

# COVID-19 and the heart

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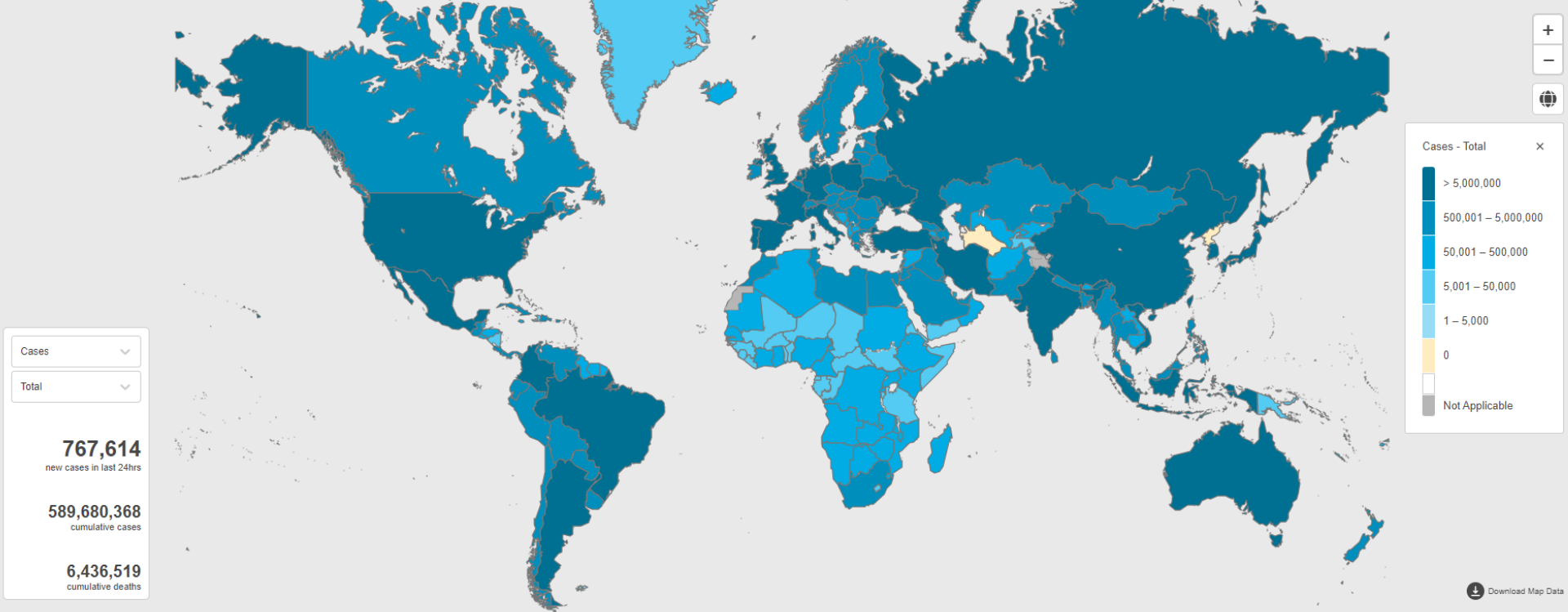
# disclosures

- research support from FDA to investigate the outcomes of COVID-vaccine associated myocarditis

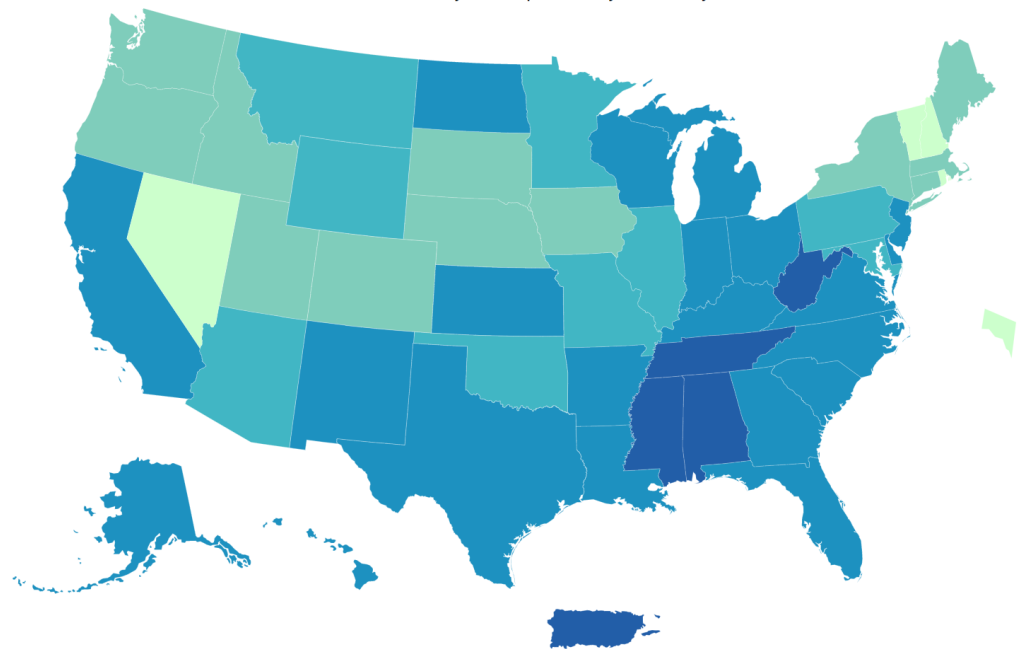
# disclaimer



- I am a pediatric cardiologist
- not all things COVID (and the heart) will be covered

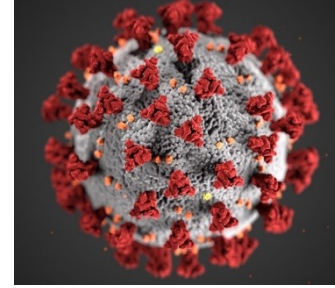


US COVID-19 7-Day Case Rate per 100,000, by State/Territory



WHO, August 17, 2022

- ▶ Dec 12, 2019: Wuhan, China: illness reported
- ▶ Dec 31, 2019: WHO informed
- ▶ Jan 7, 2020: novel Coronavirus isolated
- ▶ Feb 2, 2020: US travel restrictions
- ▶ Mar 11, 2020: WHO: “COVID19 is a pandemic”
- ▶ Mar 13, 2020: US national emergency
- ▶ May 1, 2020: EUA for remdisivir
- ▶ Dec 11, 2020: EUA for Pfizer-BioNTech vaccine
- ▶ Dec 18, 2020: EUA for Moderna vaccine
- ▶ Apr 2021: reports of myocarditis after mRNA vaccines
- ▶ May 10, 2021: Pfizer-BioNTech for 12-18 year olds
- ▶ Nov 2, 2021: Pfizer-BioNTech for 5-11 year olds
- ▶ Dec 1, 2021: Omicron in US
- ▶ Apr 29, 2022: 75% of children and adolescents are seropositive
- ▶ May 29, 2022: Booster recommended for >12 year olds
- ▶ June 18, 2022: Pfizer-BioNTech and Moderna for >6 months olds
- ▶ Aug, 2022: ~1 in 5 adults have at least one health condition that may be attributable to a previous COVID-19 infection
- ▶ Aug 27, 2022: 93.9M cases, 1.04M deaths in the US
- ▶ Aug 31, 2022: Bivalent boosters



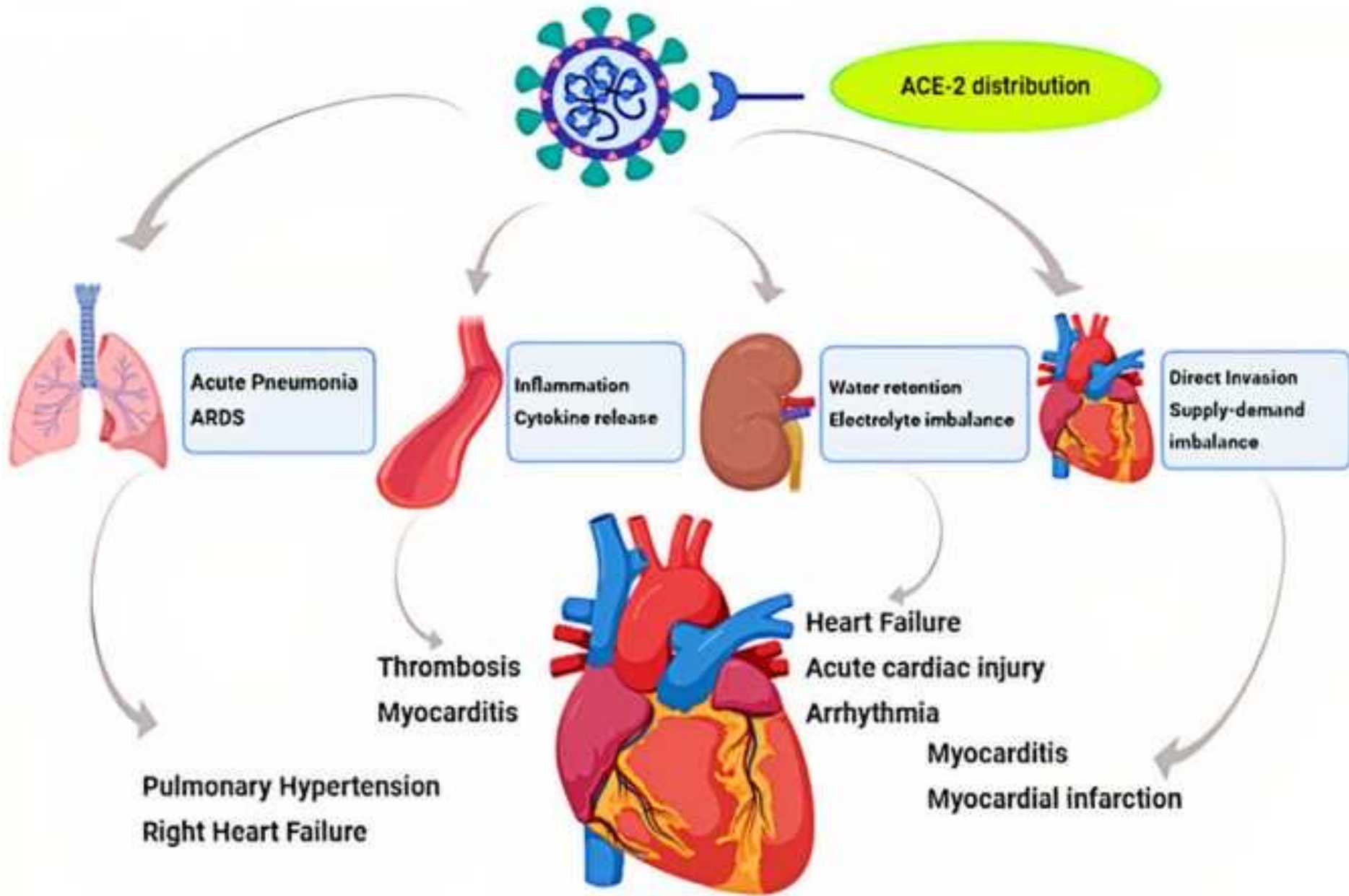
- COVID19 and the heart
  - MIS-C
- vaccine associated myocarditis
  - long-COVID

