Definitions of Myocarditis: Current Status and Gaps in 2022

ACC Roundtable
May 2022

Leslie T. Cooper, Jr., MD

Myocarditis can be defined by:

- Histology- H and E or IPOX
- Imaging- MRI
- Hybrid Clinical + Histology
- Hybrid Clinical + Imaging
- ICD codes

These criteria are:

- Useful in different study designs.
- Have variable degrees of diagnostic certainty.
- Identify different demographic and risk profiles.

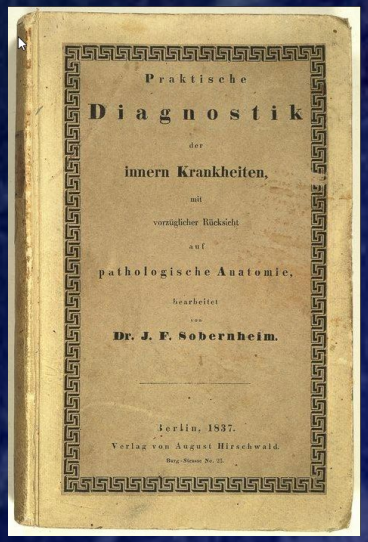
Fielder, A. Über akute interstitielle Myokarditis, Centralbl. f. inn. Med., 1900, cci, 212.

Myocarditis

Clinical Presentations- None are specific

- Chest Pain- Myopericarditis/MINOCA
- Sudden Death
- Acute Dilated Cardiomyopathy
- Chronic Dilated Cardiomyopathy
- Imaging/biomarker abnormalities without symptoms

Histological Criteria over 185 years


Praktische

Diagnostik

der

innern Krankheiten,

mit

vorzüglicher Rücksicht

auf

pathologische Anatomie,

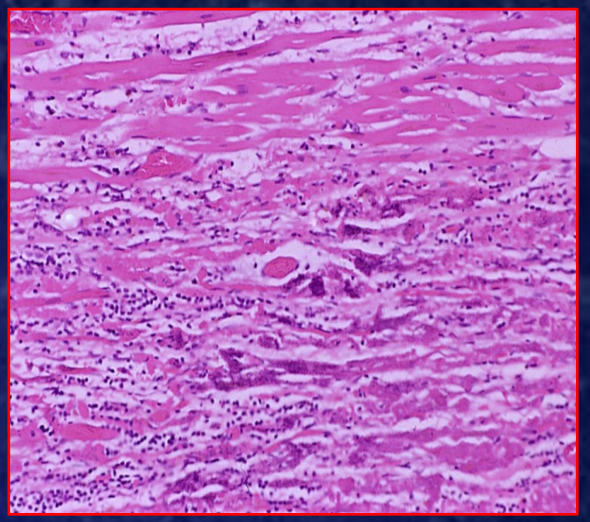
bearbeitet

von

Dr. J. F. Sobernheim.

Berlin, 1837.

Verlag von August Hirschwald.

