±	0.33	0.028
Bilirubin (mg/dL)	29	1.02	±	0.06	80	7.01	±	8.64	<0.001
INR	29	1.02	±	0.04	80	1.55	±	0.52	<0.001
MELD Score	29	7	±	0.70	80	17	±	6.65	<0.001

BMI—body mass index, ALAT—alanine aminotransferase, ASAT—aspartate aminotransferase, AP—alkaline phosphatase, γGT—gamma-glutamyltransferase, INR—international normalized ratio, MELD—model for end-stage liver disease.

Patients suffered cirrhosis due to various etiologies. These included alcoholism (31.25%), hepatitis C (12.5%), autoimmune (10%), Non-Alcoholic Steatohepatitis (NASH 10%), Primary Sclerosing Cholangitis (PSC, 8.75%), idiopathic (8.75%), and others (e.g., cystic liver, M. Wilson, bile duct carcinoma, and Caroli syndrome; 18.75%). Due to the retrospective nature of this study, severity of disease was not classified using the Child-Pugh score.

At the time of this retrospective study, all patients had undergone LTx at our transplantation center. Up until finalizing data collection (Nov. 2020) 65 patients were still alive, 13 had died, and the status of 2 patients was unknown, as no recent update nor death records were registered. Of the deceased, an average time of survival of 20 months was calculated.

3.2. Echocardiography and Strain Measurements of the Left Ventricle

ESLD patients presented increased left ventricular mass (LVM) and end-diastolic dimension (LVEDD), as well as interventricular septum (IVS) and posterior wall thickness (PW) in comparison to controls. However, no statistically relevant changes were observed in width of aortic sinus, LV end-systolic dimension (LVESD), or RWT. Most importantly, both groups were found within a normal range concerning LVEF, with healthy controls and ESLD patients averaging at 60.90 ± 4.70% and 60.00 ± 5.17% ($p = 0.274$), respectively. End-diastolic and end-systolic volumes (EDV and ESV) were also unaltered.

Mitral inflow velocities (E, A), deceleration time (DT), and peak mitral annular velocity parameters (E´ septal, E´ lateral) were collected for patients and controls when appropriate echocardiographic images were available for evaluation. DT and the calculated E/A ratio, relevant for diagnosis of diastolic dysfunction, showed no difference between the two groups and were within normal ranges (DT < 140 ms and E/A > 0.8) according to ASE/EACVI Guidelines and Standards [16]. E´ values for septal and lateral mitral annulus points were also collected and did not differ among populations. The E/e´ ratio was calculated using an average of septal and lateral measurements and was significantly higher for ESLD patients at 9.42 ($p < 0.005$).

As seen in Table 2, patients displayed overall a significantly higher average GLS ($p < 0.001$). Mid-myocardial and endo- and epi-cardial layers similarly showed significantly higher values, suggesting increased transmural movement, as illustrated in Figure 1. GCS and GRS results showed no significant changes. Standard deviation was higher in GRS than in other strain analyses.

Table 2. Echocardiographic parameters of the left ventricle.

Variables	Controls				ESLD Patients				Statistics
	n				*n*				*p*
Aorta sinus (mm)	30	29.53	±	3.60	78	30.56	±	3.49	0.176
LVEDD (mm)	30	44.80	±	5.74	80	47.59	±	6.63	0.045
LVESD (mm)	30	34.20	±	4.47	80	35.75	±	9.22	0.416
IVS (mm)	30	9.50	±	1.59	80	11.12	±	1.84	<0.001
PW (mm)	30	9.77	±	1.52	80	11.05	±	1.89	0.001
RWT	30	0.44	±	0.07	80	0.47	±	0.10	0.121
LVM (g)	30	149.27	±	51.96	80	199.11	±	62.34	<0.001
LVMI (g/m^2)	30	79.87	±	21.99	79	102.49	±	28.50	<0.001
LV $Volume_{max}$	30	107.43	±	31.03	80	118.50	±	38.52	0.161
LV $Volume_{min}$	30	59.20	±	22.73	80	57.11	±	20.24	0.642
E (m/sec)	29	0.71	±	0.16	75	0.80	±	0.22	0.058
A (m/sec)	29	0.59	±	0.17	75	0.70	±	0.23	0.035
E/A ratio	29	1.25	±	0.36	75	1.23	±	0.41	0.828
DT (ms)	29	214.10	±	50.59	75	236.43	±	56.92	0.068
e′ sept (m/sec)	28	0.13	±	0.20	75	0.08	±	0.02	0.188
e′ lat (m/sec)	28	0.10	±	0.03	69	0.10	±	0.02	0.984
E/e′ ratio	28	7.57	±	2.88	69	9.42	±	2.88	0.005
TR (m/sec)	16	2.41	±	0.33	65	2.53	±	0.38	0.232
LVEF (%)	30	60.90	±	4.70	79	60.00	±	5.17	0.274
Strain Analysis (%)									
GLS average	30	−18.73	±	2.95	80	−21.39	±	4.06	<0.001
GLS mid-myocardial	30	−18.56	±	2.63	80	−21.26	±	4.05	<0.001
GLS endocardial	30	−21.34	±	3.00	80	−24.16	±	4.58	<0.001
GLS epicardial	30	−16.28	±	2.39	80	−18.75	±	3.62	<0.001
GCS	22	−17.16	±	5.06	55	−19.85	±	6.69	0.093
GRS	22	30.77	±	21.22	55	35.92	±	18.79	0.298