- COVID19 and the heart

- MIS-C

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# pathomechanisms

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- ACE-2 receptor mediated direct damage
- dysregulated RAAS
- cytokines
- dysregulated immunocytes
- hypoxia induced myocardial injury, oxidative stress, acidosis
- microvascular damage
- angiospasm

# cardiac manifestations of acute COVID 19

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- cardiac involvement
  - myocarditis
  - coronary ischemia
  - cardiac arrest
  - heart failure, cardiomyopathy
  - arrhythmia
  - pulmonary hypertension
  - pulmonary embolism


# COVID19 and CHD

Pediatric Cardiology  
<https://doi.org/10.1007/s00246-021-02751-6>

ORIGINAL ARTICLE

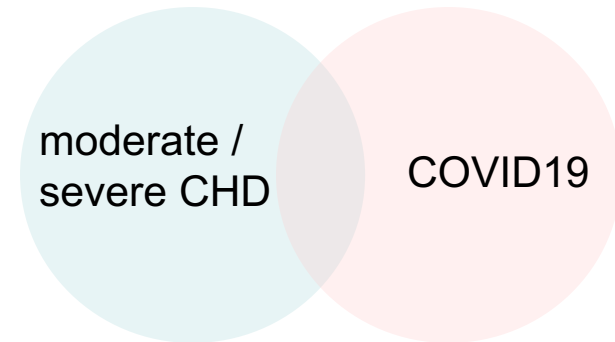


## Worse Hospital Outcomes for Children and Adults with COVID-19 and Congenital Heart Disease

Danielle D. Strah<sup>1</sup> · Katie A. Kowalek<sup>2</sup> · Kevin Weinberger<sup>1</sup> · Jenny Mendelson<sup>2</sup> · Andrew W. Hoyer<sup>3</sup> · Scott E. Klewer<sup>3</sup> · Michael D. Seckeler<sup>3</sup> 

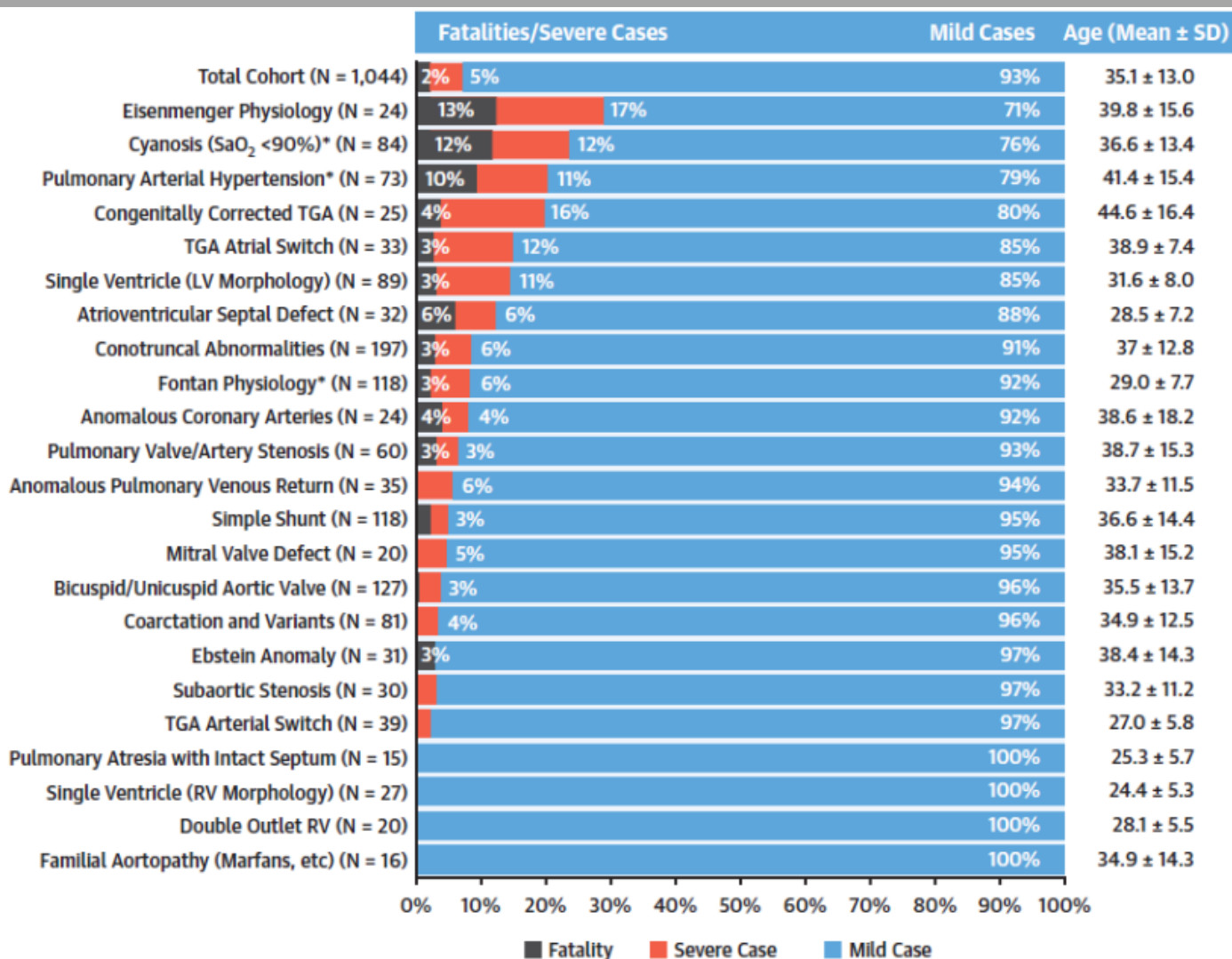
Pediatr Cardiol 2021

- 9,478 total pediatric COVID-19
  - 160 (1.7%) with CHD
- 658,230 total adult COVID-19
  - 389 (0.06%) with CHD



- younger
- longer LOS
- more complications
- higher mortality
- higher costs

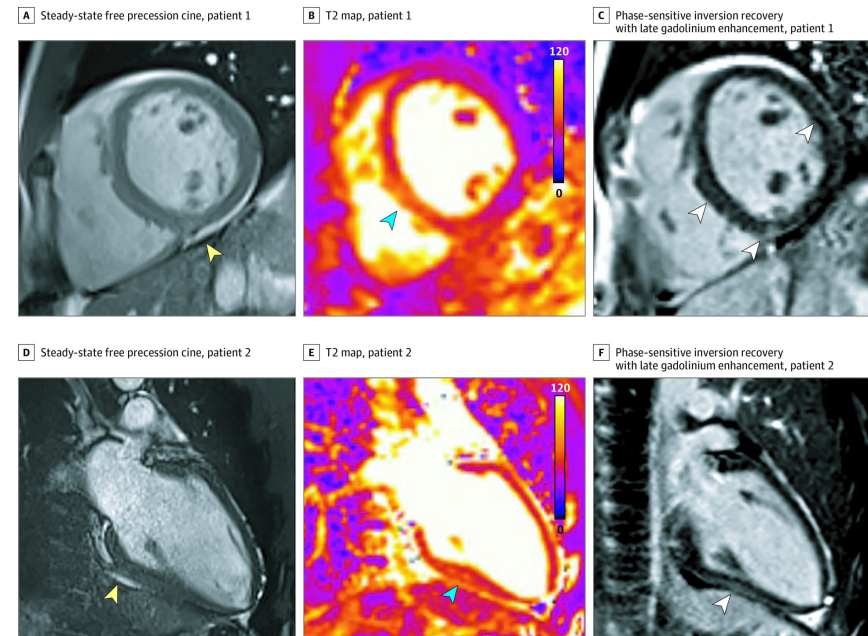
# COVID19 and CHD



- male sex
- diabetes
- cyanosis
- pulmonary hypertension
- renal insufficiency
- heart failure
- worse functional status

# COVID19 in athletes

- 26 competitive college athletes
- no troponin elevations
- normal fx
- 4 (15%) had myocarditis by CMR
  - all males
  - 2 had symptoms



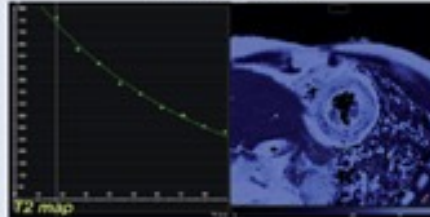
# updated Lake Louise Criteria



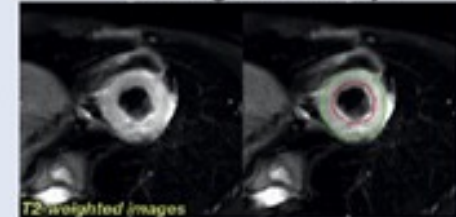
## Main Criteria

**Myocardial Edema**  
(T2-mapping or T2W images)

Regional or global increase  
of native T2



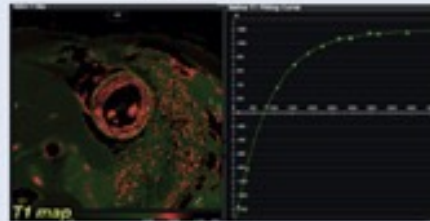
Regional or global increase  
of T2 signal intensity



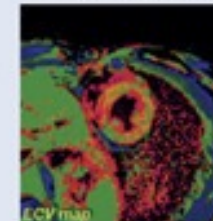
OR

**Non-ischemic Myocardial Injury**  
(Abnormal T1, ECV, or LGE)

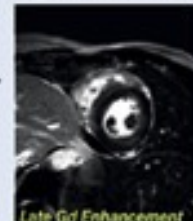
Regional or global increase  
of native T1



Regional or global  
increase of ECV



Regional LGE  
signal increase



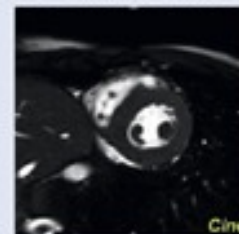
OR

OR

## Supportive Criteria

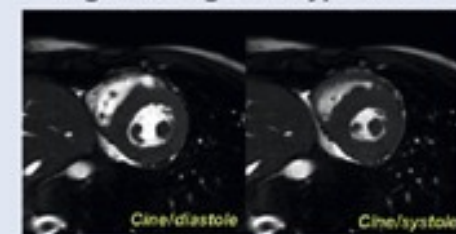
**Pericarditis**  
(Effusion in cine images or  
abnormal LGE, T2, or T1)

