10th Annual Update on Liver Disease: A Multidisciplinary Approach
March 4, 2023

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Cirrhotic Cardiomyopathy

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Disclosure Slide

No Disclosures Relevant to this presentation

Consultant (Heart Failure Clinical Trials):

Orchestra Biomed

Endotronix

Cardiac Output at rest in Laennec's cirrhosis

THE CARDIAC OUTPUT AT REST IN LAENNEC'S CIRRHOSIS[1]

By HENRY J. KOWALSKI[2] AND WALTER H. ABELMANN

(From the Thorndike Memorial Laboratory, Second and Fourth Medical Services [Harvard], and the Department of Medicine, Harvard Medical School, Boston, Mass.)

(Submitted for publication April 29, 1953; accepted June 12, 1953)

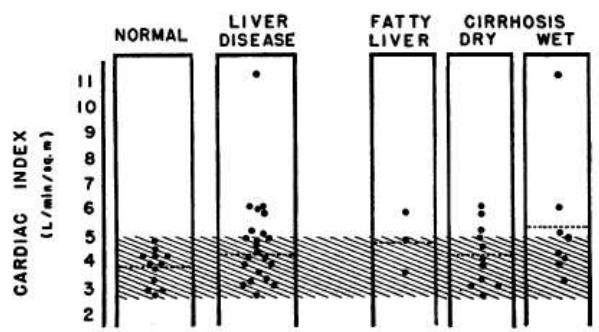

FIG. 1. SCATTER OF CARDIAC INDEX

Patients with Lae
occidental beri-beri
background of cons
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beri-beri (1) and in
gests an elevated c
beri-beri, this has b
our knowledge, dir
blood flow have not
disease. Increased
in patients with Lae
the frequent occurrence of warm extremities, cutaneous vascular spiders, wide pulse pressure, and capillary pulsations in the nail beds.

The present study reports measurements of the resting cardiac output, blood pressure, and peripheral resistance in patients with chronic alcoholism and disease of the liver.

ad enlargement of the
18) had cutaneous vas-
abnormally high Brom-

made clinically when
r and laboratory evi-
the following: icterus,
edema, splenomegaly,

in the morning without
mbent. An indwelling
brachial artery and a
right antecubital vein.
est for at least twenty
minutes.

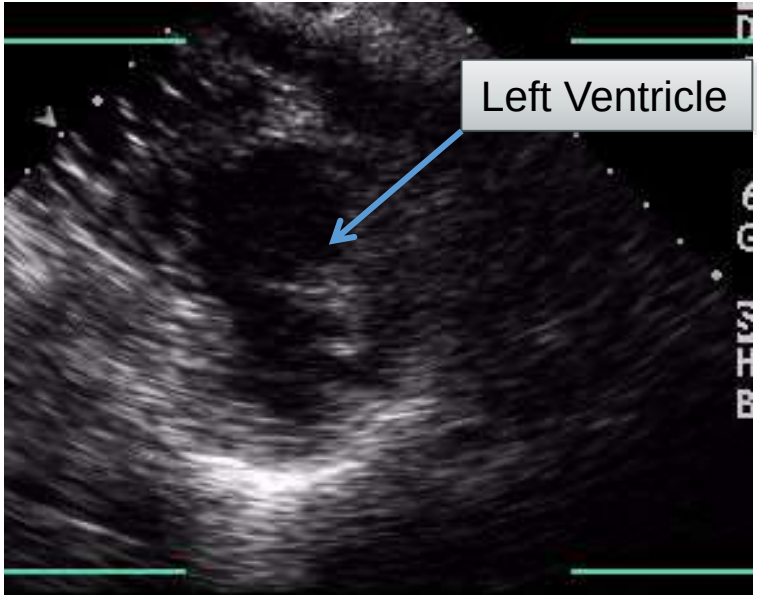
Cardiac output

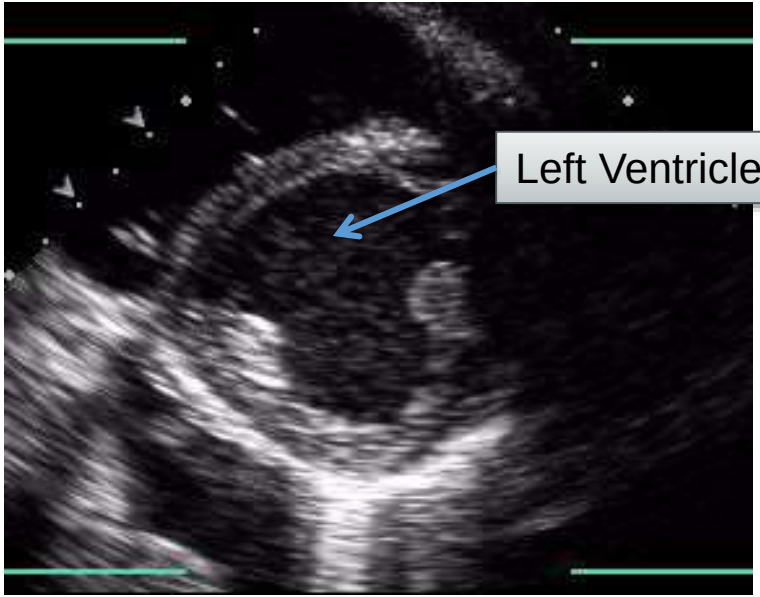
The cardiac output was determined by the dye-injection method as described by Hamilton and his co-workers (8). Five mg. of a 0.5 per cent solution of Evans blue dye were injected rapidly through the venous needle from a tuberculin syringe previously calibrated by weighing. The dead space of the indwelling needle was known and accounted

Cardiovascular Syndromes in Liver Disease

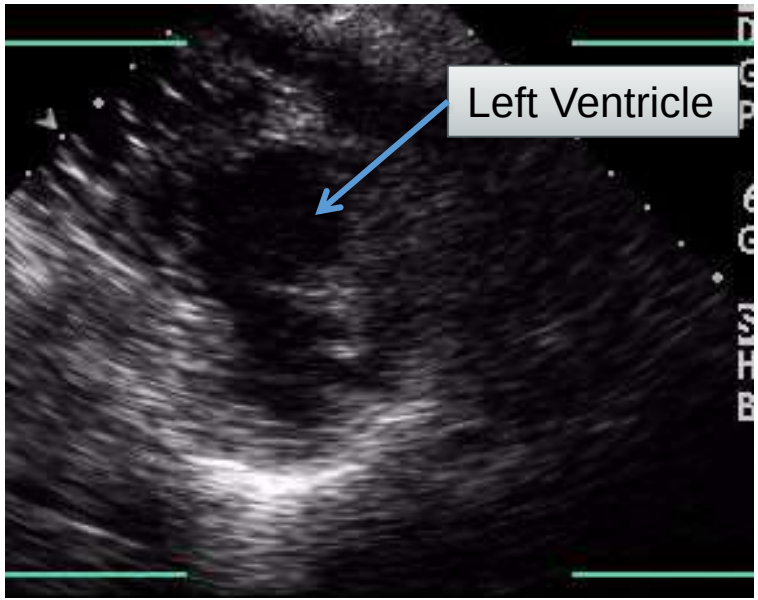
I. Portopulmonary Arterial Hypertension
II. Hepatopulmonary Syndrome
III. Non-alcoholic Fatty Liver Disease, Metabolic Syndrome and Cardiovascular Disease
IV. Cirrhotic Cardiomyopathy