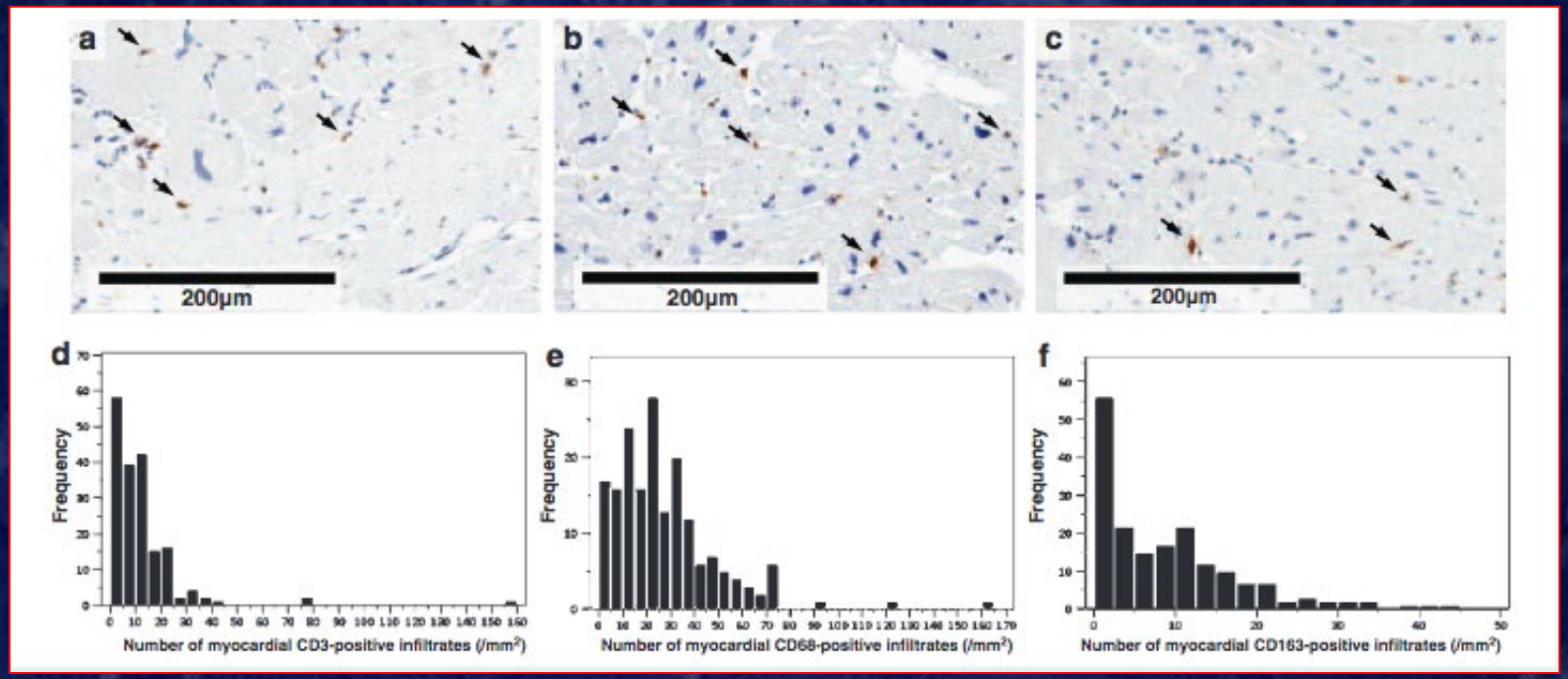


Sobernheim, J. F., 1837

- Myocarditis: An inflammatory infiltrate and associated myocyte necrosis or damage not characteristic of an ischemic event
- Ongoing, Resolving, Resolved

Am J Cardiovasc Pathol 1987 Jan;1(1):3-14

Immunohistochemical Stains for the Diagnosis of Myocarditis



CD3 **CD68** **CD163**

Nakayama et al EJHF 2017

Meta-analysis of Immunohistology and Histology for the Diagnosis of Myocarditis

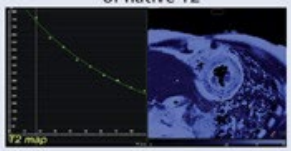
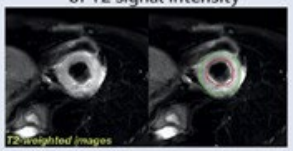
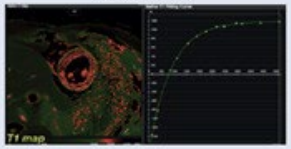
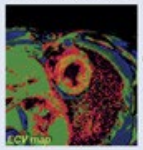
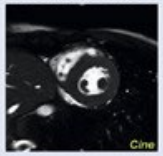
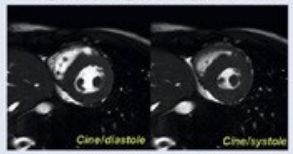
- n=61 publications with 10,491 patients
- Dallas criteria + in 8.04% (95%-CI: 5.08–12.5%; subset of 30 publications w/ 3,274 patients
- IHC + DCMi in 50.8% (95% CI: 47.7–53.8%; range: 18.4 – 91.7%)
- 13 different IHC protocols- need for standardization