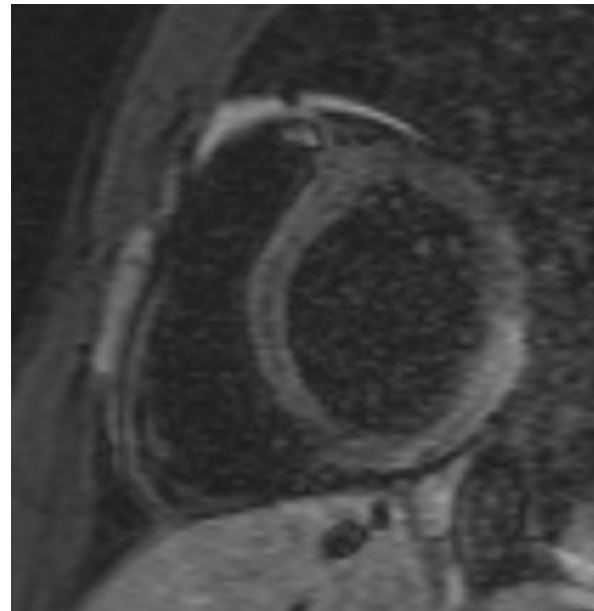
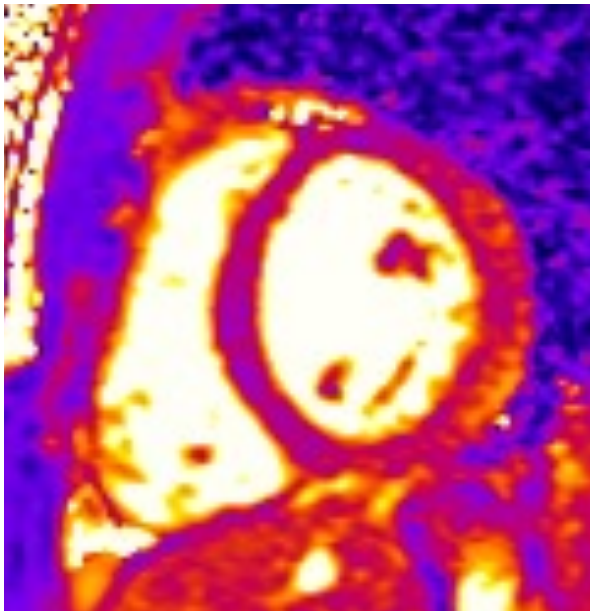
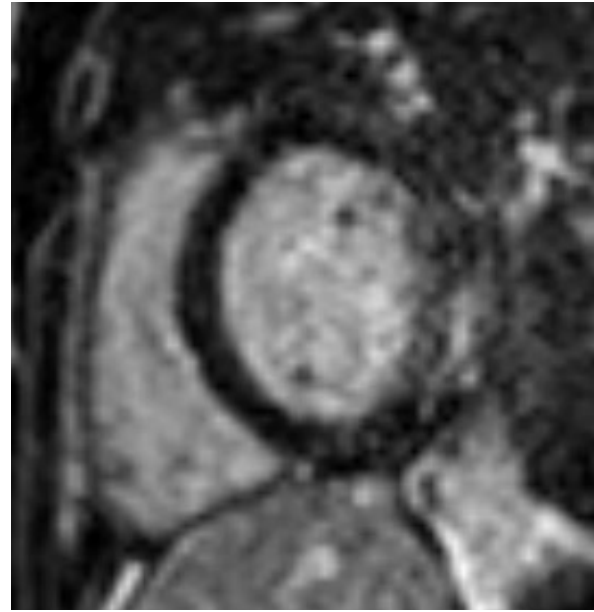
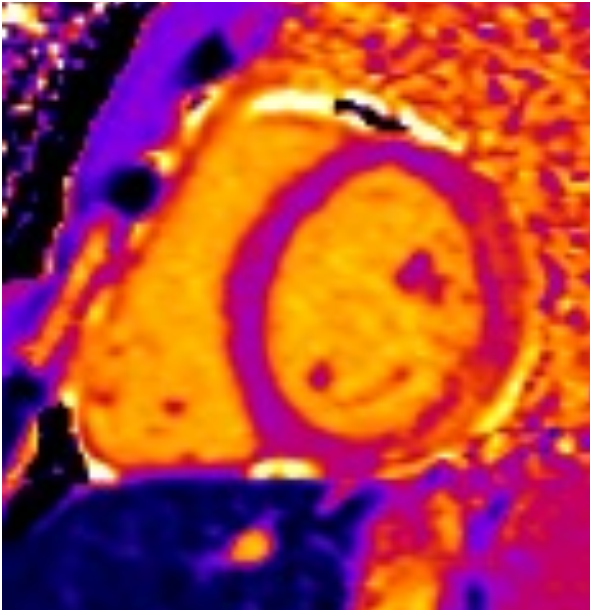
Pericardial effusion



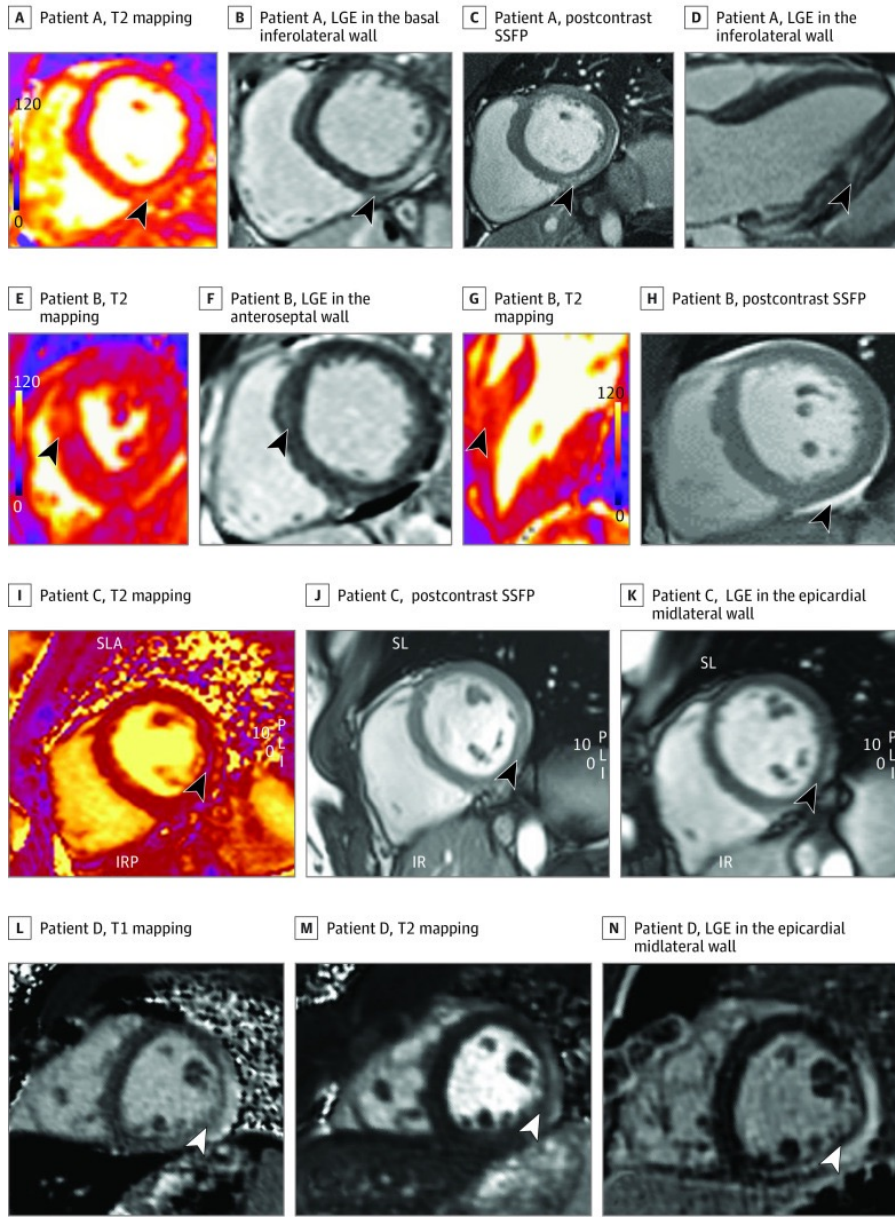
**Systolic LV Dysfunction**  
(Regional or global wall  
motion abnormality)

Regional or global hypokinesis



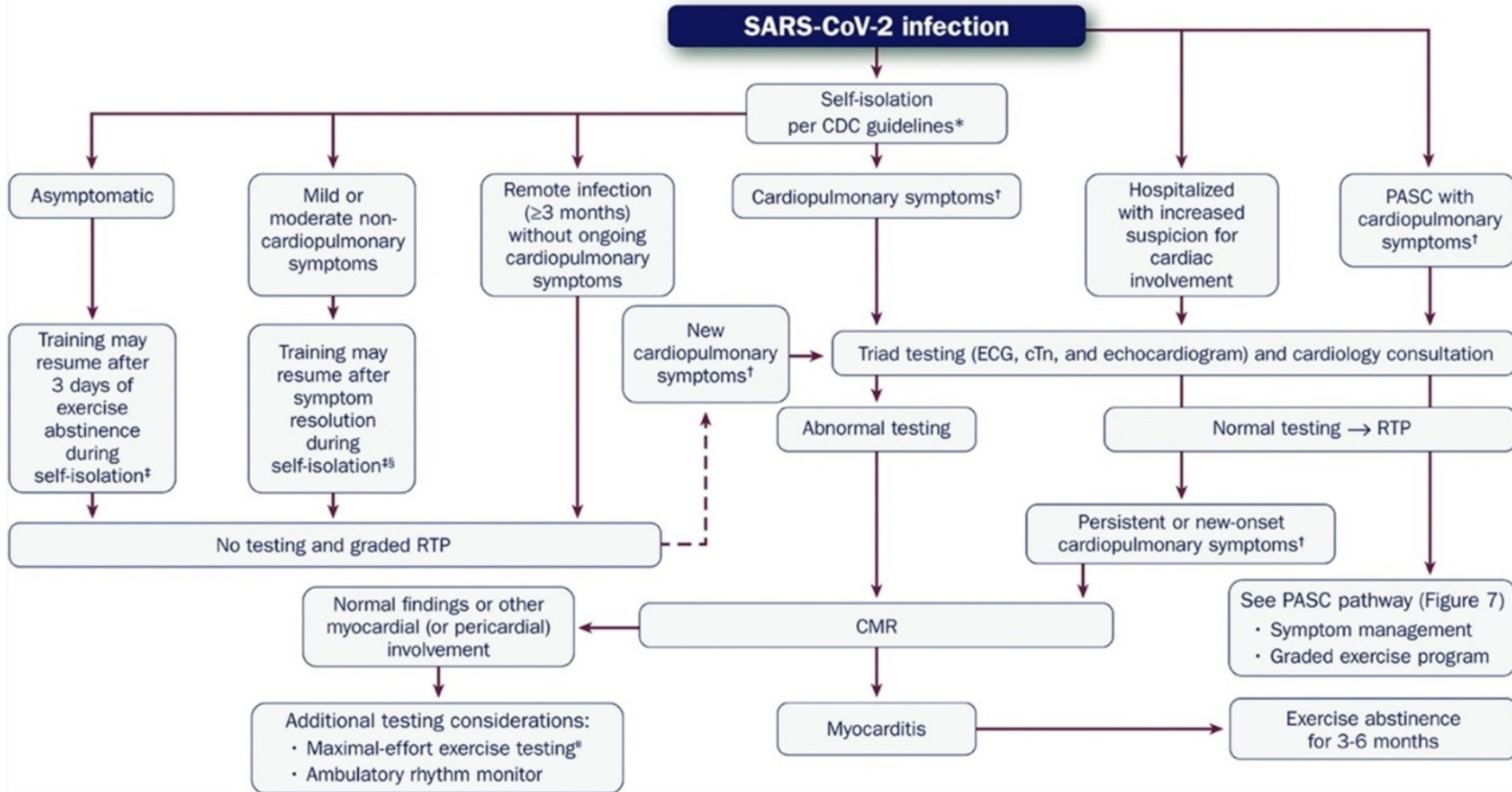


- 1597 competitive college athletes
- 37 (27 male) had myocarditis (2.3%)
- 5 diagnosed without CMR