LV—left ventricle, LVEDD—end-diastolic diameter, LVESD—end-systolic diameter, IVS—interventricular septum, PW—posterior wall thickness, RWT—relative wall thickness, LVM—LV mass, LVMI—LV mass index, TR—tricuspid regurgitation velocity, E—transmitral inflow velocity at early diastole, A—transmitral inflow velocity at late diastole, e′ sept/lat—septal/lateral mitral annular diastolic velocities, DT—deceleration time, LVEF—ejection fraction, GLS—global longitudinal strain, GCS—global circumferential strain, GRS—global radial strain.

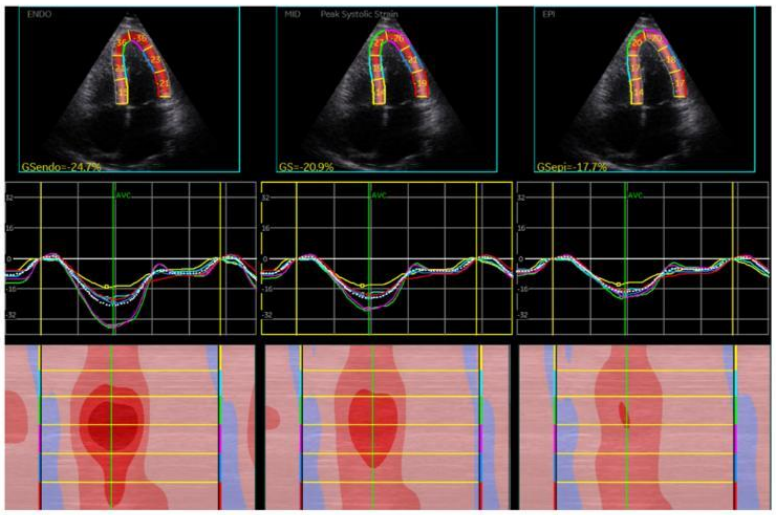

Figure 1. Example of left ventricular (LV) multilayer global longitudinal strain (GLS) in transthoracic echocardiography (TTE) four-chamber view.

GLS analysis subdivided into different cirrhosis etiologies showed no significant difference between the groups (Table 3). Of note, subgroups partly contain a limited number of patients.

Table 3. Comparison of Global Longitudinal Strain (GLS) and left atrial (LA) reservoir strain for different etiologies of cirrhosis in patients.

Etiology	Average GLS			LA Reservoir Strain		
Idiopathic (n = 7)	−22.06	±	4.16	40.91	±	15.53
Alcoholic (n = 25)	−20.91	±	4.12	30.28	±	10.03
HCV (n = 10)	−22.44	±	4.01	33.70	±	9.15
NASH (n = 8)	−20.05	±	4.76	33.32	±	12.82
PSC (n = 7)	−20.85	±	3.19	34.00	±	11.10
Autoimmune (n = 8)	−24.73	±	4.66	33.95	±	10.46
Others (n = 15)	−20.35	±	3.11	31.50	±	8.49
p	0.143			0.748		

HCV—Hepatitis C Virus Infection, NASH—Non-alcoholic steatohepatitis, PSC—Primarily sclerosing cholangitis

3.3. Echocardiography and Strain Measurements of the Left Atrium

Volumetric echocardiographic results are not reported for each patient and control due to ECG quality (i.e., p-wave not precisely distinguishable) or missing BMI in one patient, thus limiting the available data points. Nonetheless, elevated LA volumes were recorded at the end of ventricular systole (i.e., maximum dilation), beginning of p-wave, and end of ventricular diastole (i.e., minimal contraction) in ESLD patients, reaching statistical relevance with $p < 0.001$ for all three values. Consequently, all calculated values for LAVI reached similar significance when comparing patients to controls.