Katzman, et al Heart Failure Rev (25) 2020

Echo is Nonspecific in Acute Myocarditis

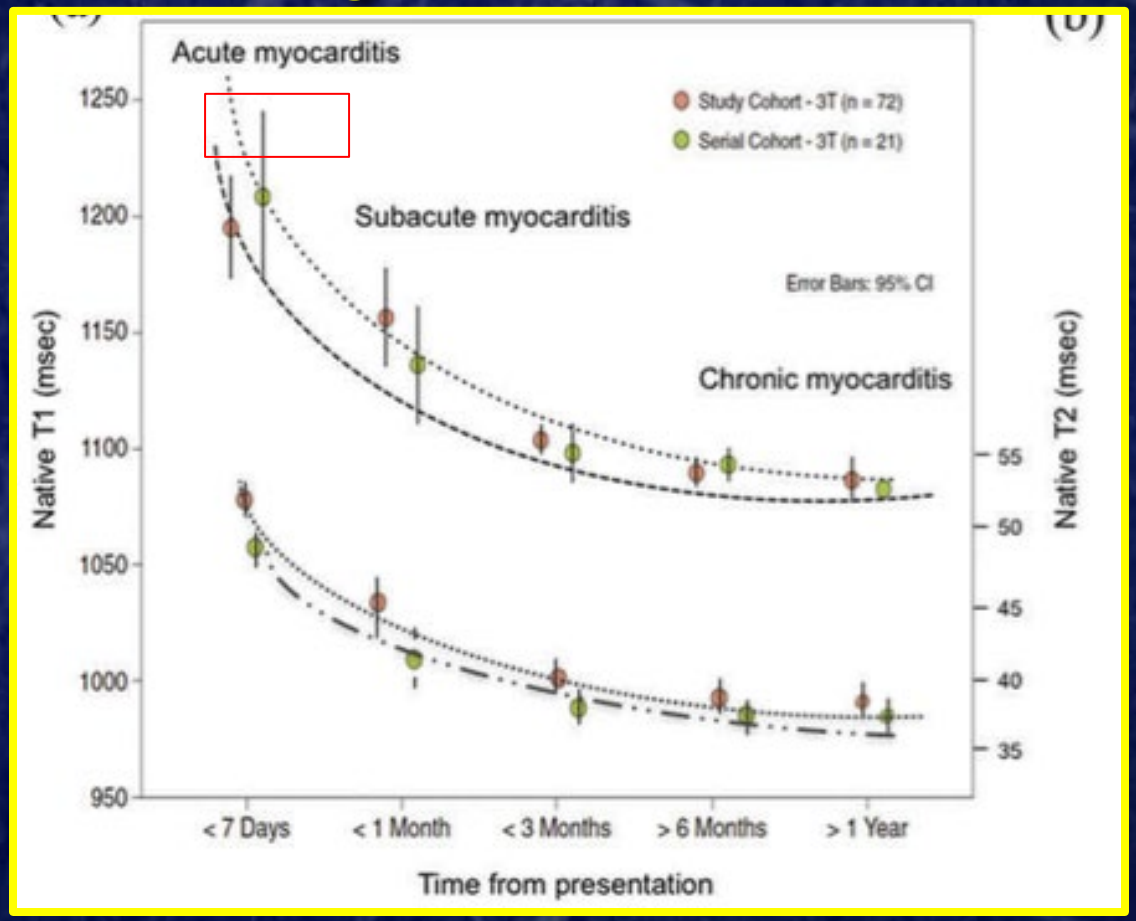
LLC2 criteria, ability to identify active inflammation and fibrosis in RV free wall and Epicardium

CENTRAL ILLUSTRATION: Overview of the Updated Lake Louise Criteria

	2018 Lake Louise Criteria	CMR Image Examples
Main Criteria	**Myocardial Edema** (T2-mapping or T2W images)	Regional or global increase of native T2  or Regional or global increase of T2 signal intensity 
	Non-ischemic Myocardial Injury (Abnormal T1, ECV, or LGE)	Regional or global increase of native T1  or Regional or global increase of ECV  or Regional LGE signal increase 
Supportive Criteria	**Pericarditis** (Effusion in cine images or abnormal LGE, T2, or T1) **Systolic LV Dysfunction** (Regional or global wall motion abnormality)	Pericardial effusion  Regional or global hypokinesis 