# return to play, adult

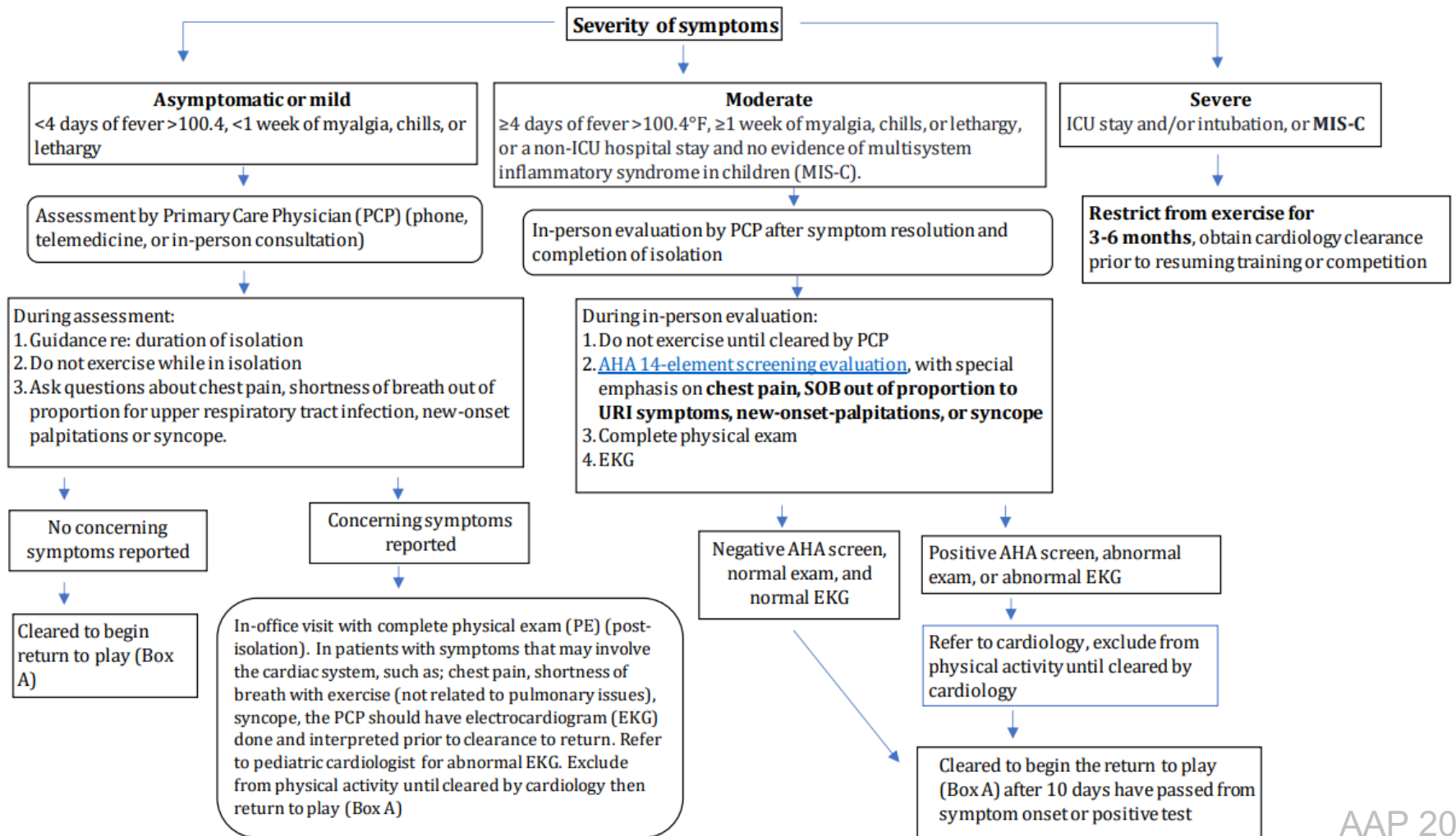


# return to play, children

## Return to play after COVID-19 infection

Adapted from the AAP COVID-19 Interim Guidance: Return to Sports and Physical Activity by Anna Zuckerman, MD, FAAP and Jonathan Flyer, MD, FAAP, FACC.

For detailed guidance, please refer to the [AAP COVID-19 Interim Guidance: Return to Sports and Physical Activity](#). (Last updated 2/18/2022)



**New cases (per 1M)**



**New deaths (per 1M)**



# Outcomes of Cardiovascular Magnetic Resonance Imaging in Patients Recently Recovered From Coronavirus Disease 2019 (COVID-19)

Valentina O. Puntmann, MD, PhD; M. Ludovica Carerj, MD; Imke Wieters, MD; Masia Fahim; Christophe Arendt, MD; Jędrzej Hoffmann, MD; Anastasia Shchendrygina, MD, PhD; Felicitas Escher, MD; Mariuca Vasa-Nicotera, MD; Andreas M. Zeiher, MD; Maria Vehreschild, MD; Eike Nagel, MD

2020

- 100 patients
- CMR 71 (64-92) days after COVID
- hs troponin elevated in 5%
- decreased EF, enlarged LV, increased T1, T2
- LGE 22%
- abnormal T1 73%
  - higher in hospitalized patients
- abnormal T2 60%