All LA phasic volumetric values showed a consistent significant increase for patients. However, this change was not seen when values were indexed, as only the LA passive emptying fraction (i.e., conduit phase) reached statistical significance, while LA total and active emptying fractions (i.e., reservoir and contractile phases) showed no difference between the two groups (Table 4).

Table 4. Echocardiographic parameters of the left atrium.

Variables	n	Controls			n	ESLD Patients			Statistics p
LA $Volume_{max}$ (mL)	30	28.85	±	17.21	80	75.13	±	49.52	<0.001
LA $Volume_{pre\text{-}A}$ (mL)	22	16.65	±	8.64	60	40.68	±	28,90	<0.001
LA $Volume_{min}$ (mL)	30	9.00	±	6.11	80	21.27	±	14.95	<0.001
$LAVI_{max}$ (mL/m^2)	30	15.37	±	8.65	79	38.73	±	24.04	<0.001
$LAVI_{pre\text{-}A}$(mL/m^2)	22	8.90	±	4.23	59	21.24	±	15.04	<0.001
$LAVI_{min}$ (mL/m^2)	30	4.83	±	3.27	79	10.90	±	7.11	<0.001
LA TotEV (mL)	30	19.85	±	13.15	80	53.86	±	38.48	<0.001
LA PassEV (mL)	22	9.96	±	6.14	60	35.71	±	32.13	<0.001
LA ActEV (mL)	22	8.45	±	5.45	60	19.81	±	18.61	0.001
LA TotEF (%)	30	68	±	17	80	71	±	11	0.872
LA PassEF (%)	22	39	±	13	60	45	±	16	0.052
LA ActEF (%)	22	51	±	18	60	48	±	16	0.213
Strain Analysis (%)									
Reservoir strain	30	39.97	±	9.74	80	32.86	±	10.65	0.002
Conduit strain	30	21.12	±	7.40	80	15.38	±	6.94	<0.001
Contractile strain	30	18.85	±	5.08	80	17.48	±	7.37	0.352
Strain Rate Analysis (1/s)									
Reservoir SR	30	1.66	±	0.44	80	1.39	±	0.40	0.003
Conduit SR	30	−1.92	±	0.72	80	−1.23	±	0.47	<0.001
Contractile SR	30	−2.43	±	0.68	80	−1.87	±	0.64	<0.001

LA—left atrium, LAVI—left atrium volume index, pre-a—pre-atrial contraction, TotEV—total emptying volume, PassEV—passive emptying volume, ActEV—active emptying volume, TotEF—total emptying fraction, PassEF—passive emptying volume, ActEF—active emptying volume, SR—strain rate.

Speckle tracking analysis was preformed likewise for all three atrial phases and demonstrated reduced LA strain in reservoir and conduit phasic functions with $p = 0.002$ and $p < 0.001$, respectively. LA contractile strain was unaltered. A significant decrease in strain rate was observed in ESLD patients for all atrial phases. Speckle tracking analysis is exemplarily depicted in Figure 2.