Cirrhotic Cardiomyopathy

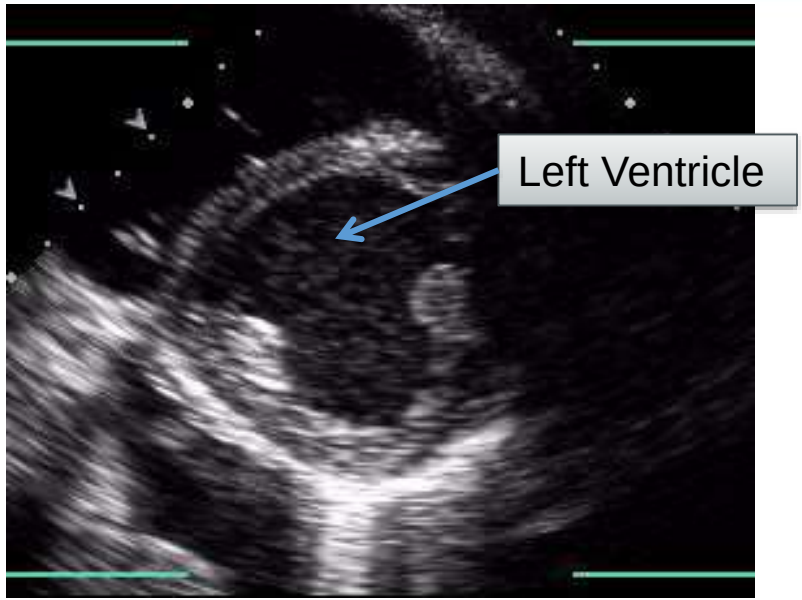




Dobutamine Stress Echo



Baseline

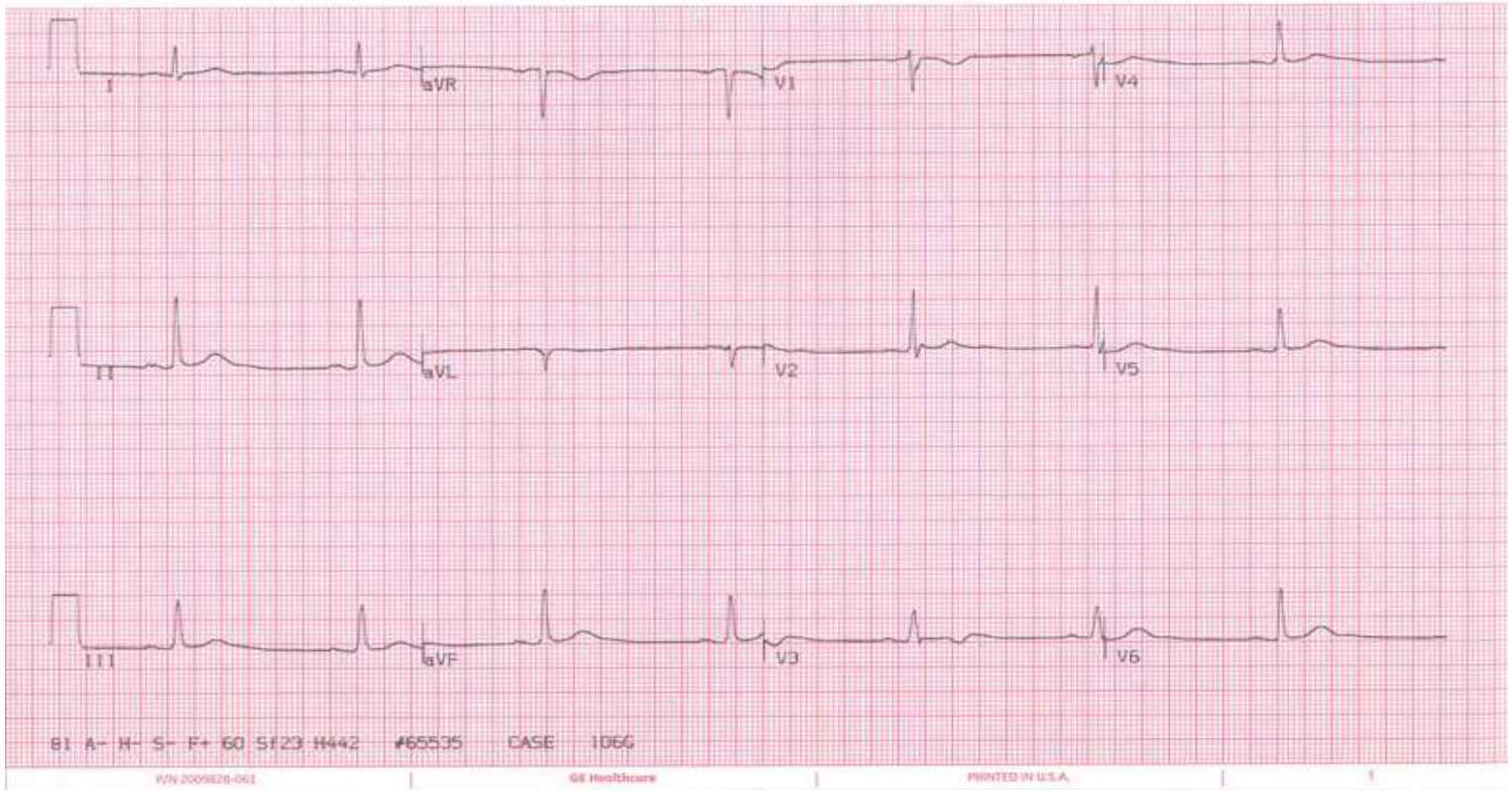


Peak dobutamine dose of 50 ug/kg/min -

Systolic dysfunction: Blunted increase in cardiac output and HR with exercise, volume challenge or pharmacological stimuli or; Resting ejection fraction 55%

Chronotropic Incompetence

At peak dobutamine dose of 50 ug/kg/min



Cirrhotic Cardiomyopathy

Cardiac dysfunction in patients with cirrhosis of any etiology characterized by impaired contractile responsiveness to stress and/or altered diastolic relaxation with electrophysiological abnormalities in the absence of other known cardiac disease

As Cirrhotic Cardiomyopathy manifests (only) under stress it remains an underrecognized condition

Cardiac muscle dysfunction, systolic and/or diastolic in patients with ESLD in the absence of known heart disease (2019).

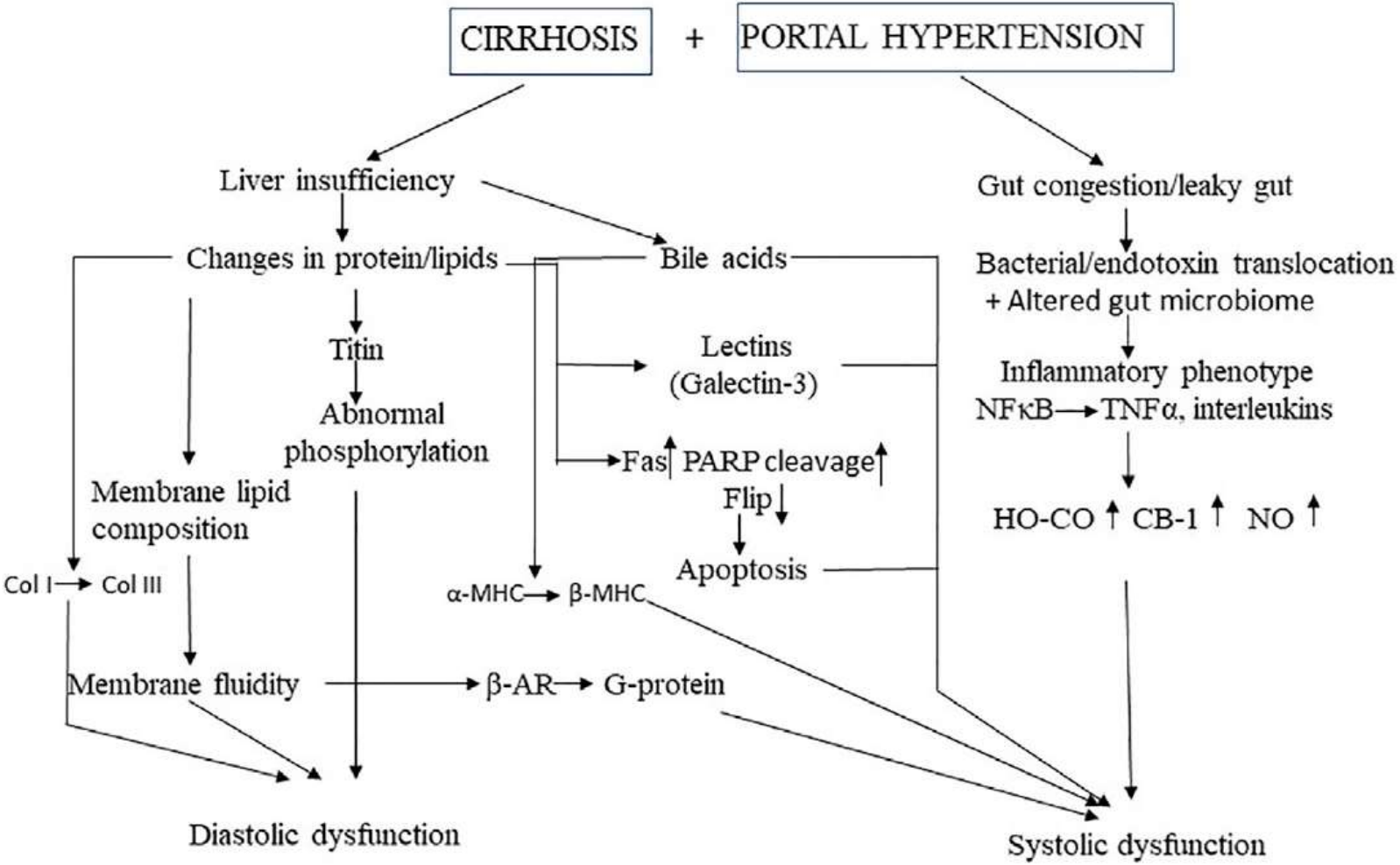
The heart at rest may manifest no cardiac dysfunction

Cirrhotic Cardiomyopathy
The Heart, when the Liver Fails

Two concurrent mechanistic pathways:

- Inflammatory phenotype due to portal hypertension with intestinal congestion resulting in bacteria/endotoxin translocation into the systemic circulation and cytokine storm: TNFa, IL-1B, IL-6 with cardiac dysfunction (apotosis, hypertrophy, fibrosis). Also NO, CO and endocannabinoid CB-1 pathways that mediate myocardial depression and B adrenergic blockade
- Protein/Lipid Synthetic/Metabolic defects: Abnormalities in Titin ad Collagen synthesis leading to diastolic dysfunction; increase in bile acids with switch from α to β MHC; abnormal sarcolemmal and cell membranes with abnormal Ca flux

Liu et al. (2022) Pathogenic Mechanisms Underlying Cirrhotic Cardiomyopathy. Front. Netw. Physiol. 2:849253. doi: 10.3389/fnetp.2022.849253



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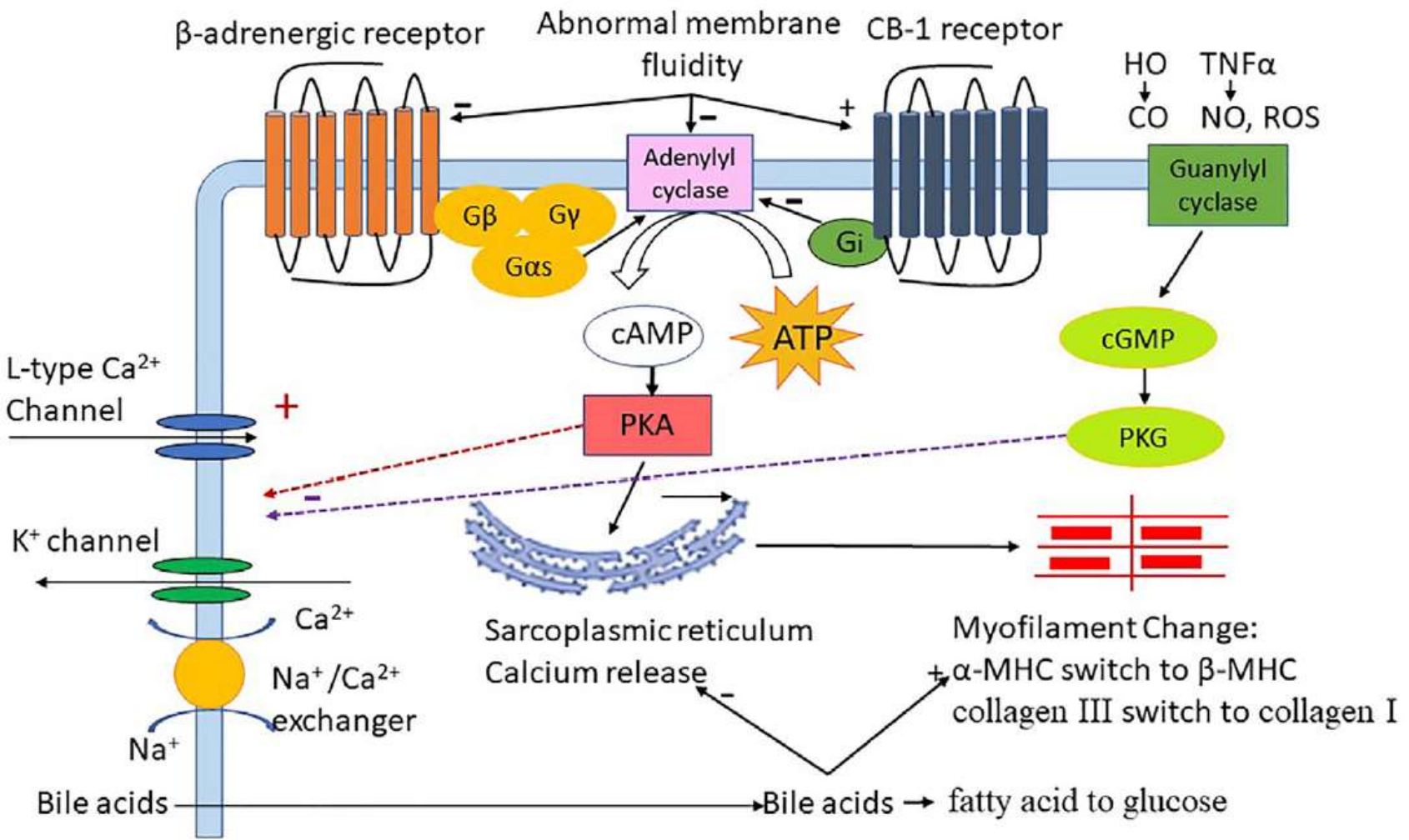
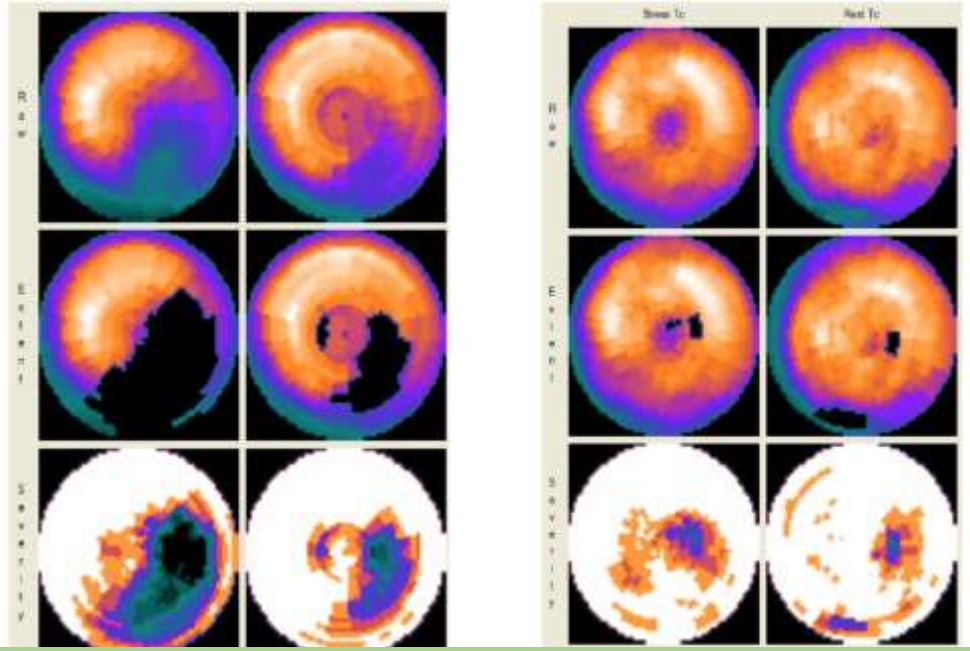