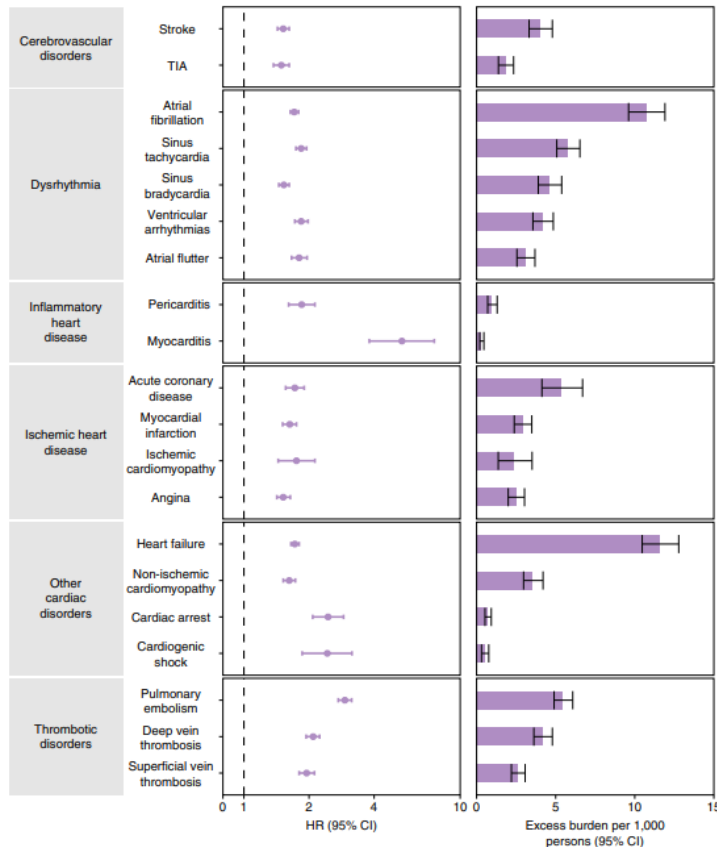
2022

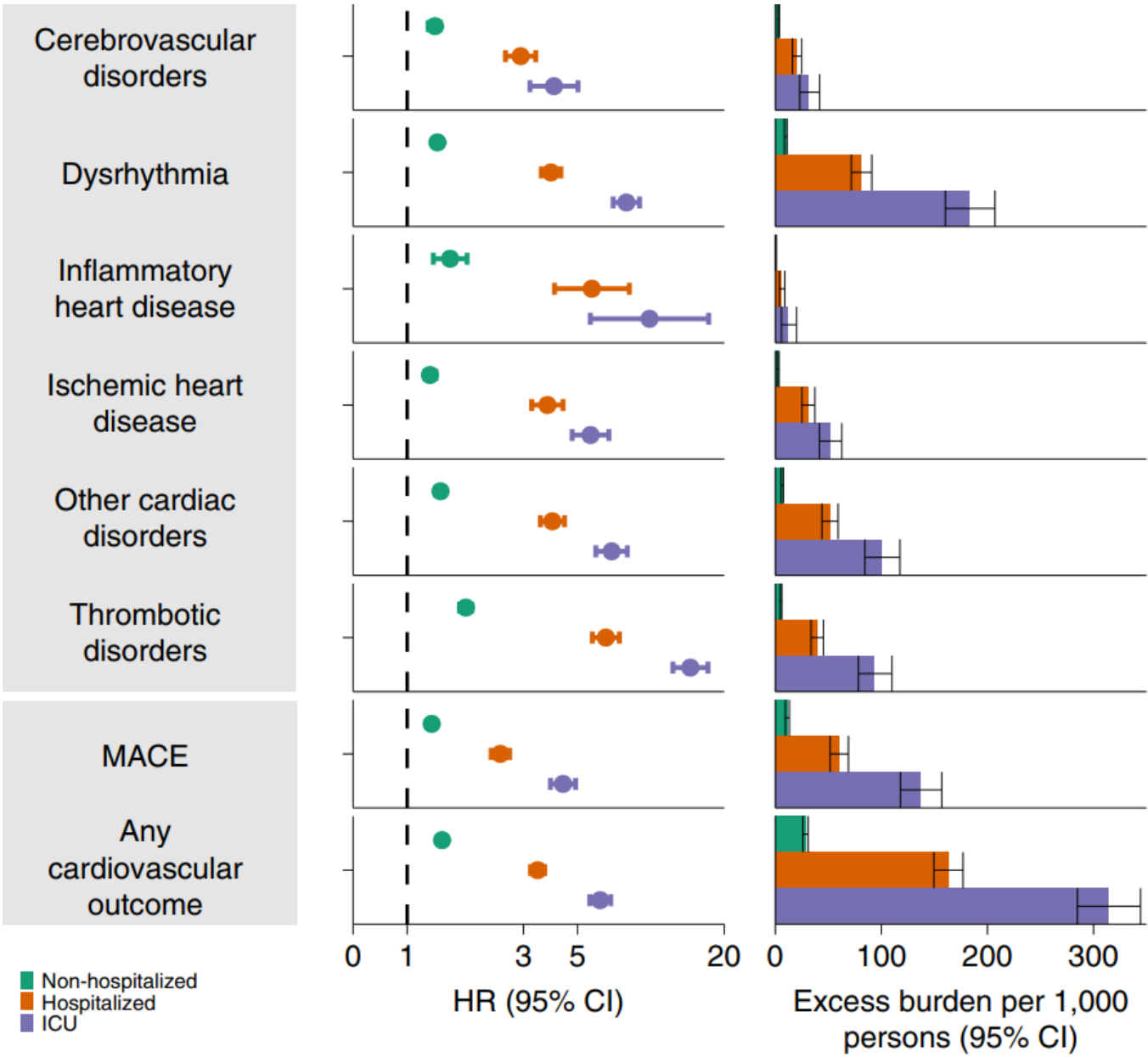
OPEN

# Long-term cardiovascular outcomes of COVID-19

Yan Xie <sup>1,2,3</sup>, Evan Xu <sup>1,4</sup>, Benjamin Bowe <sup>1,2</sup> and Ziyad Al-Aly <sup>1,2,5,6,7</sup> ✉

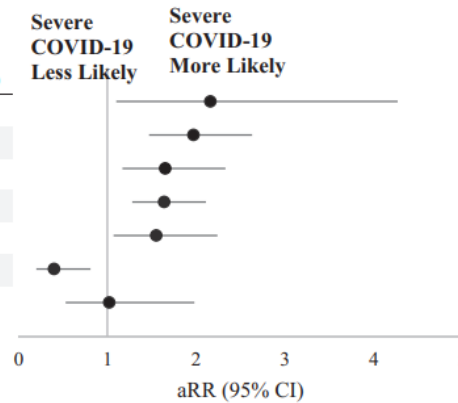
- 153,760 individuals with COVID-19
- 5,637,647 contemporary controls; 5,859,411 historical controls





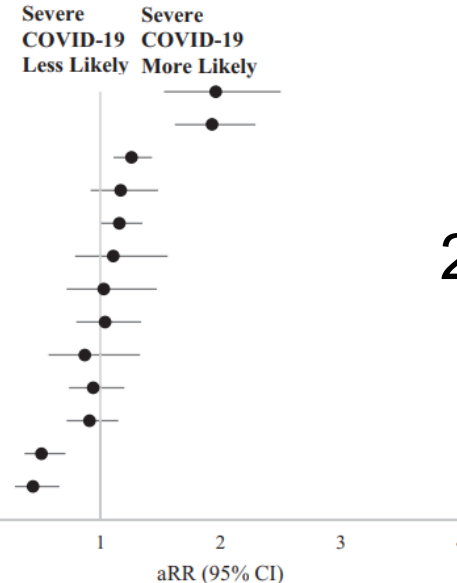
# what about children?

| Underlying Medical Condition | Severe Disease<br><i>n</i> = 164 |        | No Severe Disease<br><i>n</i> = 581 |        | Bivariate Models |            | Multivariable Models <sup>a</sup> |            |
|------------------------------|----------------------------------|--------|-------------------------------------|--------|------------------|------------|-----------------------------------|------------|
|                              | <i>n</i>                         | (%)    | <i>n</i>                            | (%)    | RR               | (95% CI)   | aRR                               | (95% CI)   |
| Chronic lung disease         | 21                               | (12.8) | 17                                  | (2.9)  | 2.8              | (2.0, 3.9) | 2.2                               | (1.1, 4.3) |
| Neurologic disorder          | 27                               | (16.5) | 22                                  | (3.8)  | 2.9              | (2.2, 3.8) | 2.0                               | (1.5, 2.6) |
| Cardiovascular disease       | 23                               | (14.0) | 34                                  | (5.9)  | 2.0              | (1.5, 2.7) | 1.7                               | (1.2, 2.3) |
| Prematurity <sup>b</sup>     | 39                               | (23.8) | 61                                  | (10.5) | 2.1              | (1.5, 2.9) | 1.6                               | (1.3, 2.1) |
| Airway abnormality           | 12                               | (7.3)  | 12                                  | (2.1)  | 2.4              | (1.4, 4.1) | 1.6                               | (1.1, 2.2) |
| Feeding tube dependent       | 11                               | (6.7)  | 22                                  | (3.8)  | 1.6              | (1.0, 2.6) | 0.4                               | (0.2, 0.8) |
| Other <sup>c</sup>           | 11                               | (6.7)  | 25                                  | (6.7)  | 1.5              | (0.8, 2.7) | 1.0                               | (0.5, 2.0) |



<2 years

| Underlying Medical Condition           | Severe Disease<br><i>n</i> = 527 |        | No Severe Disease<br><i>n</i> = 1,021 |        | Bivariate Models |            | Multivariable Models <sup>a</sup> |            |
|--|----------------------------------|--------|---------------------------------------|--------|------------------|------------|-----------------------------------|------------|
|  | <i>n</i>                         | (%)    | <i>n</i>                              | (%)    | RR               | (95% CI)   | aRR                               | (95% CI)   |
| Feeding tube dependence                | 49                               | (9.3)  | 32                                    | (3.1)  | 2.0              | (1.7, 2.2) | 2.0                               | (1.5, 2.5) |
| Diabetes mellitus (type I or 2)        | 53                               | (10.1) | 35                                    | (3.4)  | 1.9              | (1.6, 2.3) | 1.9                               | (1.6, 2.3) |
| Obesity <sup>d</sup>                   | 191                              | (36.2) | 287                                   | (28.1) | 1.3              | (1.1, 1.5) | 1.2                               | (1.0, 1.4) |
| Chronic lung disease <sup>e</sup>      | 32                               | (6.1)  | 38                                    | (3.7)  | 1.5              | (1.2, 1.8) | 1.2                               | (0.9, 1.5) |
| Developmental delay                    | 84                               | (15.9) | 104                                   | (10.2) | 1.4              | (1.3, 1.6) | 1.2                               | (1.0, 1.4) |
| Immunocompromised condition            | 37                               | (7.0)  | 85                                    | (8.3)  | 0.9              | (0.6, 1.2) | 1.1                               | (0.8, 1.6) |
| Airway abnormality                     | 18                               | (3.4)  | 16                                    | (1.6)  | 1.6              | (1.1, 2.3) | 1.0                               | (0.7, 1.5) |
| Cardiovascular disease                 | 32                               | (6.1)  | 57                                    | (5.6)  | 1.1              | (0.8, 1.4) | 1.0                               | (0.8, 1.3) |
| Chronic metabolic disease <sup>e</sup> | 12                               | (2.3)  | 28                                    | (2.7)  | 0.9              | (0.6, 1.4) | 0.9                               | (0.6, 1.3) |
| Asthma                                 | 120                              | (22.8) | 240                                   | (23.5) | 1.0              | (0.8, 1.2) | 0.9                               | (0.7, 1.2) |
| Neurologic disorder <sup>e</sup>       | 34                               | (6.5)  | 66                                    | (6.5)  | 1.0              | (0.8, 1.3) | 1.9                               | (0.7, 1.2) |
| Blood disorder                         | 25                               | (4.7)  | 96                                    | (9.4)  | 0.5              | (0.4, 0.7) | 0.5                               | (0.4, 0.7) |
| Other <sup>f</sup>                     | 17                               | (3.2)  | 80                                    | (7.8)  | 0.5              | (0.3, 0.7) | 0.4                               | (0.3, 0.7) |



2-17 years

- COVID19 and the heart

- MIS-C

- vaccine associated myocarditis

- POTS and long-COVID



# pediatric inflammatory multisystem syndrome, temporally associated with SARS-CoV-2 (PIMS-TS) or multisystem inflammatory syndrome in children (MIS-C)



Published Online  
May 6, 2020  
[https://doi.org/10.1016/S0140-6736\(20\)31094-1](https://doi.org/10.1016/S0140-6736(20)31094-1)

## Hyperinflammatory shock in children during COVID-19 pandemic

South Thames Retrieval Service in London, UK, provides paediatric intensive care support and retrieval

to 2 million children in South East England. During a period of 10 days in mid-April, 2020, we noted an unprecedented cluster of eight children with hyperinflammatory shock, showing features similar to atypical Kawasaki disease, Kawasaki disease shock syndrome,<sup>1</sup> or toxic shock

syndrome (typical number is one or two children per week). This case cluster formed the basis of a national alert.

All children were previously fit and well. Six of the children were of Afro-Caribbean descent, and five of the children were boys. All children except one were well above the 75th centile

We suggest that this clinical picture represents a new phenomenon affecting previously asymptomatic children with SARS-CoV-2 infection manifesting as a hyperinflammatory syndrome with multiorgan involvement similar to Kawasaki disease shock syndrome. The

## What is the new illness affecting children, and is it linked to coronavirus?

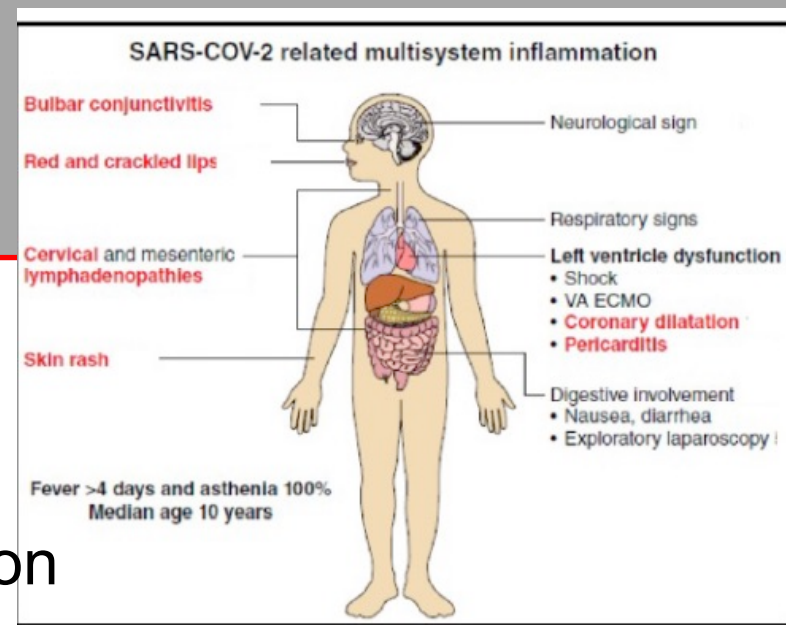
**In recent weeks, a small number of children have been treated in ICU for a severe immune reaction**