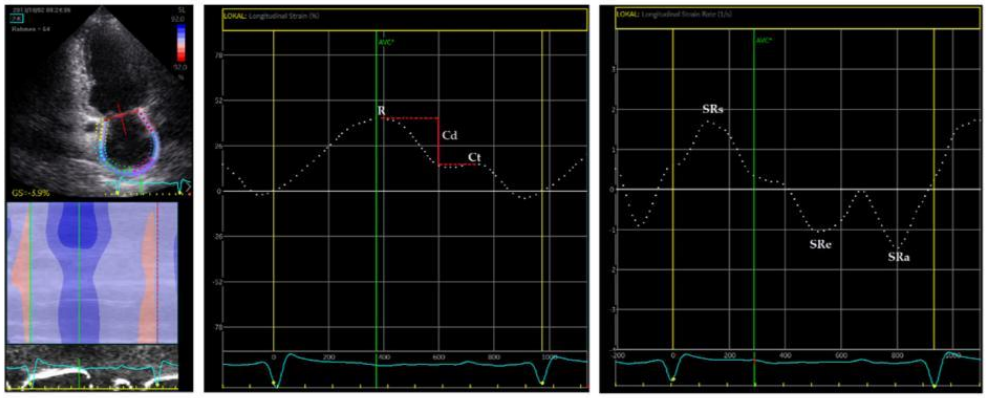

Figure 2. Example of LA strain and strain rate measurements measured in TTE two-chamber view. R—reservoir strain, Ct—contractile strain, Cd—conduit strain, SRs—reservoir strain rate, SRe—conduit strain rate, SRa—contractile strain rate.

3.4. Prevalence of CCM in Study Cohort

When applying the criteria proposed by the CCC [1], 27.5% of the patients could be diagnosed with CCM. Among the patients, 14/80 (17.5%) showed systolic dysfunction, yet rather mild (average LVEF: 57%; average GLS: 16%). Regarding diastolic function, nine patients presented indeterminate function after initial evaluation. Further evaluation of these patients using LA strain according to the CCC recommendations was performed. Ultimately, 58 patients presented normal diastolic function, 12 grade I (15%), 7 grade II (8.75%), and 3 grade III (3.75%) dysfunction. Interestingly, 62% of the patients with normal diastolic function also showed a reduced LA reservoir strain.

3.5. Correlation Analysis in ESLD Patients

Correlation analyses are summarized in Table 5. The most noteworthy correlations found were concerning GLS. All LV global longitudinal strains measured (epi-, endo- and mid-myocardial) consistently correlated with ALAT, ASAT, bilirubin, and the INR, each to an extent of $p < 0.01$. This indicates that higher laboratory markers are associated with increased GLS (more negative) values. Hence, correlations between the endo-, epi- and mid-myocardial GLS and MELD are comprehensible since MELD score is based upon previously mentioned laboratory markers. GLS of individual myocardial layers correlated with MELD to a similar extend, with epicardial reaching $r = -0.379$, mid-myocardial $r = -0.360$, and endocardial $r = -0.346$.

In addition, correlation analysis of LA parameters with laboratory markers and MELD were computed. The results show that LA strain and strain rate tend to correlate comparatively consistently with liver enzymes ALAT and ASAT, creatinine and the INR when compared with LA phasic volumetric parameters.

Table 5. Correlation analysis in ESLD patient cohort.

Variables	*r*							
	ALAT (U/L)	ASAT (U/L)	AP (U/L)	γGT (U/L)	Creatinine (mg/dL)	Bilirubin	INR	MELD Score
Left ventricle								
GLS average	**−0.306** **	**−0.297** **	**0.065**	**0.192**	**−0.084**	**−0.328** **	**−0.324** **	**−0.361** **
GLS mid-myocardial	**−0.304** **	**−0.294** **	0.071	0.190	−0.090	**−0.325** **	**−0.325** **	**−0.360** **
GLS endocardial	**−0.302** **	**−0.300** **	0.080	0.198	−0.063	**−0.313** **	**−0.338** **	**−0.346** **
GLS epicardial	**−0.306** **	**−0.296** **	0.037	0.173	−0.114	**−0.349** **	**−0.293** **	**−0.379** **
Left atrium								
R strain	**0.275** *	**0.301** **	0.079	0.018	**−0.271** *	**0.228** *	0.162	0.111
Ct strain	**0.223** *	**0.316** **	0.205	0.025	**−0.239** *	**0.228** *	0.119	0.127
Cd strain	0.186	0.191	−0.032	−0.001	−0.155	0.160	0.107	0.058
SRs	**0.249** *	**0.234** *	0.004	−0.030	**−0.246** *	0.198	0.179	0.144
SRe	**−0.273** *	−0.217	−0.141	−0.130	**0.250** *	**−0.272** *	−0.014	−0.102
SRa	**−0.315** **	**−0.274** *	−0.024	−0.121	**0.288** **	−0.105	0.055	0.068
TotEV	0.010	−0.022	−0.078	−0.174	**0.296** **	0.076	**0.324** **	**0.273** *
PassEV	−0.040	−0.076	−0.003	−0.113	**0.323** *	0.085	0.227	0.227
ActEV	−0.087	−0.147	**−0.330** **	−0.158	0.155	−0.126	**0.345** **	0.058
TotEF	**0.282** *	0.158	0.072	−0.067	−0.145	0.102	−0.041	0.012
PassEF	0.209	0.195	**0.317** *	0.070	0.090	**0.281** *	−0.038	0.226
ActEF	**0.317** *	0.156	−0.094	−0.088	−0.233	−0.029	0.111	−0.046