Liu et al. (2022) Pathogenic Mechanisms Underlying Cirrhotic Cardiomyopathy. Front. Netw. Physiol. 2:849253. doi: 10.3389/fnetp.2022.849253

Autonomic Dysfunction

Cirrhosis

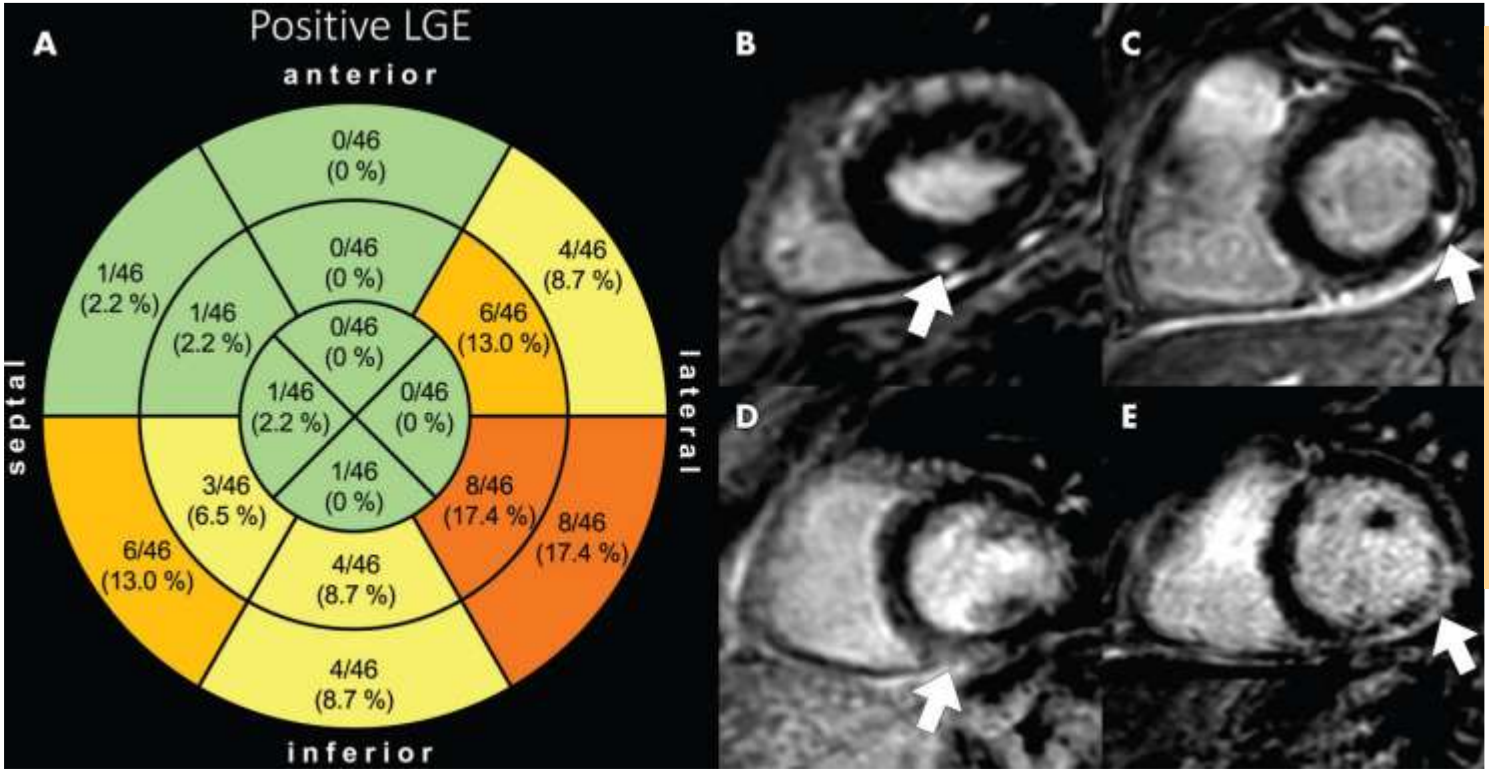


Control

γ-Camera imaging with *m*IBG reflects noradrenaline concentrations, storage, release and uptake

Møller, S. et al. Cardiac sympathetic imaging with mIBG in cirrhosis and portal hypertension: relation to autonomic and cardiac function. Am. J. Physiol. Gastrointest. Liver Physio 303: 2012

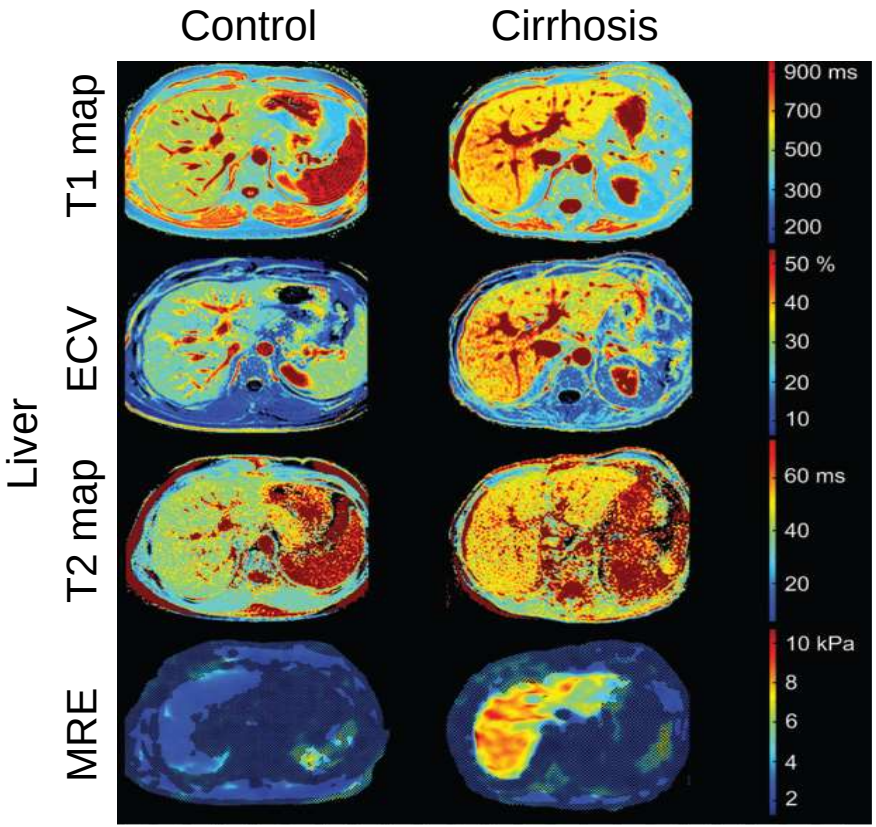
Cirrhotic Cardiomyopathy



Patients with liver cirrhosis with positive LGE. A, Distribution of positive LGE according to myocardial segments indicate involvement of inferolateral/septal walls, B, C, focal and, D, E, diffuse pattern (arrows).

Isaak et al. Radiology 2020; 297:51–61

Cirrhotic Cardiomyopathy



Hepatic and cardiac MRI in a healthy control and participant with Child-Pugh class B cirrhosis. Quantitative maps are given for hepatic and cardiac T1 relaxation times, extracellular volume fraction (ECV), T2 relaxation time, and MR elastography (MRE)–based liver stiffness. Quantitative parameters are considerably higher in participant with cirrhosis.