- **NHS warns of rise in children with new illness that may be linked to coronavirus**



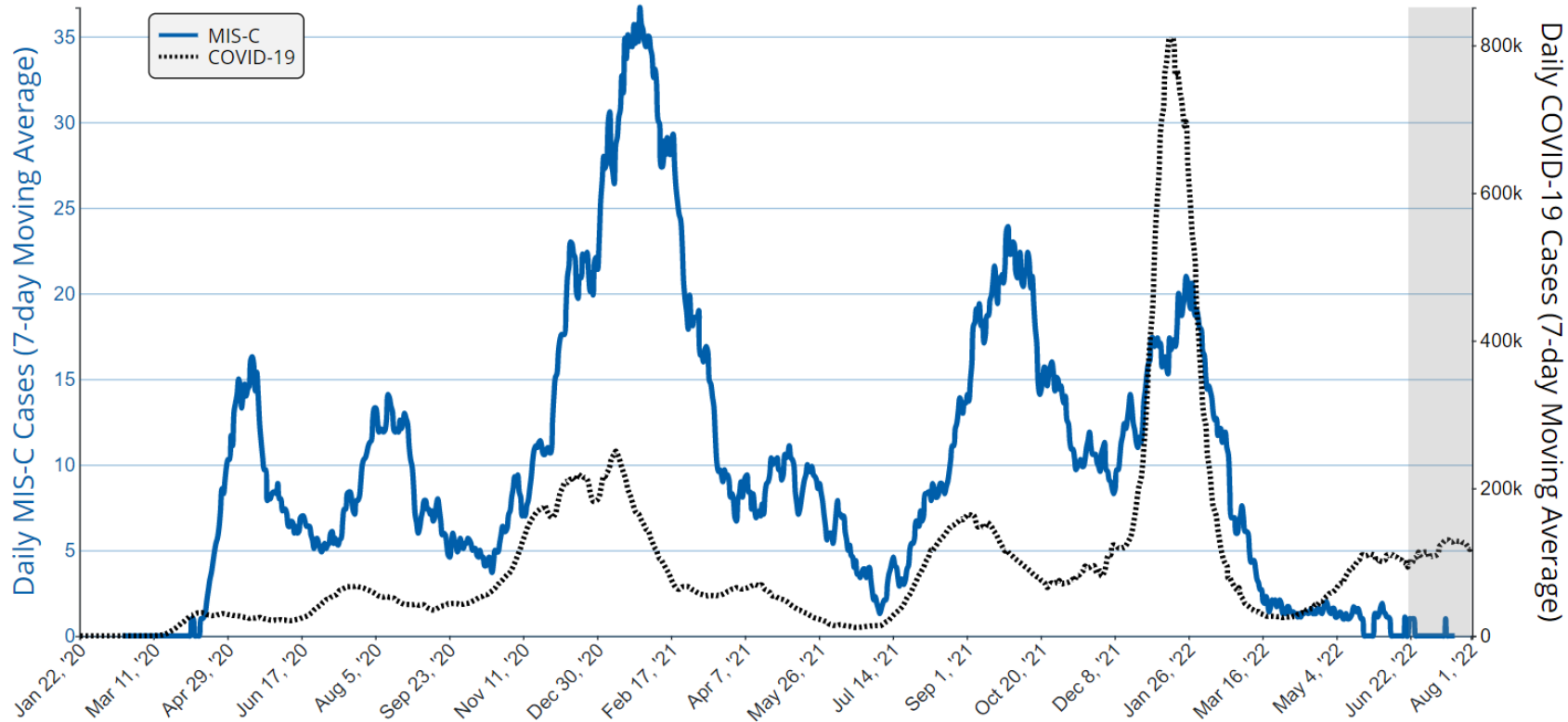
# MIS-C, CDC 5/2020

- fever
- inflammatory labs
- severe illness requiring hospitalization
- with multisystem organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurological)
- no alternative plausible diagnoses
- positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test
- or COVID-19 exposure within the 4 weeks prior to the onset of symptoms



# MIS-C, epidemiology

Daily MIS-C Cases and COVID-19 Cases Reported to CDC (7-Day Moving Average)



|                           | <b>MIS-C</b>      | <b>severe acute COVID-19</b> |
|---------------------------|-------------------|------------------------------|
| Age                       | 5-11 years        |                              |
| Ethnicity                 | Blacks, hispanics |                              |
| Respiratory symptoms      | +++               | +++                          |
| Pneumonia                 | +                 | ++                           |
| ARDS                      | +                 | +                            |
| Cardiac dysfunction       | ++                | (+)                          |
| Mucocutaneous involvement | +++               | (+)                          |
| Inflammatory markers      | +++               | ++                           |
| Gastrointestinal symptoms | +++               | +                            |
| Ventilation               | ++                | ++                           |
| Vasopressor support       | +++               | +                            |
| Mortality                 | 1.9%              | 1.4%                         |

adapted from Feldstein, JAMA 2021

# Risk factors for multisystem inflammatory syndrome in children – A population-based cohort study of over 2 million children

*Samuel Rhedin,<sup>a,b,\*</sup> Cecilia Lundholm,<sup>a</sup> AnnaCarin Horne,<sup>c</sup> Awad I. Smew,<sup>a</sup> Emma Caffrey Osvald,<sup>a,d</sup> Araz Haddadi,<sup>b</sup> Tobias Alfvén,<sup>b,e</sup> Robin Kahn,<sup>f,g</sup> Petra Król,<sup>f</sup> the Swedish Pediatric MIS-C Consortium,<sup>#</sup> Bronwyn Haasdyk Brew,<sup>a,h</sup> and Catarina Almqvist<sup>a,d</sup>*

Lancet Reg Health Eur 2022

## MIS-C in children with

- male sex
- age 5-11 years
- foreign-born parents
- asthma
- obesity
- life-limiting condition

# MIS-C, cardiac involvement

## Multisystemic Inflammatory Syndrome in Children

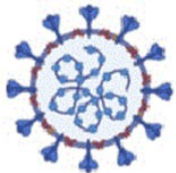
### Pathophysiology



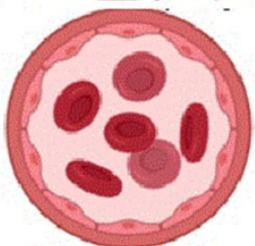
Cardiomyocyte Invasion



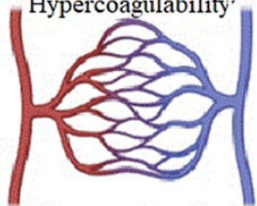
Dysregulated Inflammatory Response



SARS CoV2 Infection



Endothelial Injury and Hypercoagulability



Microvascular Injury

### Clinical Manifestaion

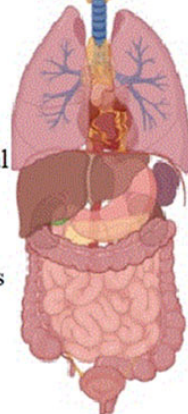


Fever

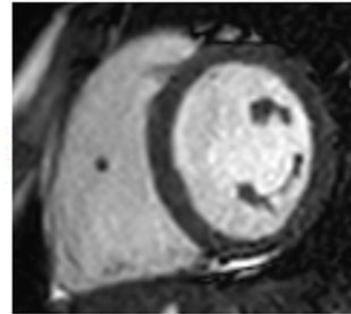


Elevated C-reactive Protein/  
Inflammtory Markers  
Elevated BNP and Troponin

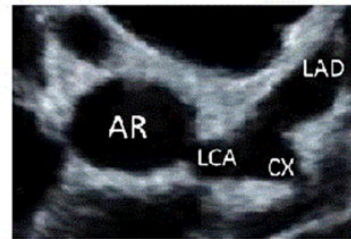
- Multisystem Involvement:
- 1- Shock/Cardiac
  - 2- Gastrointestinal
  - 3- Coagulopathy
  - 4- Lung (mild)
  - 5- Renal
  - 6- Mucocutaneous