Significant correlations are given in bold for visualization purposes. * marks $p < 0.05$, ** marks $p < 0.01$. GLS – global longitudinal strain, R—reservoir, Ct—contractile, Cd—conduit, SRs—reservoir strain rate, SRe—conduit strain rate, SRa—contractile strain rate, TotEV—total emptying volume, PassEV—passive emptying volume, ActEV—active emptying volume, TotEF—total emptying fraction, PassEF—passive emptying volume, ActEF—active emptying volume, ALAT—alanine aminotransferase, ASAT—aspartate aminotransferase, AP—alkaline phosphatase, γGT—gamma-glutamyltransferase, INR—international normalized ratio (INR), MELD—model for end-stage liver diseas.

3.6. Mortality Analysis in ESLD Patients

Kaplan-Meier curves were computed for LA reservoir, conduit, and contractile strain. While none reached statistical significance, it should be noted that reservoir ($p = 0.123$) and conduit ($p = 0.286$) strain demonstrated a trend towards patients with pathological values being at higher risk of mortality after LTx (Figure 3). Perhaps the sample size remains too small. No such trend was observed for contractile strain ($p = 0.434$). Similarly, Cox regression analysis identified none of the tested variables as predictors of mortality: LA reservoir ($p = 0.099$), conduit strain ($p = 0.236$), contractile strain ($p = 0.432$), GLS ($p = 0.993$), MELD ($p = 0.797$), and BMI ($p = 0.921$).