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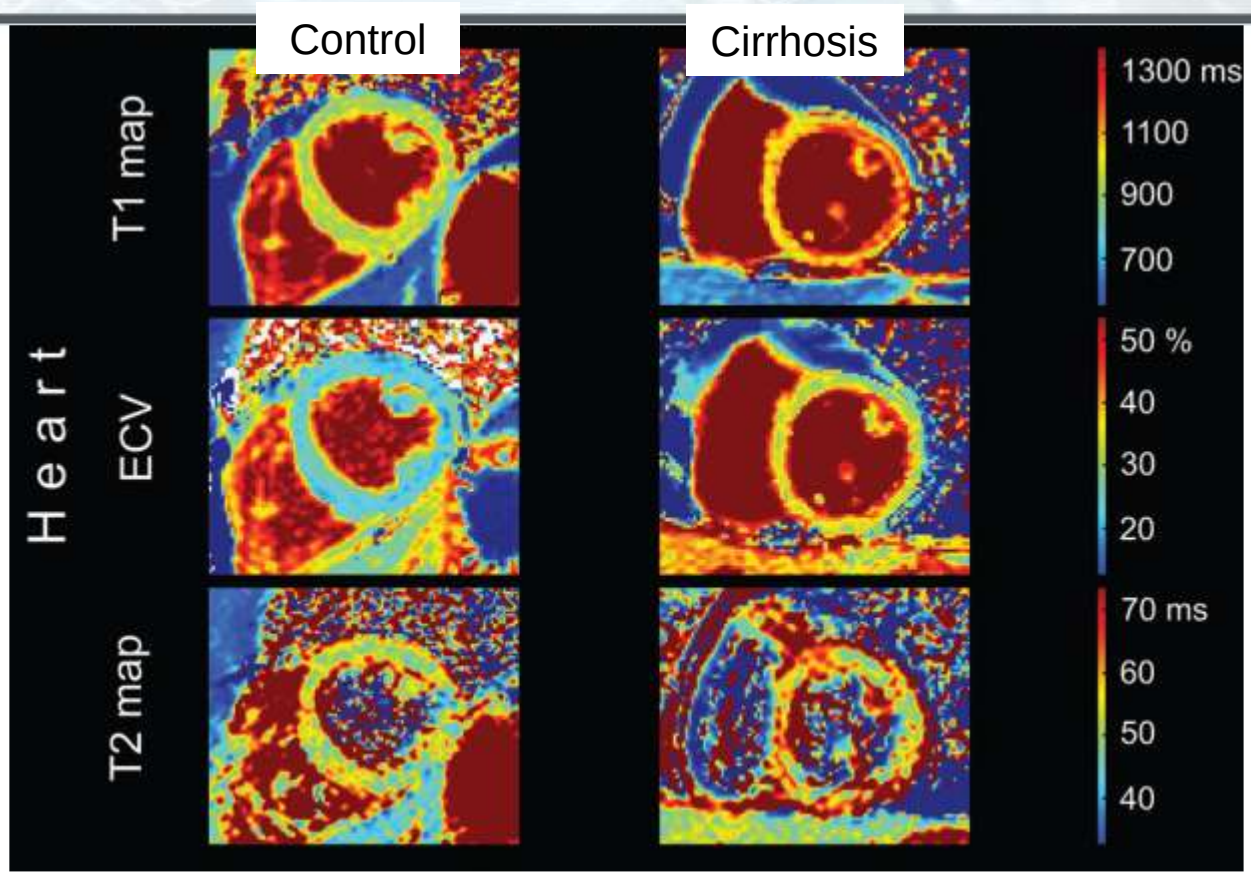
Cirrhotic Cardiomyopathy



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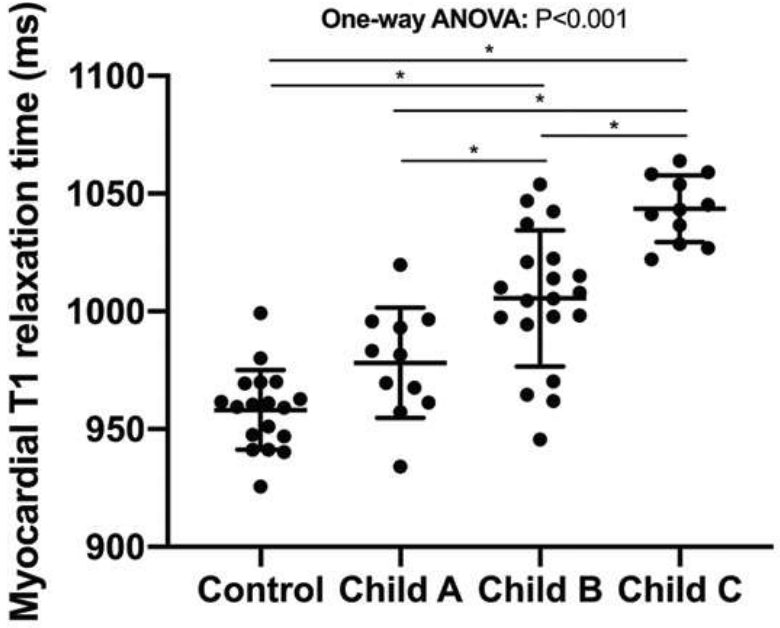
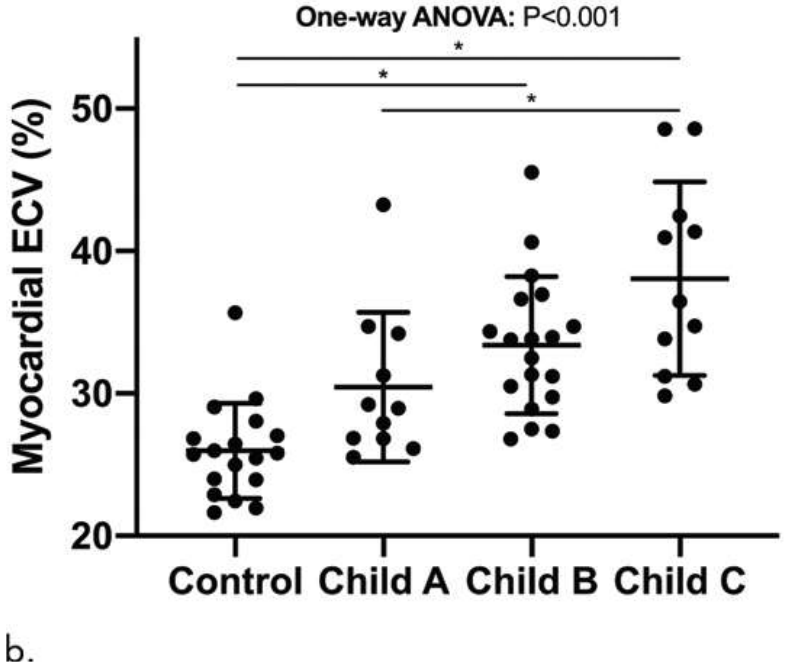
Cirrhotic Cardiomyopathy

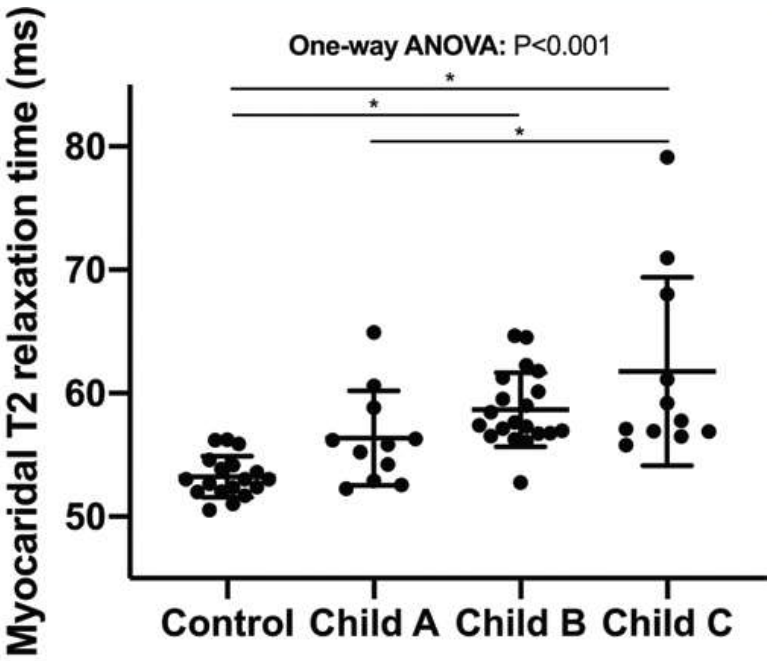


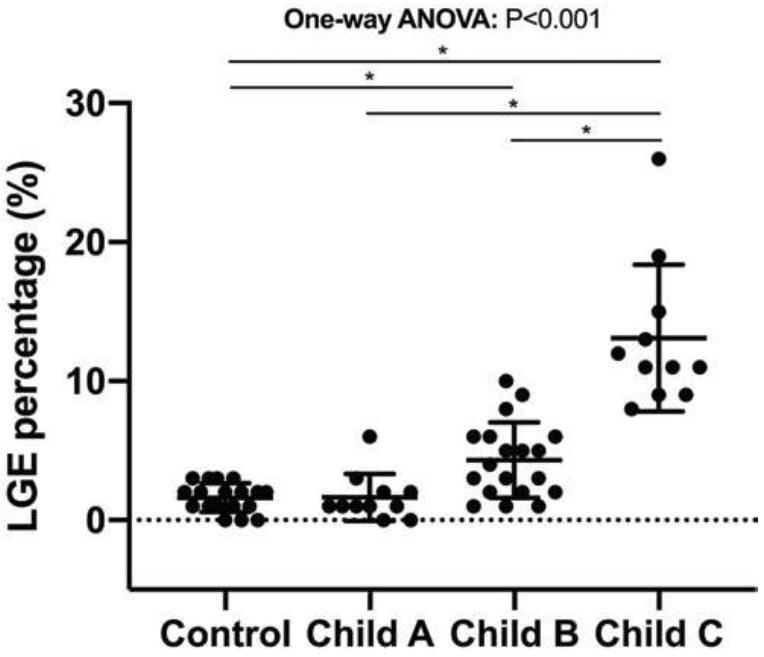


Quantitative myocardial MRI parameters in control group and in clinically subclassified cirrhosis gr
(Child-Pugh classes A, B, and C)

Isaak et al. Radiology 2020; 297:51

Cirrhotic Cardiomyopathy

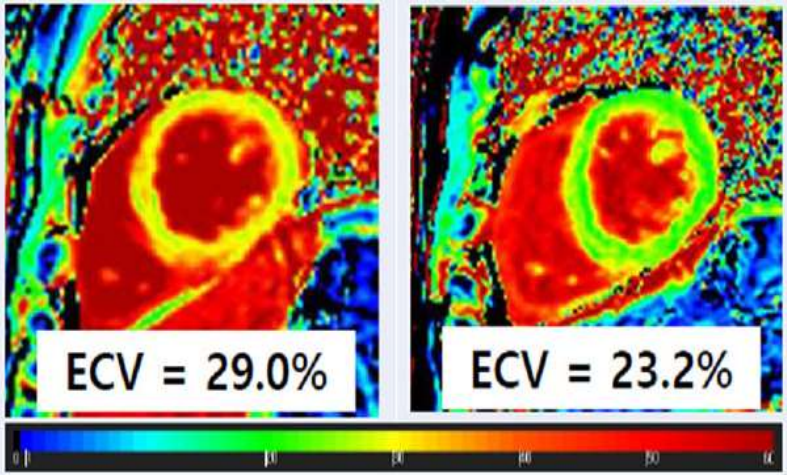


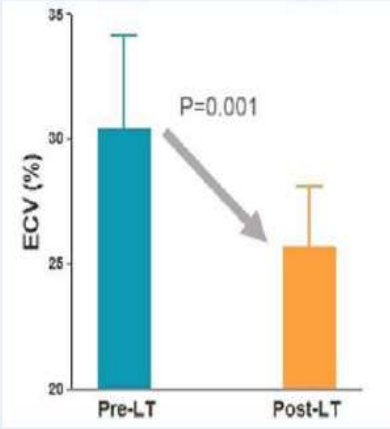


Quantitative myocardial MRI parameters in control group and in clinically subclassified cirrhosis group (Child-Pugh classes A, B, and C)