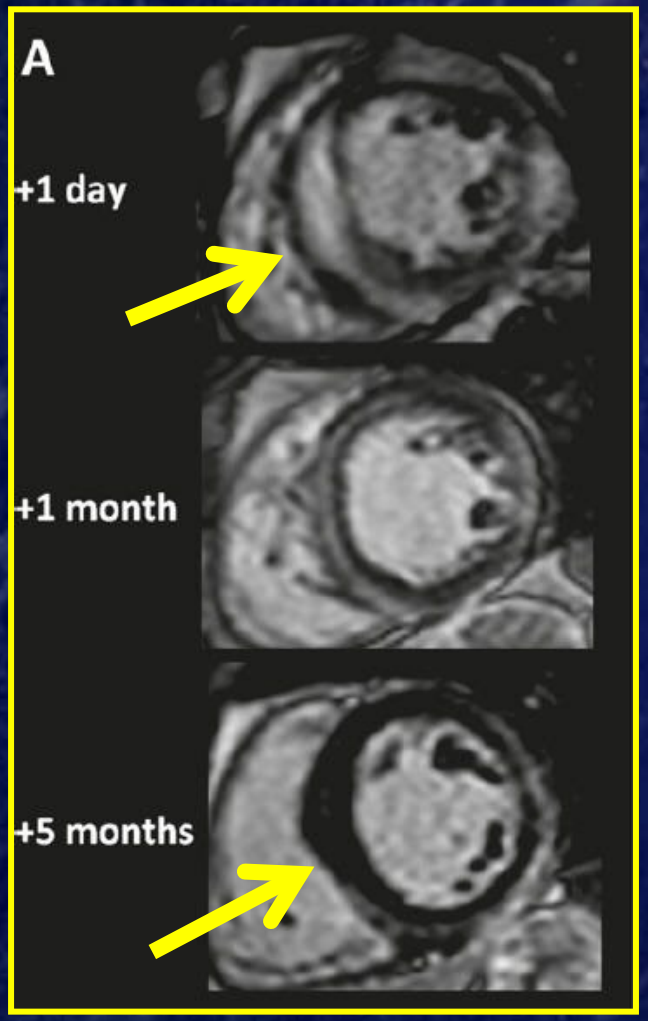
Ferreira, V.M. et al. J Am Coll Cardiol. 2018;72(24):3158-76.

Time Course of Native T1 and T2 Recovery in Acute Myocarditis



Hinojar R et al. JACC Cardiovasc Imaging. 2015
Hinojar R J Cardiovasc Magn Reson. BioMed Central; 2014