### Cardiac Manifestation



Ventricular Dysfunction



Coronary Dilation and Aneurysms



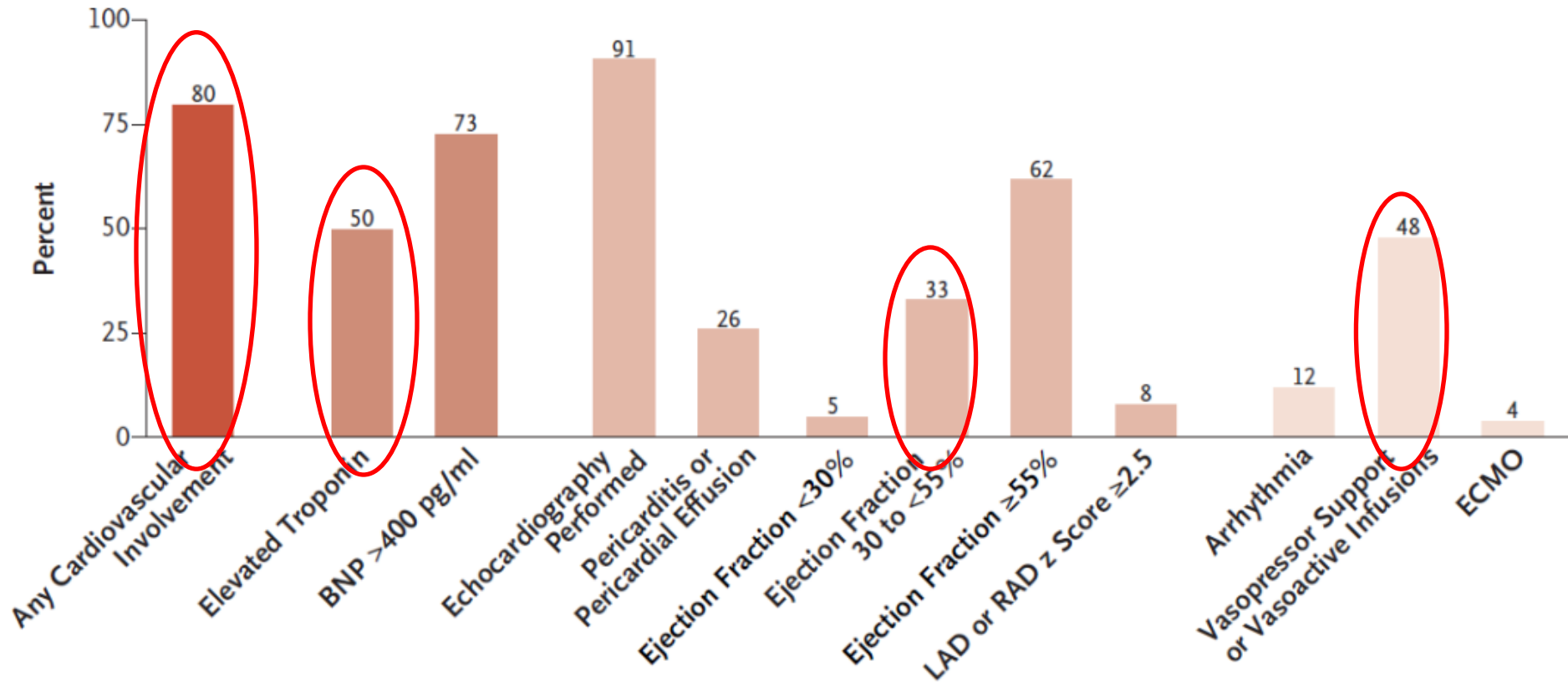
ECG and Conduction Abnormalities

# MIS-C, cardiac involvement

| <b>Symptom Category</b>       | <b>0–5 Years<br/>(N=31)</b> | <b>6–12 Years<br/>(N=42)</b> | <b>13–20 Years<br/>(N=26)</b> |
|-------------------------------|-----------------------------|------------------------------|-------------------------------|
| Dermatologic or mucocutaneous | 87.1                        | 78.6                         | 61.5                          |
| Gastrointestinal              | 74.2                        | 83.3                         | 80.8                          |
| KD or atypical KD             | 48.4                        | 42.9                         | 11.5                          |
| Myocarditis                   | 38.7                        | 50.0                         | 73.1                          |
| Neurologic                    | 12.9                        | 38.1                         | 38.5                          |

# MIS-C, cardiac involvement

## A Cardiovascular Involvement



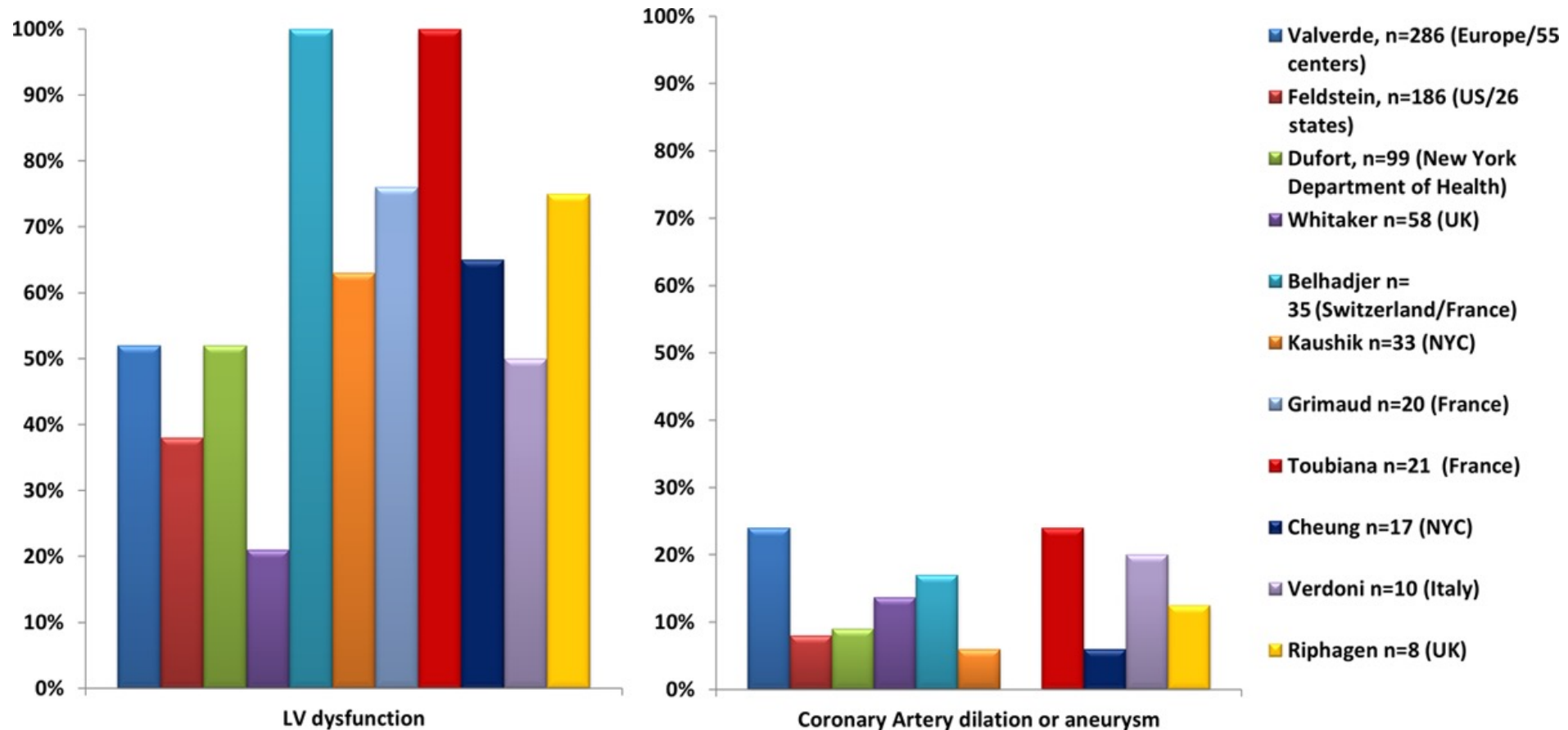


# EKG and rhythm abnormalities

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- EKG abnormalities common
  - non-specific ST segment changes
  - prolonged QTc
- atrial arrhythmias
  - ectopy
  - fibrillation
- ventricular arrhythmias
  - ectopy
  - tachycardia
- heart block

# MIS-C, cardiac involvement



# MIS-C, cardiac w/u

- monitor
- EKG
- BNP, troponin
- CXR
- echocardiogram
- (CMR)

RESEARCH

Open Access



# Myocardial involvement in children with post-COVID multisystem inflammatory syndrome: a cardiovascular magnetic resonance based multicenter international study—the CARDOVID registry

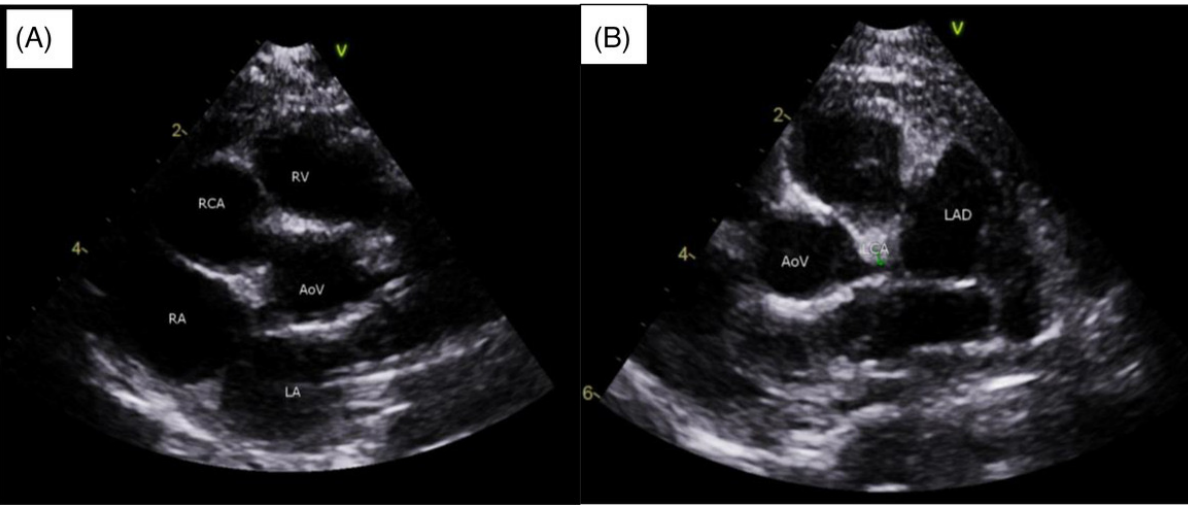
Florence A. Aeschlimann<sup>1</sup>, Nilanjana Misra<sup>2</sup>, Tarique Hussein<sup>3</sup>, Elena Panaioli<sup>4,5</sup>, Jonathan H. Soslow<sup>6</sup>, Kimberly Crum<sup>6</sup>, Jeremy M. Steele<sup>7</sup>, Steffen Huber<sup>8</sup>, Simona Marcora<sup>9</sup>, Paolo Brambilla<sup>10</sup>, Supriya Jain<sup>11</sup>, Maria Navallas<sup>12</sup>, Valentina Giuli<sup>13</sup>, Beate Rücker<sup>14</sup>, Felix Angst<sup>15</sup>, Mehul D. Patel<sup>16</sup>, Arshid Azarine<sup>17</sup>, Pablo Caro-Domínguez<sup>18</sup>, Annachiara Cavaliere<sup>19</sup>, Giovanni Di Salvo<sup>19</sup>, Francesca Ferroni<sup>20</sup>, Gabriella Agnoletti<sup>20</sup>, Laurent Bonnemains<sup>21,22</sup>, Duarte Martins<sup>23</sup>, Nathalie Boddaert<sup>4,24</sup>, James Wong<sup>14</sup>, Kuberan Pushparajah<sup>14,25</sup> and Francesca Raimondi<sup>4,5,24,25,26\*</sup> 

- 111 patients, median age 10 years
- 20 had myocarditis
- 65% with LVEF <55% (21% at discharge)
- LGE in 20%
- edema in 16%
- 20% LLC+