Isaak et al. Radiology 2020; 297:51–61

Cirrhotic Cardiomyopathy Cardiac Changes in Liver Cirrhosis

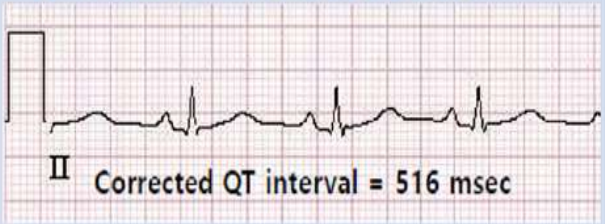
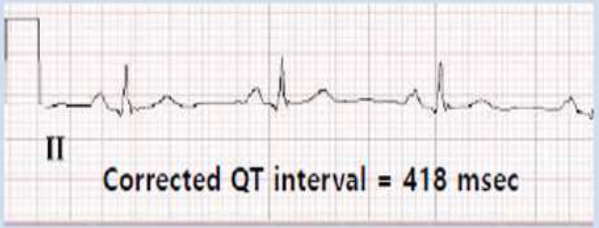
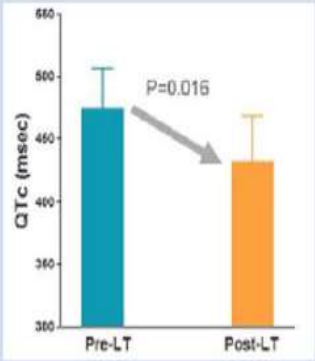
	Before liver transplantation	1 year after liver transplantation
Increased myocardial ECV		Normalized myocardial ECV



Myocardial structural, functional, and electrophysiological changes pre- and post-liver transplantation. Extracellular volume fraction; Global longitudinal strain; corrected QT interval

Kim et al. Journal of Cardiovascular Magnetic Resonance (2020) 22:25

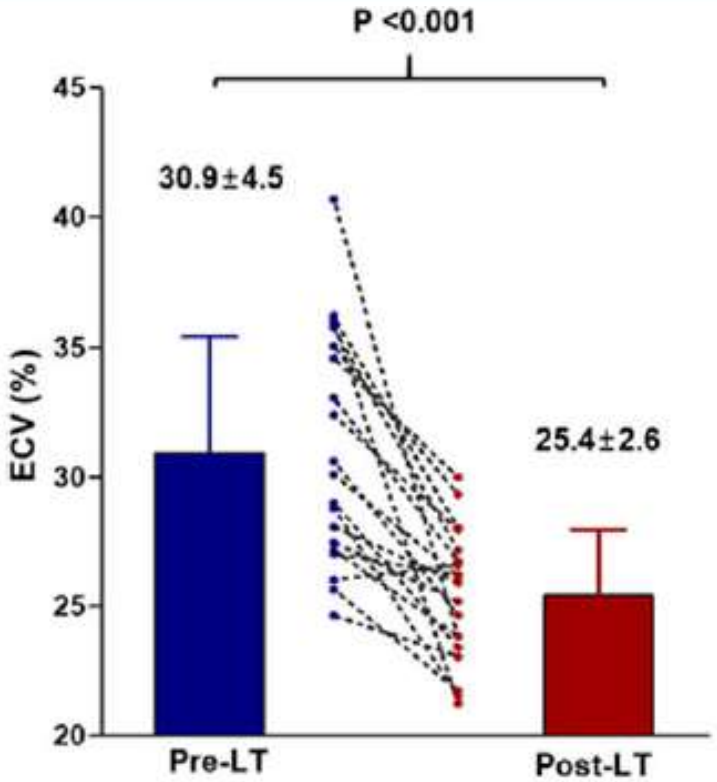
Cirrhotic Cardiomyopathy Cardiac Changes in Liver Cirrhosis

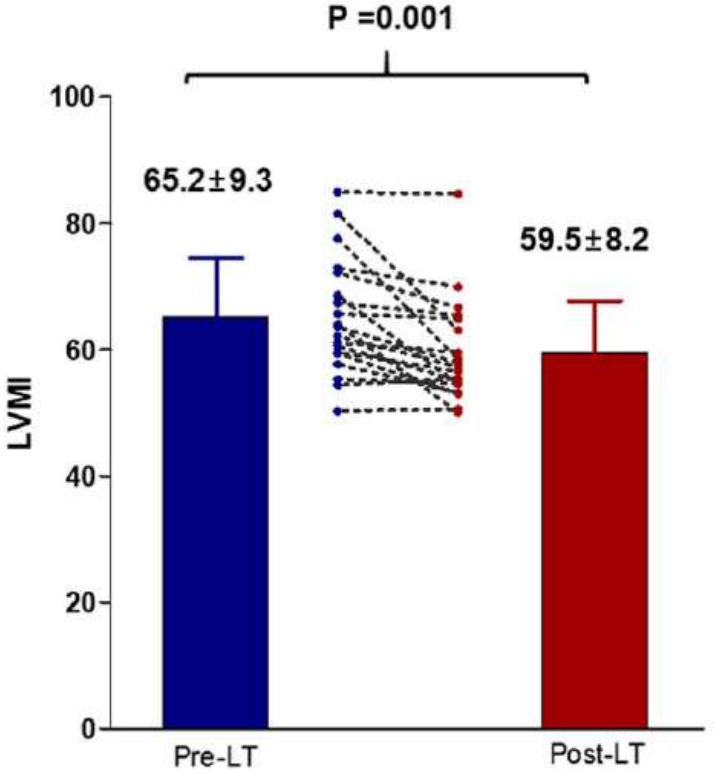
	Before liver transplantation	1 year after liver transplantation	
Electrophysi-ology	Prolonged corrected QT interval 	Normalized corrected QT interval 	

Myocardial structural, functional, and electrophysiological changes pre- and post-liver transplantation. ECV, extracellular volume fraction; GLS, left ventricular global longitudinal strain; QTc, corrected QT interval

Kim et al. Journal of Cardiovascular Magnetic Resonance (2020) 22:25

Cirrhotic Cardiomyopathy





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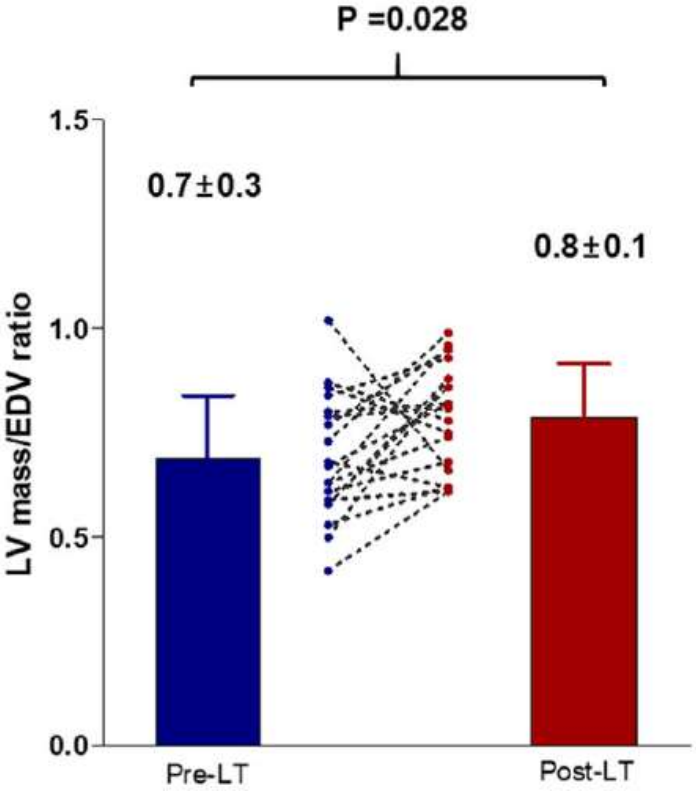
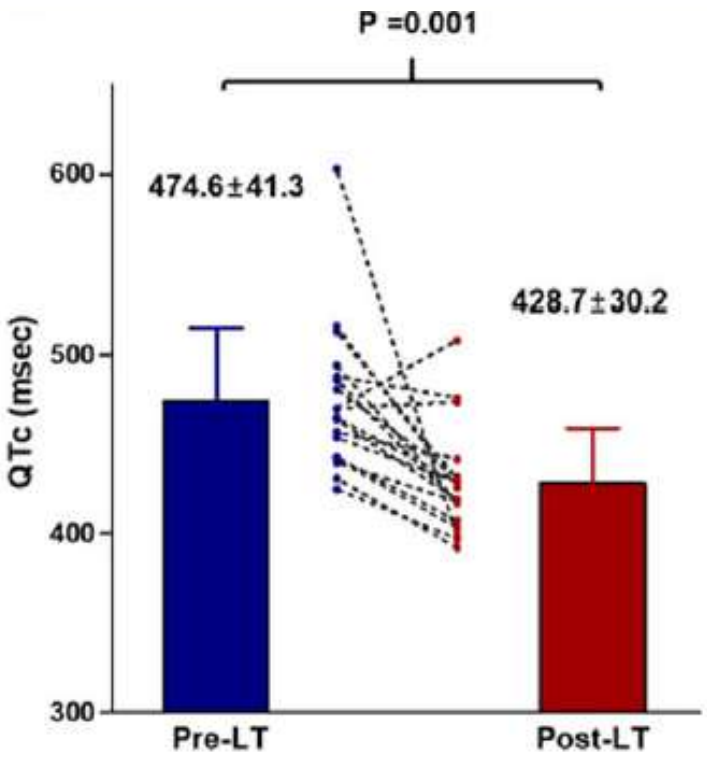
Cirrhotic Cardiomyopathy





Kim et al. Journal of Cardiovascular Magnetic Resonance (2020) 22:25

Cirrhotic Cardiomyopathy: 2005 Criteria

World Congress of Gastroenterology Criteria (2005)

Systolic Dysfunction	Diastolic Dysfunction	Supportive Criteria
Any of the following	Any of the following	• Electrophysiological abnormalities
• LVEF >55% Blunted contractile response on stress testing	• Deceleration time >200ms	• Abnormal chronotropic response
• LV ejection fraction <55%	• IVRT >80 milliseconds	• Electromechanical uncoupling
	• E/A <1	• Prolonged QTc interval
		• Enlarged left atrium
		• Increased myocardial mass
		• Increased BNP
		• Increased proBNP
		• Increased troponin I

Izzy et al. Hepatology. 2020 January ; 71(1): 334–345. doi:10.1002/hep.30875.