MRI findings change over first months



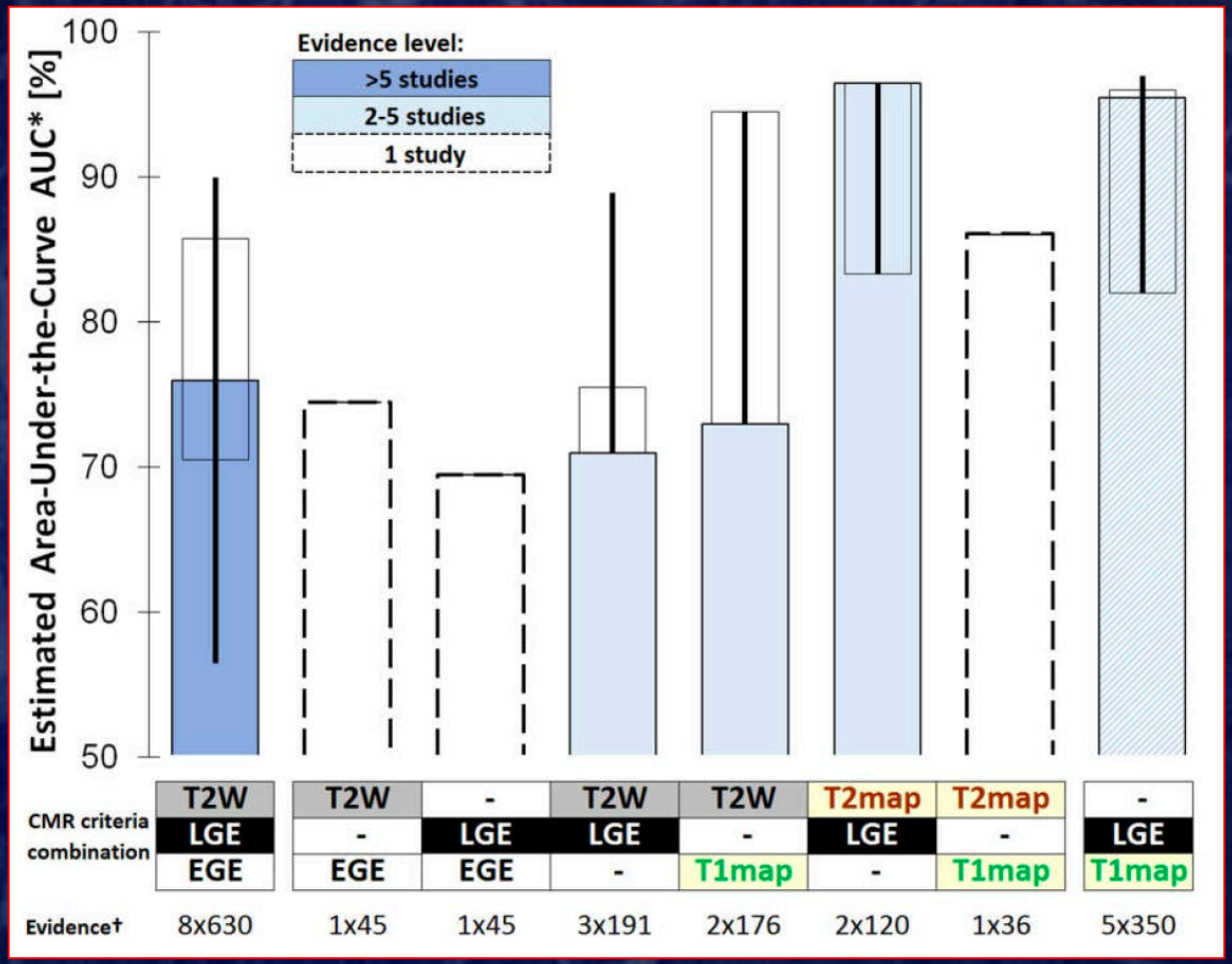
Widespread enhancement with near transmural involvement of the septum and lateral wall; increased wall thickness

Near complete resolution of septal LGE

Monney, P. et al. Heart, August 2011

MRI Criteria for Acute Myocarditis

Lake Louise 2



Ferreira, et al. J Am Coll Cardiol 2018

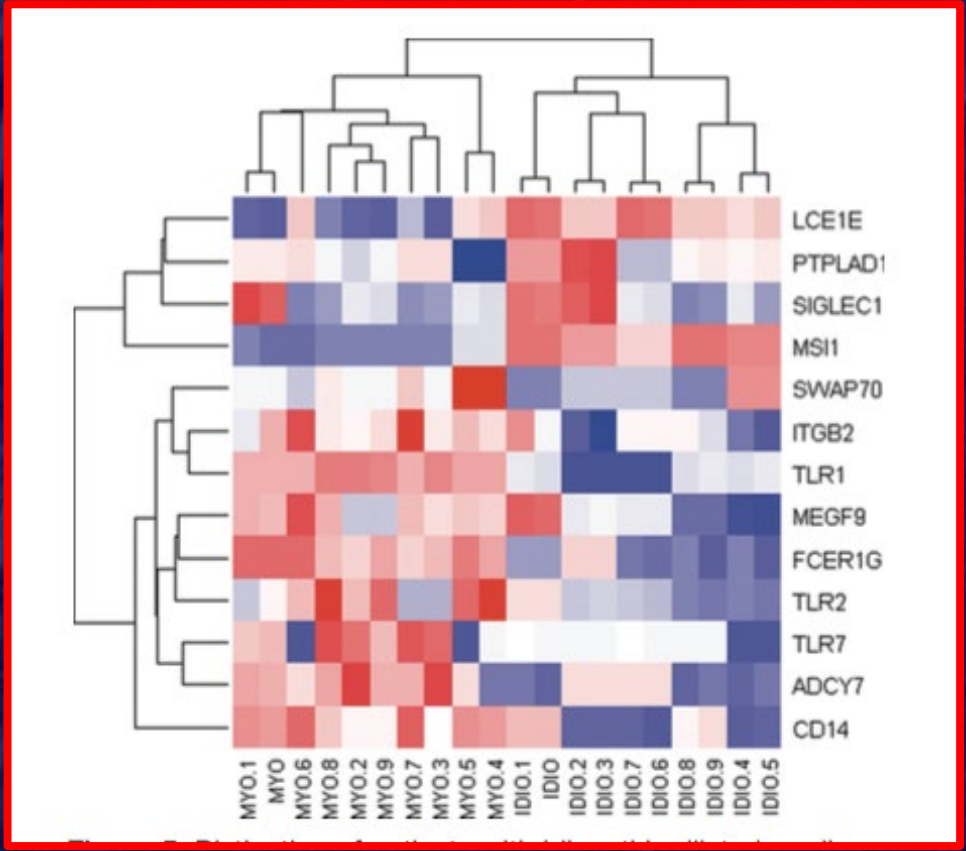
CDC Case Definition Criteria for Myocarditis