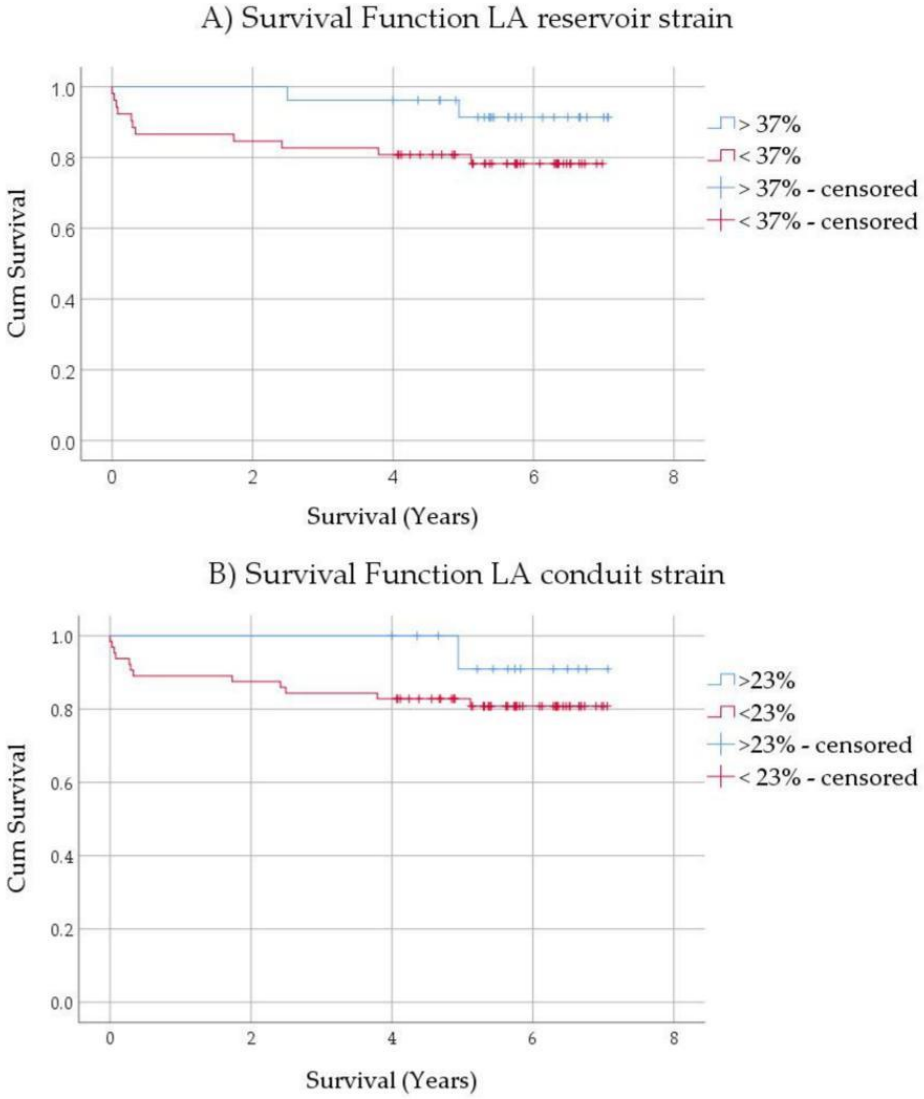

Figure 3. Kaplan-Meier curves for left atrial (**A**) reservoir (p = 0.123) and (**B**) conduit (p = 0.286) strain, showing trend towards increased post-transplant mortality. LA: left atrium

4. Discussion

The present study evaluated left heart function in ESLD patients using established echocardiographic techniques and extending this inquiry by employing 2D speckle tracking technology. This study presents the first evaluation of left atrial strain and strain rate in ESLD patients.

Our results indicate significantly elevated GLS for ESLD patients, while LVEF values were unaltered. Data on GLS in cirrhotic patients with normal LVEF are limited and conflicting [17–20]. Mechelinck et al. recently reported that both low and high GLSs occur in ELSD patients and are both negative prognostic factors [20]. While a reduced GLS

represented a subclinical systolic dysfunction, an increased GLS was associated with more advanced liver diseases [20]. Supporting this finding, we established a correlation of LV GLS with various liver-specific laboratory markers and MELD score. Kim et al. observed normalization of elevated GLS in cirrhosis within one-year post-transplantation, showing the therapeutic value of LTx for systolic function [19].

The deformation of cardiac fibers throughout all layers illustrates the increased myocardial stress in the context of a hyperdynamic circulatory syndrome, which has long been described in cirrhotic patients and is attributed to the heart's response to splanchnic arterial vasodilation and decreased systemic vascular resistance [2,8,21,22]. Transmural, systolic activation detected in this study can also be additionally supported by elevated GCS and GRS trends when comparing patients to controls, although results do not reach statistical relevance. In addition to ventricular deformation changes, we observed an increase in LVEDD, IVS, PW, and LVM, which suggests cardiac remodeling in ESLD patients [23–25]. Patients presented with significantly increased LVMI (102.49 ± 28.50 vs. 79.87 ± 21.99 g/m^2), thus trending towards concentric hypertrophy [26].

Based on the accumulating evidence that GLS is a useful value for the assessment of systolic function, the recently updated criteria for the diagnosis of CCM by the CCC included the evaluation of GLS (normal range absolute GLS $\geq$ 18%) in addition to LVEF (normal range >50%) [1,10].

DD has been described as an early marker for CCM [8] and can be identified through four conventional variables: mitral annular velocities (e´ septal and lateral), E/e´ratio, LAVI, and tricuspid regurgitation velocity (TR vel) [16]. According to the ASE/EACVI guidelines and as it has also been proposed by the CCC, diastolic function, as well as its severity, is diagnosed based on these four criteria [1,16]. Considering our results of the parameters, only LAVI was significantly elevated. With an E/A ratio >0.8, normal diastolic function can be stated according to the abovementioned guidelines. The E/e´ ratio also showed a significant increase; however, with a value of 9.42 ± 2.88, patients presented indeterminate results which do not allow clear interpretation [16,19,27]. Hence, diagnosis of DD in ESLD patients could not be validated through conventional parameters.

STE analysis of the left atrium has been proposed as an alternative approach for LV filling pressure and diastolic function assessment, as it displays the physiology of left atrial function which closely follows LV dynamics [28,29]. Remodeling of the LA has been proposed as a measure of diastolic burden and a predictor of cardiovascular outcomes such as new atrial fibrillation, heart failure, or cardiovascular death [29]. Our study demonstrated significant changes in left atrial strain and strain rates (SR) in cirrhosis. While volumetric measurements could not discriminate a convincing difference in LA phasic function, LA reservoir and conduit strain as well as strain rate in all phases were significantly reduced in ESLD patients compared to control. In agreement with this finding, several studies reported that myocardial LA analyses using STE have advantages over volumetric LA measurements [30,31].