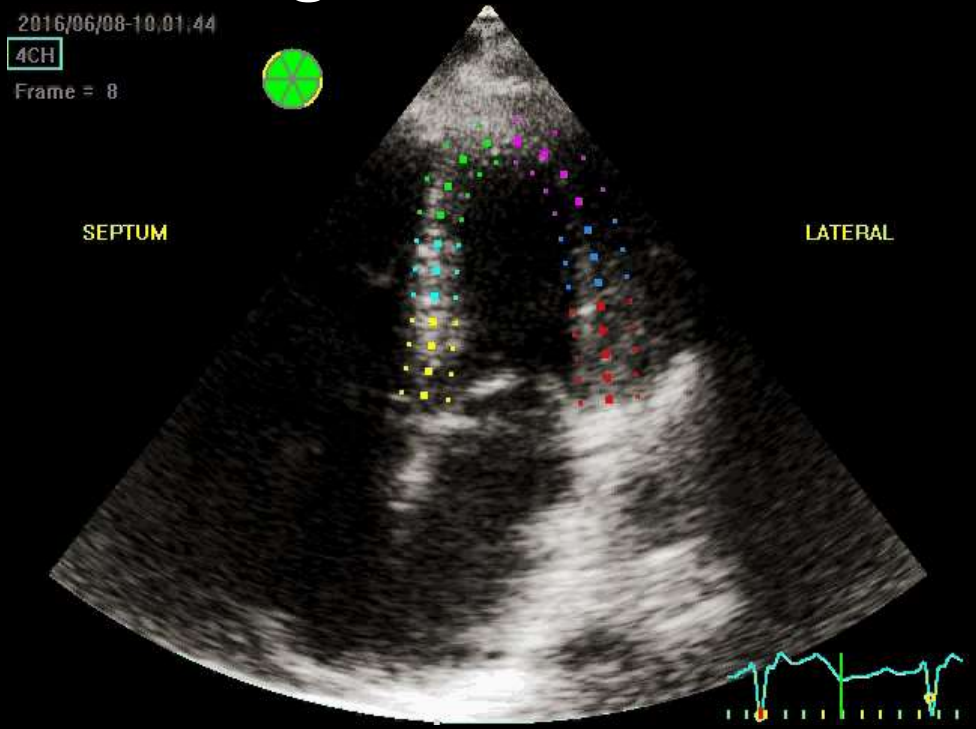
Cirrhotic Cardiomyopathy: 2019 Criteria

Proposed criteria by the Cirrhotic Cardiomyopathy Consortium (2019)

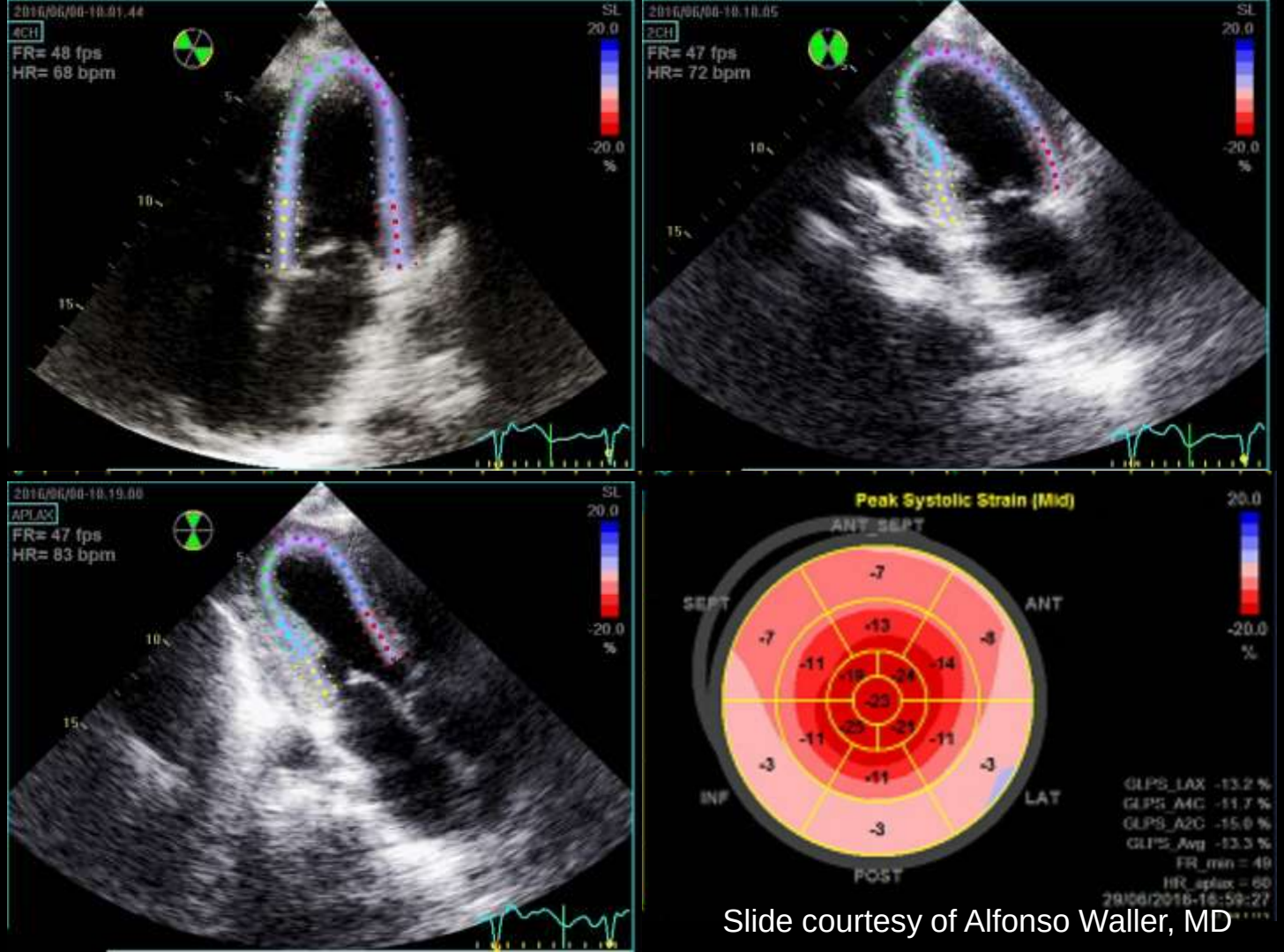
Systolic Dysfunction	Advanced Diastolic Dysfunction	Areas for Future Research Which Require Further Validation
Any of the following:	≥3 of the following:	Abnl chronotropic or inotropic response
LVEF ≤50%	Septal e′ velocity <7cm/sec	Electrocardiographic changes
Absolute GLS <18%	E/e′ ratio ≥15	Electromechanical uncoupling
	LAVI >34 mL/m^2	Myocardial mass change
	TR velocity > 2.8 m/sec	Serum biomarkers
		Chamber enlargement
		CMRI

Izzy et al. Hepatology. 2020 January ; 71(1): 334–345. doi:10.1002/hep.30875.

Longitudinal Strain



Slide courtesy of Alfonso Waller, MD, Rutgers NJMS



Slide courtesy of Alfonso Waller, MD

Cirrhotic Cardiomyopathy

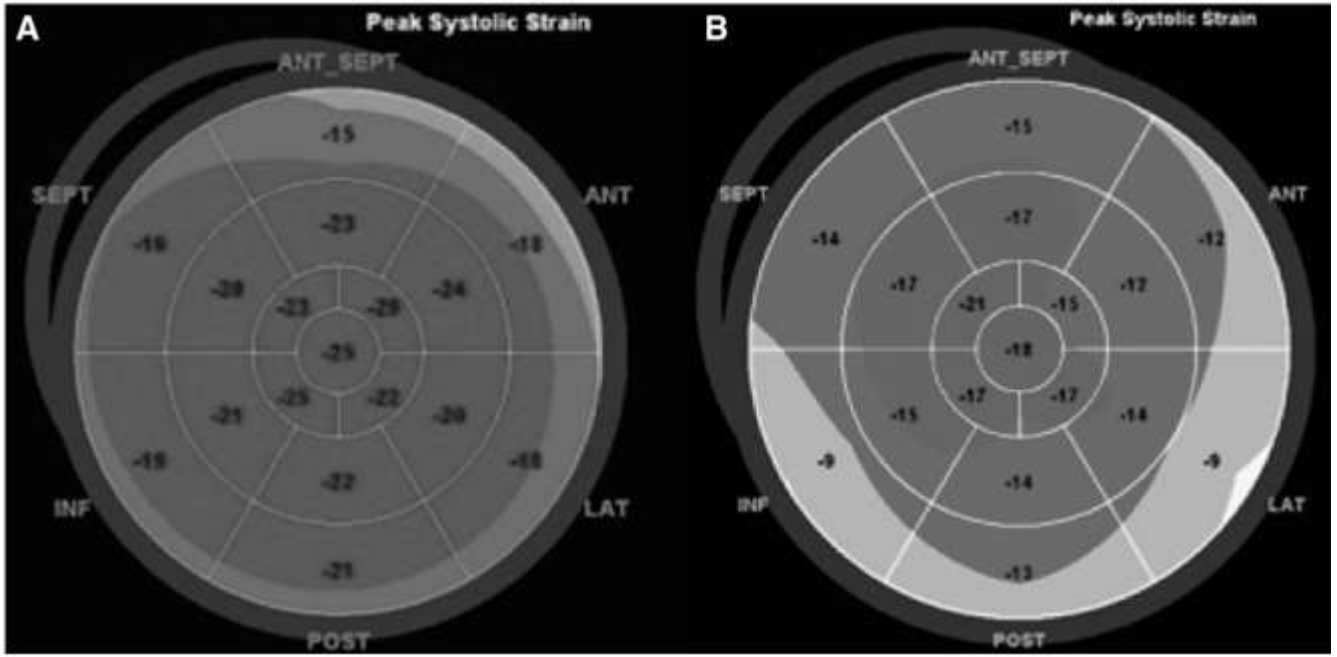
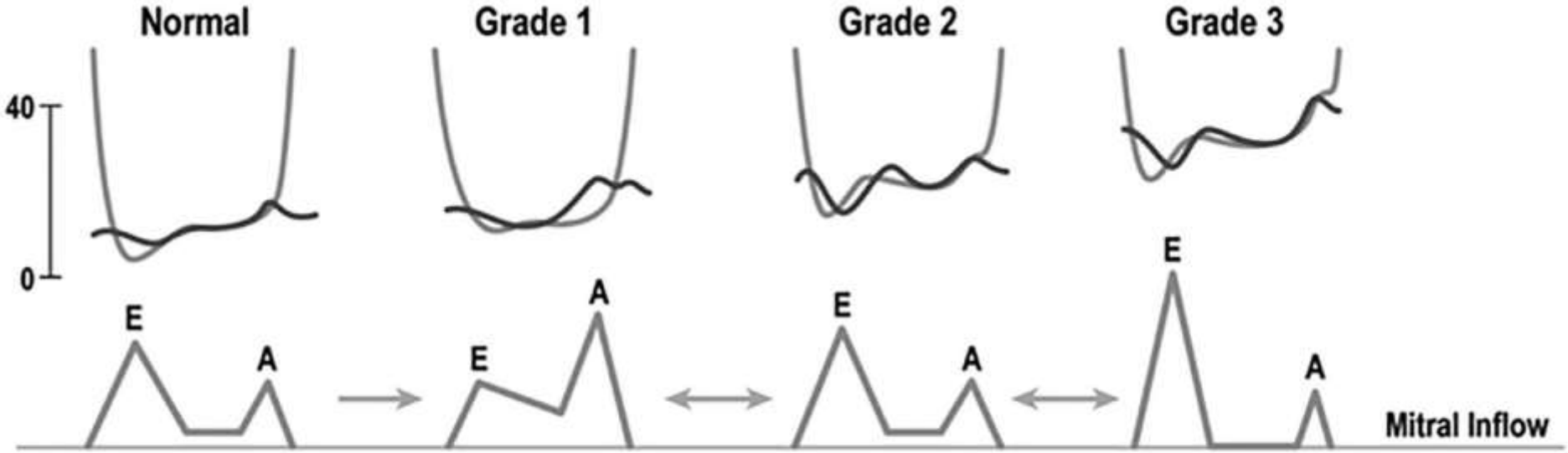


Illustration of strain imaging as a surrogate for cardiac systolic function. This “Bull’s eye” diagram of the myocardium shows (A) normal strain imaging (global longitudinal strain of −21%) and (B) abnormal strain imaging (global longitudinal strain of −14%). Diminished strain in patients with end stage liver disease in the absence of known heart disease is diagnostic of cirrhotic cardiomyopathy.