Suspect case	Probable case	Confirmed case
Dyspnea, palpitations, or chest pain of probable cardiac origin, with either one of the following: (a) ECG abnormalities beyond normal variants, not documented previously, including: a) ST-segment/T-wave abnormalities, b) Paroxysmal or sustained atrial or ventricular arrhythmias, c) AV nodal conduction delays or intraventricular conduction defects, d) Continuous ambulatory ECG monitoring that detects frequent atrial or ventricular ectopy, OR (b) Focal or diffuse depressed LV function of indeterminate age identified by an imaging study	Meets criteria for suspected myocarditis, in the absence of other likely cause of symptoms. In addition, meets one of the following: (a) Elevated cardiac enzymes (troponin-I, troponin-T, or creatine kinase-MB), OR (b) New onset or increased degree of severity of focal or diffuse depressed LV function by imaging, OR (c) Abnormal imaging indicating myocardial inflammation (cardiac MRI with gadolinium, gallium-67 scanning, anti-myosin antibody scanning)	Histopathologic evidence of myocarditis by endomyocardial biopsy or autopsy.

https://www.cdc.gov/mmwr/preview/mmwrhtml/mm5212a2.htm

Transcriptomic Biomarkers for the Accurate Diagnosis of Myocarditis

Bettina Heidecker, MD; Michelle M. Kittleson, MD, PhD; Edward K. Kasper, MD; Ilan S. Wittstein, MD; Hunter C. Champion, MD, PhD; Stuart D. Russell, MD; Ralph H. Hruban, MD; E. Rene Rodriguez, MD; Kenneth L. Baughman, MD†; Joshua M. Hare, MD



RT-PCR from EMB: *TLR1*, *TLR2*, *TL7*, and *CD14* overexpressed In LM vs DCM

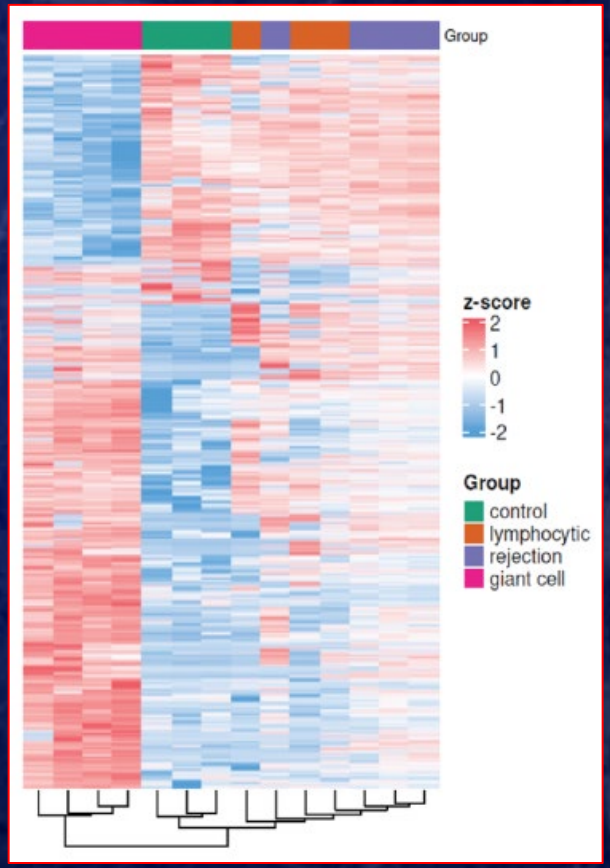
Circulation, 2011
***J Thorac CV Surg*. 2008**