In the current recommendations for the diagnosis of CCM by the CCC, the evaluation of LA strain was included to further evaluate patients with indeterminate diastolic function [1]. In this study, nine patients presented indeterminate function after initial evaluation, out of which four were categorized in advanced diastolic dysfunction (grade II or III) with the use of LA strain. However, a substantial number of patients with normal diastolic function (62%) also showed a reduced LA reservoir strain. Reduced LA strain has been associated with heart failure with preserved EF (HFpEF) and is suggested as an early marker of such, as conduit and reservoir functions decline prior to definite diagnosis of DD [32], thus suggesting increased sensitivity compared to conventional parameters [11,12,31,32]. This is supported by our results as both reservoir and conduit strain are reduced significantly, while standard echocardiographic measurements are too uncertain to diagnose DD. Moreover, Kaplan-Meier curves showed a trend towards reduced post-transplant survival in patients with reduced LA reservoir and conduit strain. Considering the results of this study and the previous reports in the literature, it can be discussed whether LA strain

should belong to the parameters for the initial evaluation of diastolic function. However, data on LA strain and strain rate in cirrhotic patients are very scarce. In concordance with our results, Sampaio et al. reported a reduced LA reservoir strain and an unchanged LA contractile strain in cirrhotic patients [33]. To the best of our knowledge, this is the first time that LA strain rate analysis was conducted in cirrhotic patients. Like LA strain, a decrease in LA strain rate is associated with increased LV filling pressure and different conditions of heart disease, according to Gan et al. [11]. There are as of yet no validated algorithms and established normal values.

This study demonstrates that STE analysis of LA deformation exposes minor cardiac dysfunction in ESLD patients more accurately than conventional measurements and should be further evaluated during cardiac evaluation. To gain more insight, more studies on this subject including the evaluation of outcome parameters are needed.

5. Limitations

The most prominent limitation of this study is its retrospective nature. This limited the amount of obtained laboratory data and cardiac imaging.

In consideration of previously reported potential changes in GLS post LTx by Kim et al. [19], the lack of follow up cardiac examinations is a great limitation. These were not available for patients since they were transferred into ambulant care for annual checkups. Furthermore, the study at hand was a single-center study, which allowed for only a small number of patients and controls to be enrolled. Even though significant differences in cardiac function were observed, further investigations with a larger study cohort would be necessary to confirm the obtained results. Additionally, considering our small population, we did not focus on grouping patients according to etiology of cirrhosis. Lastly, although 2D-STE allows for angle-independent myocardial deformation and shows higher sensitivity than conventional parameters, it still presents high inter-vendor variability [9], thus requiring reference values established with the same system.

6. Conclusions

In brief, this study demonstrates that strain analysis of the left ventricle and atrium is a useful tool to detect subtle changes in left ventricular systolic and diastolic function in patients with end-stage liver disease. Using 2D-STE, we were able to demonstrate increased LV GLS and an impairment of LA atrial strain and strain rate in cirrhotic patients.

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Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by Ethics Committee of Charité—Universitätsmedizin Berlin (EA4/065/19).

Informed Consent Statement: Patient consent was waived due to retrospective nature of this study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author. The data are not publicly available due to ethical restrictions.

Conflicts of Interest: The authors declare no conflict of interest.

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Lebenslauf

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.

Vollständige Publikationsliste

- **von Köckritz F**, Braun A, Schmuck RB, Dobrindt EM, Eurich D, Heinzel FR, Pieske B, Escher F, Zhang K. Speckle Tracking Analysis Reveals Altered Left Atrial and Ventricular Myocardial Deformation in Patients with End-Stage Liver Disease. J Clin Med. 2021 Feb 24;10(5):897. doi: 10.3390/jcm10050897. PMID: 33668295; PMCID: PMC7956617.
  Impact Factor: 3.303 (“Journal Summary List 2019”)

- Zhang K, Braun A, **von Köckritz F**, Schmuck RB, Teegen EM, Cuspidi C, Heinzel F, Pieske B, Tadic M. Right Heart Remodeling in Patients with End-Stage Alcoholic Liver Cirrhosis: Speckle Tracking Point of View. J Clin Med. 2019 Aug 22;8(9):1285. doi: 10.3390/jcm8091285. PMID: 31443575; PMCID: PMC6780282.
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