Izzy et al. Hepatology. 2020 January ; 71(1): 334–345. doi:10.1002/hep.30875.

Diastolic Function/Dysfunction



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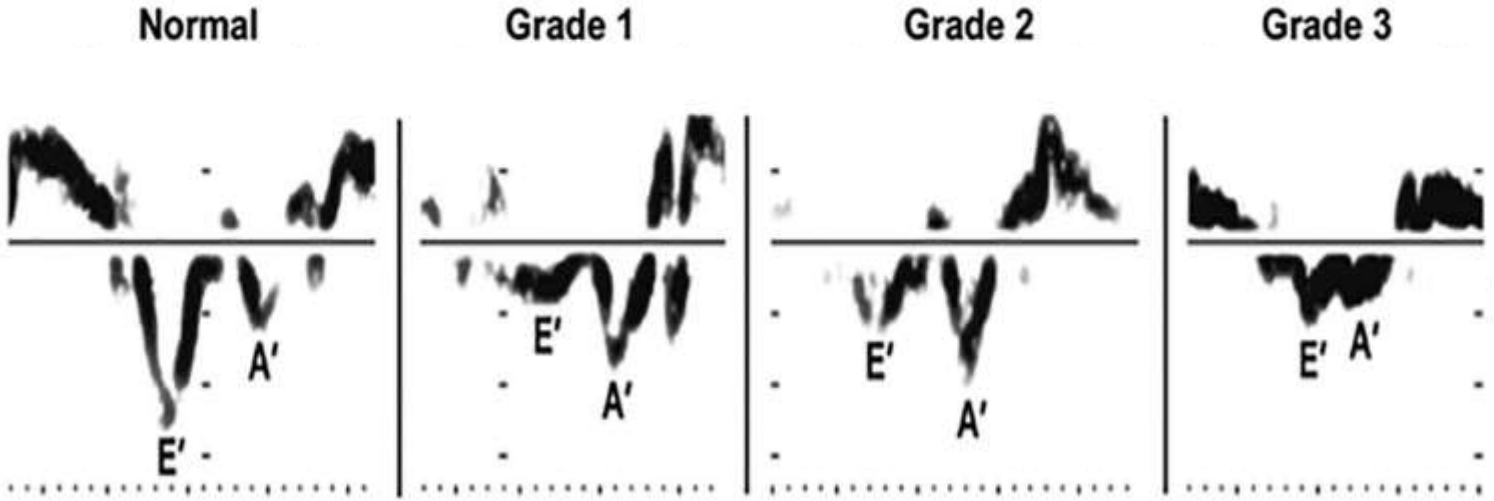
Diastolic Function/Dysfunction



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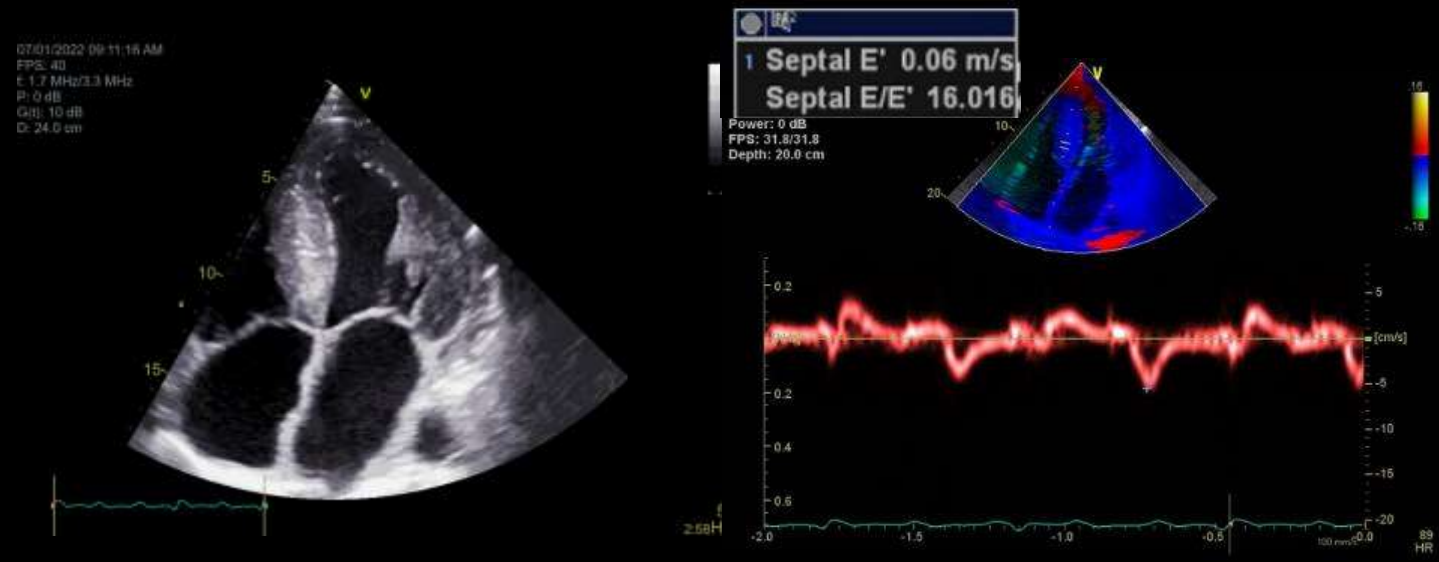
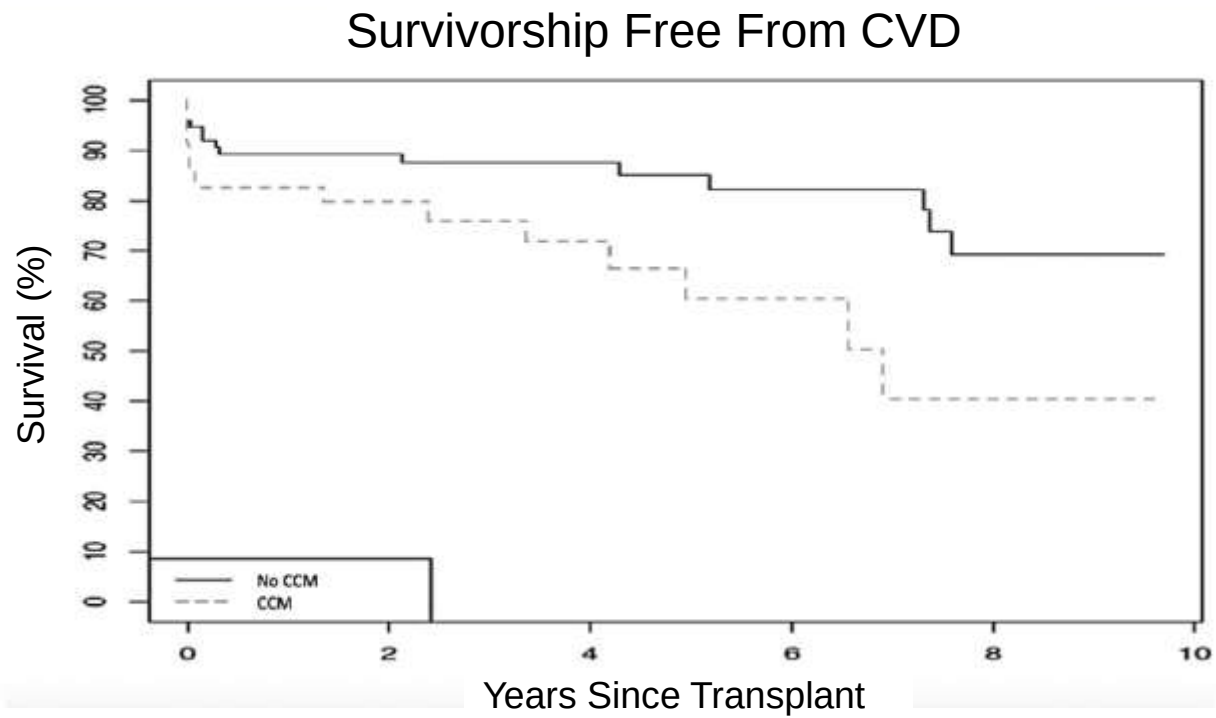
Importance of Septal E’