RESEARCH LETTER

RNA-Sequencing Reveals a Distinct Transcriptomic Signature for Giant Cell Myocarditis and Identifies Novel Druggable Targets

Kaushik Amancherla, Juan Qin, Yu Wang, Margaret L. Axelrod, Justin M. Balko, Kelly H. Schlendorf, Robert D. Hoffman, Yaomin Xu, JoAnn Lindenfeld, Javid Moslehi

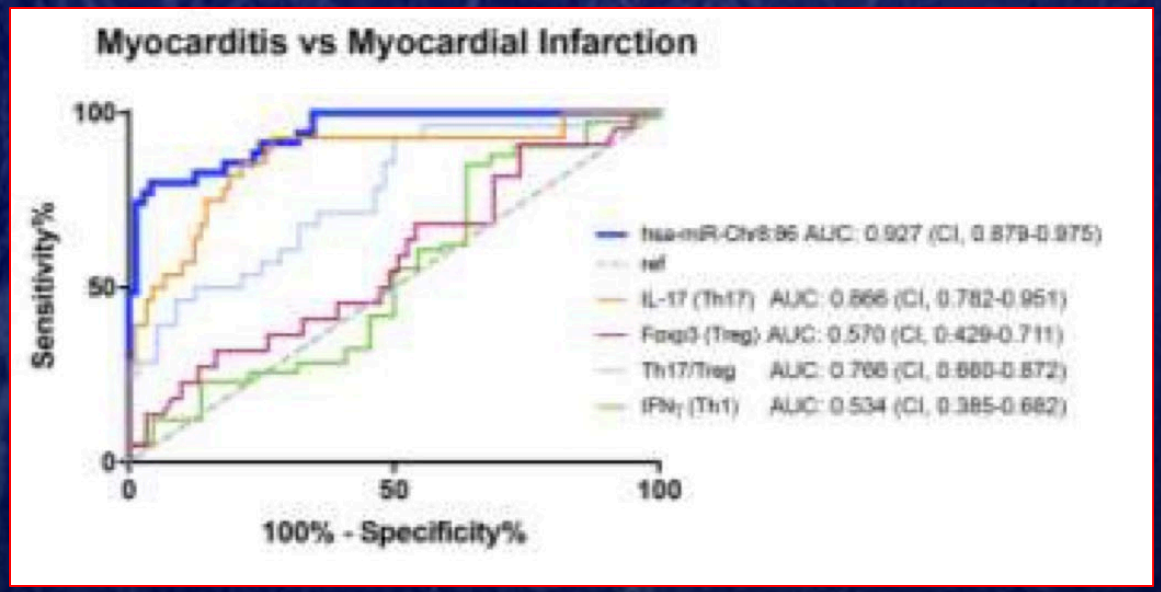
- **Pathway enrichment analysis in GCM showed that upregulated pathways were enriched for neutrophil degranulation, multiple cytokine signaling pathways, and phagocytosis**