Slide courtesy of Alfonso Waller, MD, Rutgers NJMS

Cirrhotic Cardiomyopathy

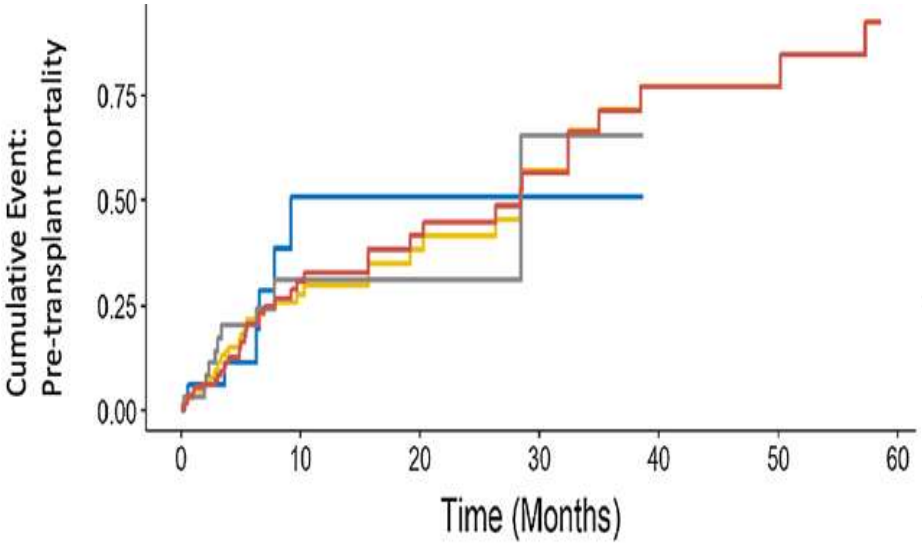


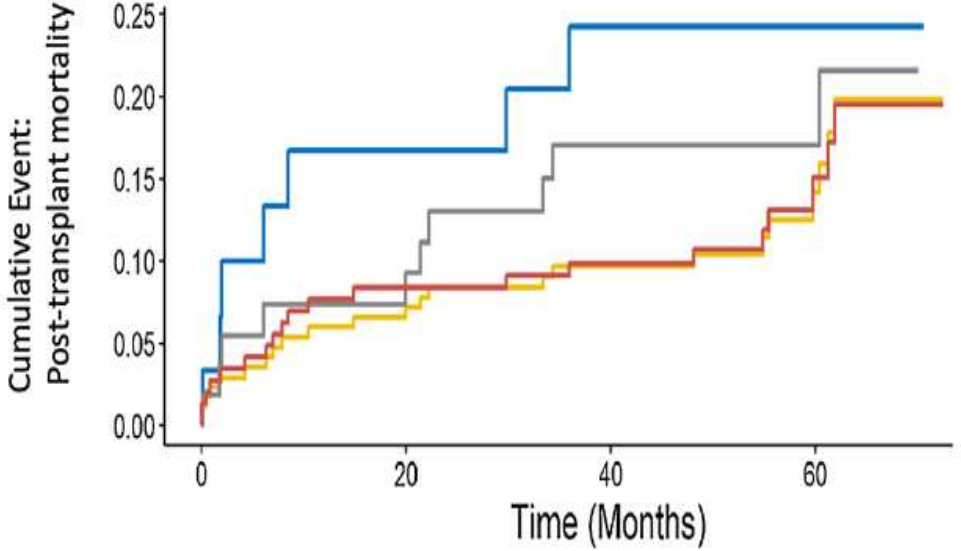
Kaplan-Meier curve illustrating association of CCM with posttransplant new CVD.

Izzy ey al. Liver Transplantation 27 876–886 2021 AASLD

Cirrhotic Cardiomyopathy

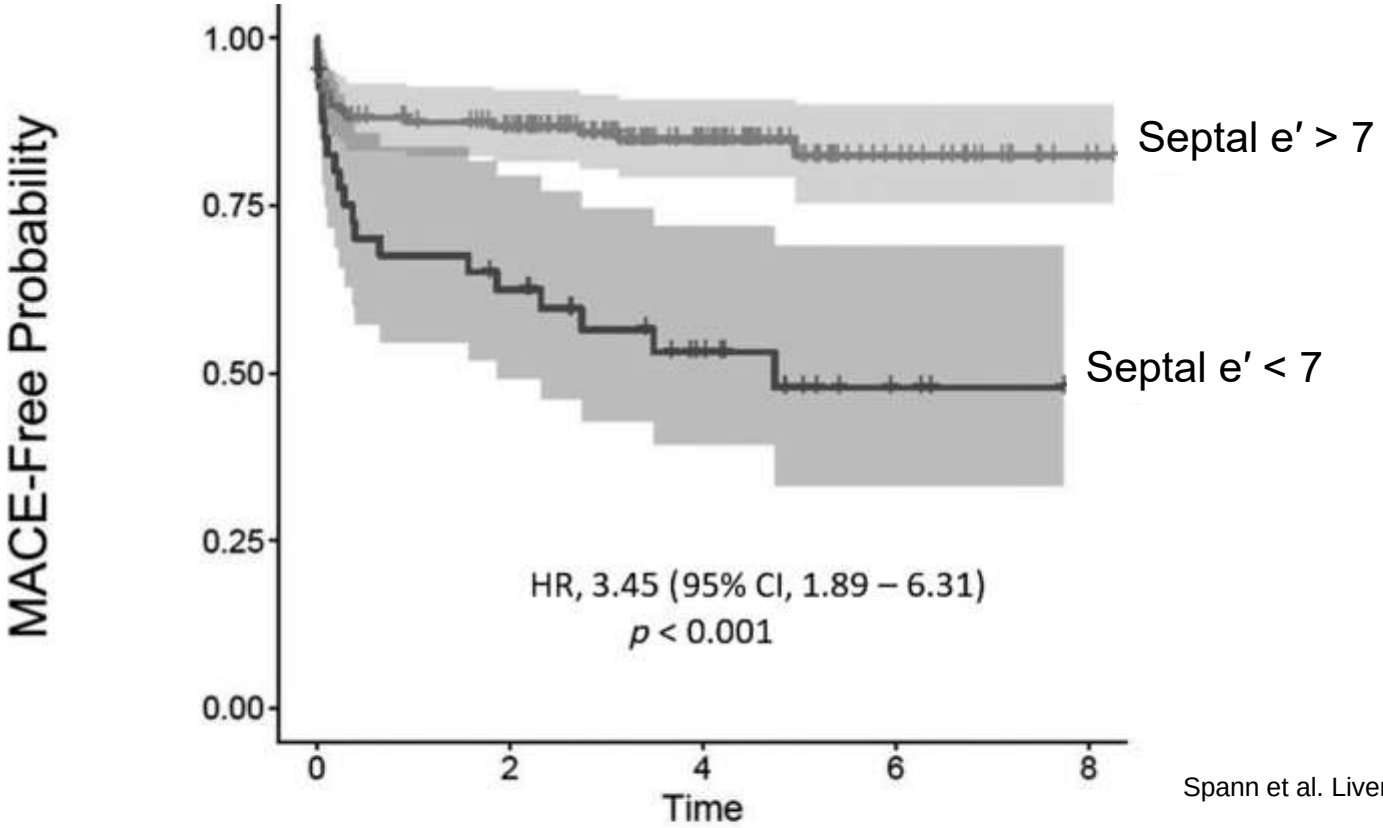
Groups: Consortium CCM, No; Consortium CCM,Yes; WGO, No; WGO, Yes;





Singh et al. Digestive Diseases and Sciences https://doi.org/10.1007/s10620-022-07412-z Feb 2022

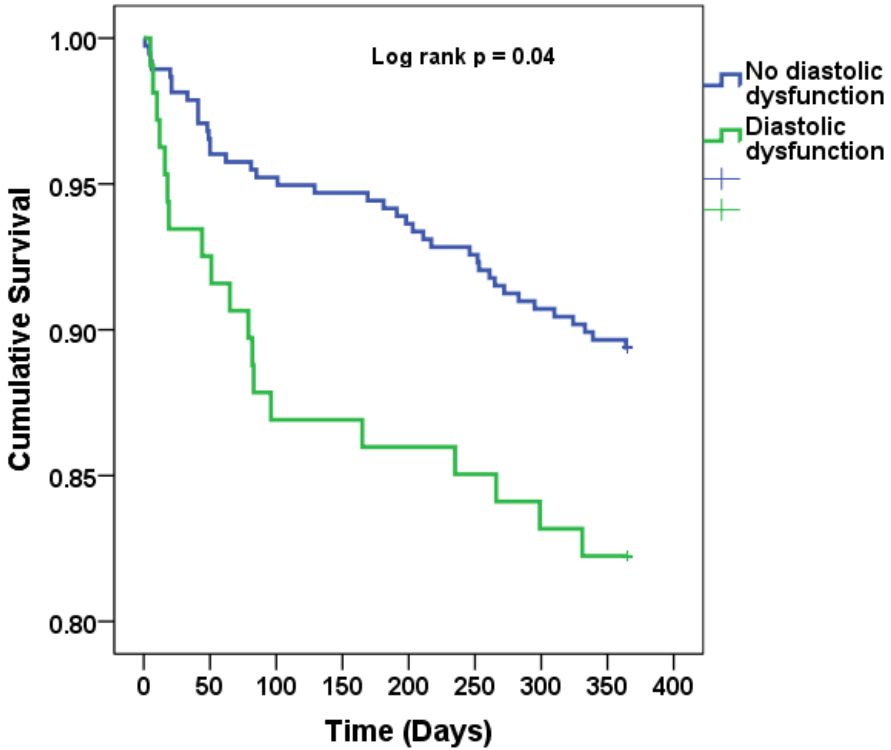
Cirrhotic Cardiomyopathy



Kaplan–Meier curves for the unadjusted MACE-free survival model stratified by septal e' diagnostic cutoff of 7 cm/s per the revised CCM criteria

Spann et al. Liver Transplantation. 2022;28:1321–1331.

LV Diastolic Dysfunction Predicts Mortality in Patients Who Underwent Liver Transplantation



Nandan Thirunahari MD, Christine Gerula, MD, Baburao Koneru MD, James Maher MD, Marc Klapholz, MD.

Cirrhotic Cardiomyopathy

Cardiac outcomes	Original CCM definition			Revised CCM definition		
	HR	95% CI	*p* value	HR	95% CI	*p* value
MACE	1.77	0.73–4.31	0.21	**1.93**	**1.05–3.56**	**0.04**
Arrhythmia	2.70	0.38–19.27	0.32	1.94	0.78–4.87	0.16
Heart failure	1.61	0.47–5.56	0.45	2.05	0.75–5.62	0.16
Cardiac arrest or cardiac death	2.06	0.44–9.67	0.36	2.68	0.97–7.38	0.06
All-cause mortality	1.15	0.47–2.86	0.76	1.25	0.59–2.65	0.56

Adjusted HRs for MACE after LT using Cox proportional hazards via inverse probability treatment weighting (controlled for diabetes mellitus, age, sex, smoking, and liver disease etiology)

Spann et al. Liver Transplantation. 2022;28:1321–1331.

Cirrhotic Cardiomyopathy

Epidemiology

- Limited data regarding true prevalence of cirrhotic cardiomyopathy because of near normal cardiac function at rest unless exposed to stress (Pharmacologic or physiologic stress, bacterial infection, TIPS or transplantation)
- ~50% of patient undergoing OLT develop some signs of cardiac dysfunction
- Majority of patients with Child-Pugh class B and C have at least one feature of CCM
- Using 2005 criteria ~65% of patients had CCM; with new criteria ~25% of patients

Future Challenges

- To better identify latent cardiac dysfunction – systolic and diastolic as they appears to affect the clinical course in both the pre-OLT and post-OLT periods
- Earlier Dx to facilitate further progression and to possibly ‘cure’ pre-transplant
- Differentiate reversible from irreversible changes in myocardial structure and function i.e. to define when is OLT curative
- No clear treatments exist; Need to develop appropriate treatments for both latent and overt myocardial abnormalities that are present in association with liver disease