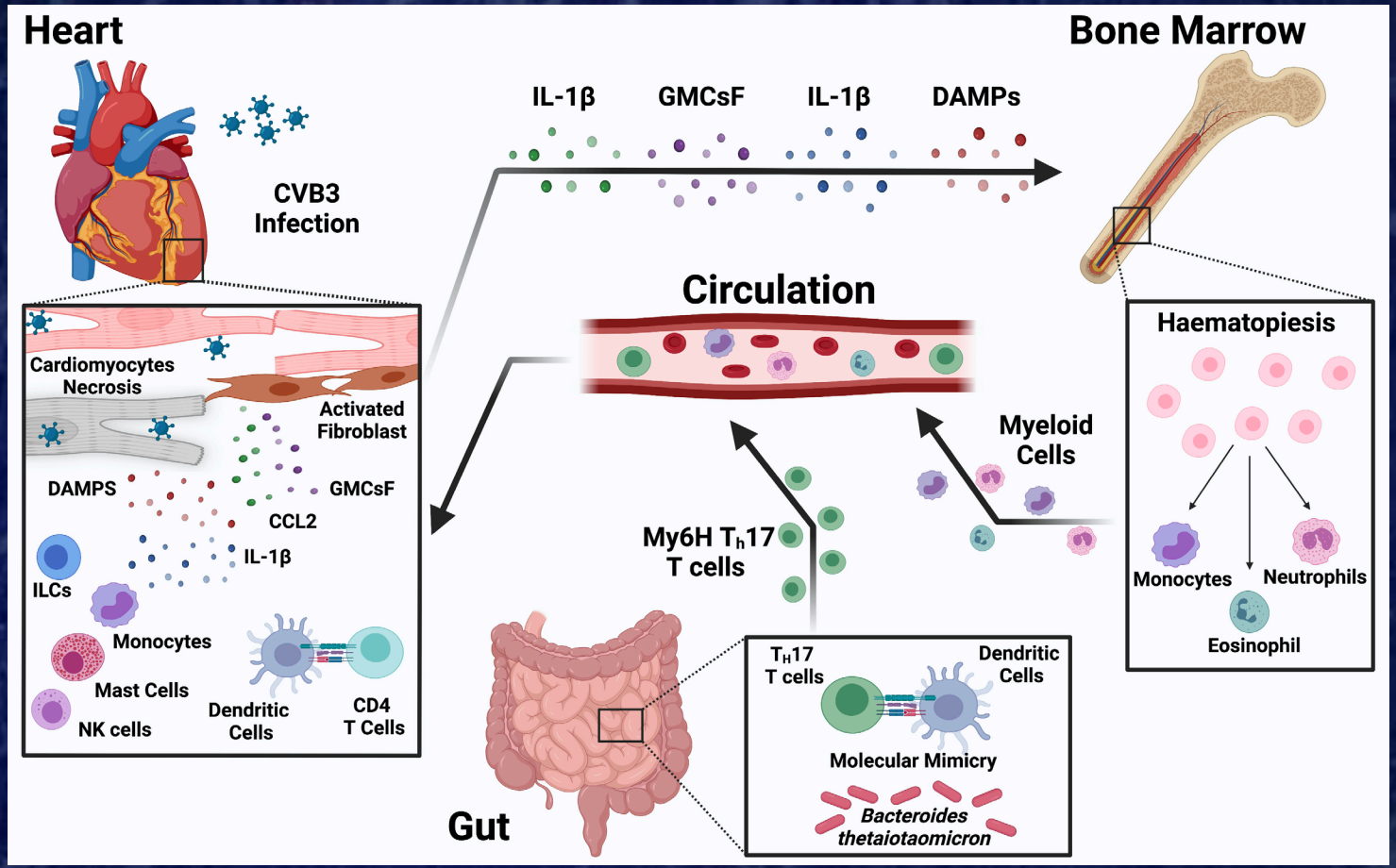
Circ Research, June 21st, 2021

A novel circulating microRNA for the detection of acute myocarditis: hsa-miR-Chr8:96

Parameter	Healthy Control	Acute Myocarditis	STEMI	NSTEMI
N	80	42	45	45
Age, years	42.31±1.21	40.36±19.40	60.31±12.61	65.69±14.41
Sex (women/men), N (%)	41 (51.25) / 39 (48.75)	10 (23.80) / 32 (76.19)	11 (24.44) / 34 (75.56)	16 (35.56) / 29 (64.44)
TFOS, days	NA	4.167±5.951	0.814±1.419	1.462±2.063



Blanco-Domínguez R, et al. NEJM May 27th , 2021


Heart
Bone Marrow
IL-1β
GMCsF
IL-1β
DAMPs
CVB3
Infection
Circulation
Haematopiesis
Cardiomyocytes
Necrosis
Activated
Fibroblast
DAMPS
GMCsF
CCL2
IL-1β
ILCs
Monocytes
Mast Cells
NK cells
Dendritic
Cells
CD4
T Cells
Myeloid
Cells
My6H T_h17
T cells
Monocytes
Neutrophils
Eosinophil
Gut
T_H17
T cells
Dendritic
Cells
Molecular Mimicry
Bacteroides
thetaiotaomicron