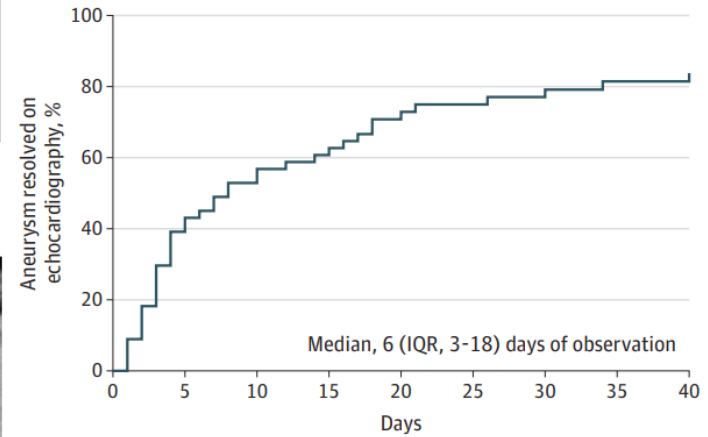
# KD



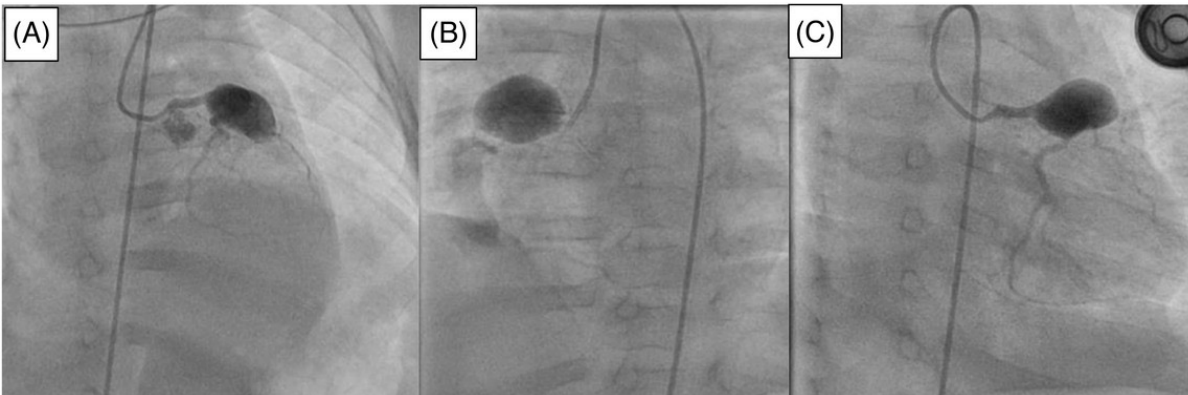
# CA aneurysms



**B** Resolution of coronary artery aneurysms



Feldstein, JAMA 2021



Drury, Echocardiography 2022

# COVID19 vs. KD

|                                   | MIS-C     | KD                 |
|-----------------------------------|-----------|--------------------|
| Age                               | 7.5 ± 3.5 | 3.0 ± 2.5          |
| Respiratory involve               | ++        | +++                |
| GI symptoms                       | +++       | +                  |
| Abnormal echo                     | 60%       | 10%                |
| Cardiovascular shock              | 50%       | <5%                |
| Troponin, BNP, D-dimers, Ferritin | +++       | +                  |
| CA aneurysms                      | 9-24%     | 25% (if untreated) |
| Giant aneurysms                   | +/-       | +                  |
|                                   |           |                    |

# MIS-C, management

- ICU, monitoring
- inotropes, ECMO
- aspirin, heparin
- i.v.Ig
- steroids
- cytokine blockers
  - IL-6 inhibitors (tocilizumab)
  - IL-1 or tumor-necrosis-factor (TNF)- $\alpha$  inhibitors (anakinra, infliximab)
- remdesivir
  
- exercise restriction

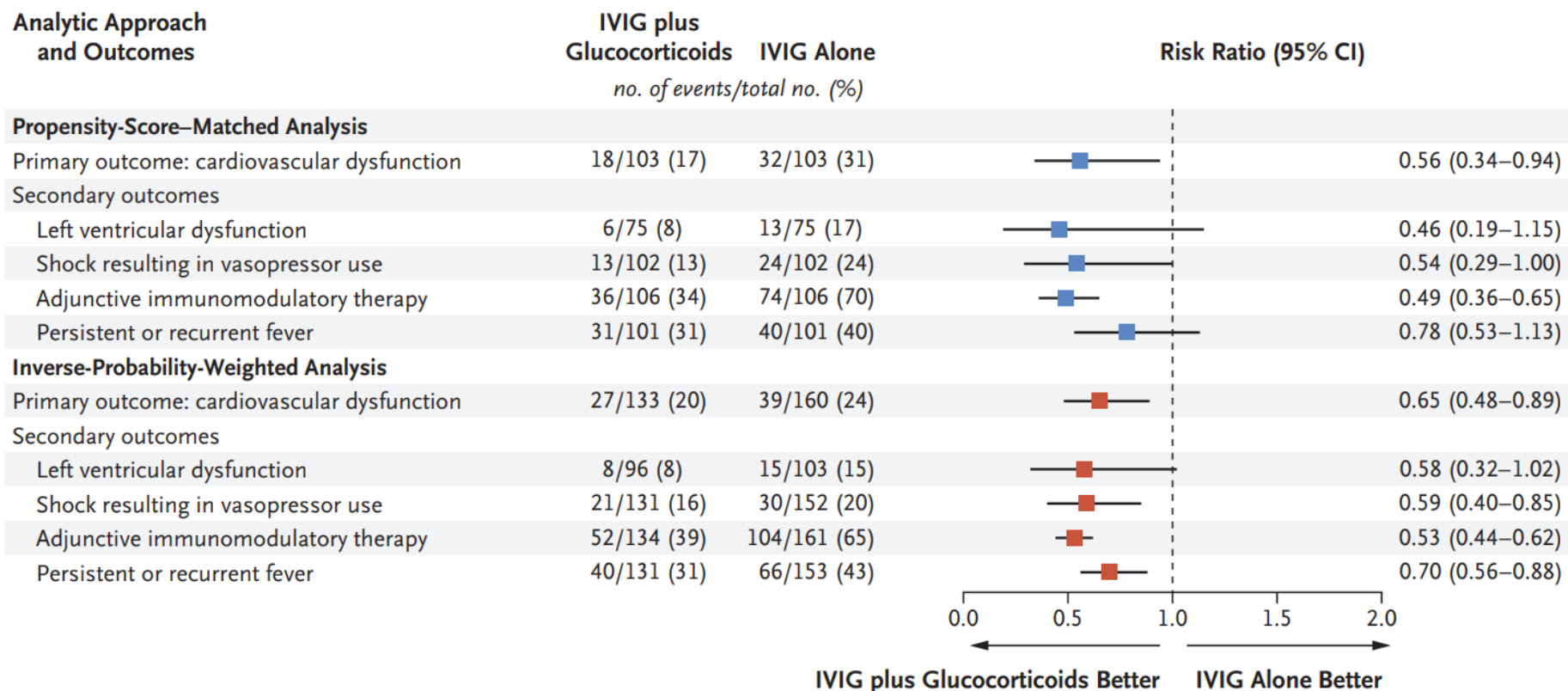


# Multisystem Inflammatory Syndrome in Children — Initial Therapy and Outcomes

Mary Beth F. Son, M.D., Nancy Murray, M.Sc., Kevin Friedman, M.D., Cameron C. Young, Margaret M. Newhams, M.P.H., Leora R. Feldstein, Ph.D., Laura L. Loftis, M.D., Keiko M. Tarquinio, M.D., Aalok R. Singh, M.D., Sabrina M. Heidemann, M.D., Vijaya L. Soma, M.D., Becky J. Riggs, M.D., *et al.*, for the Overcoming COVID-19 Investigators\*

NEJM 2021

## Analytic Approach and Outcomes



# Six Month Follow-up of Patients With Multi-System Inflammatory Syndrome in Children

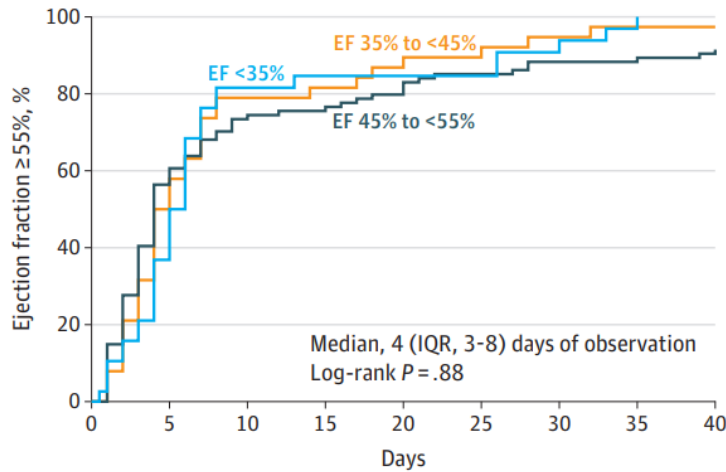
Christine A. Capone, MD, MPH,<sup>a,b,c,d</sup> Nilanjana Misra, MBBS,<sup>a,c</sup> Madhusudan Ganigara, MD,<sup>a</sup> Shilpi Epstein, MD,<sup>a,c</sup> Sujatha Rajan, MD,<sup>c,e</sup> Suchitra S. Acharya, MD, MBBS,<sup>c,f</sup> Denise A. Hayes, MD,<sup>a,b</sup> Mary Beth Kearney, RN, MA, CPNP,<sup>a,c</sup> Angela Romano, MD,<sup>a,c</sup> Richard A. Friedman, MD,<sup>a</sup> Andrew D. Blaufox, MD,<sup>a</sup> Rubin Cooper, MD,<sup>a,c</sup> Charles Schleien, MD, MBA,<sup>c</sup> Elizabeth Mitchell, MD<sup>a,c</sup>

Pediatrics 2021

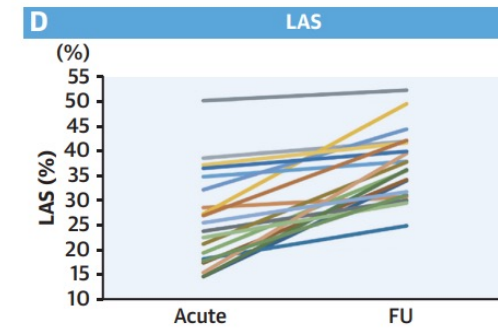
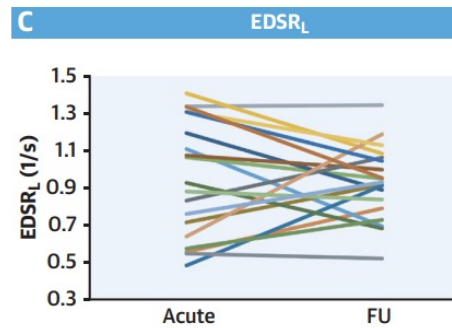
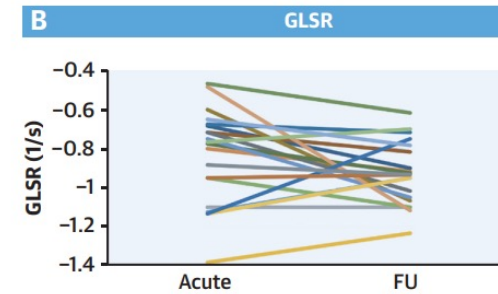
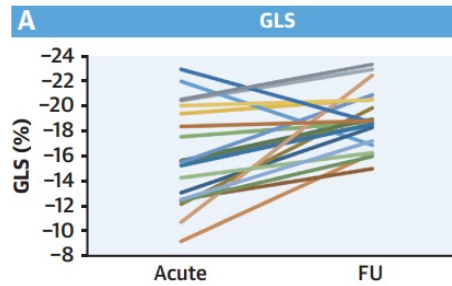
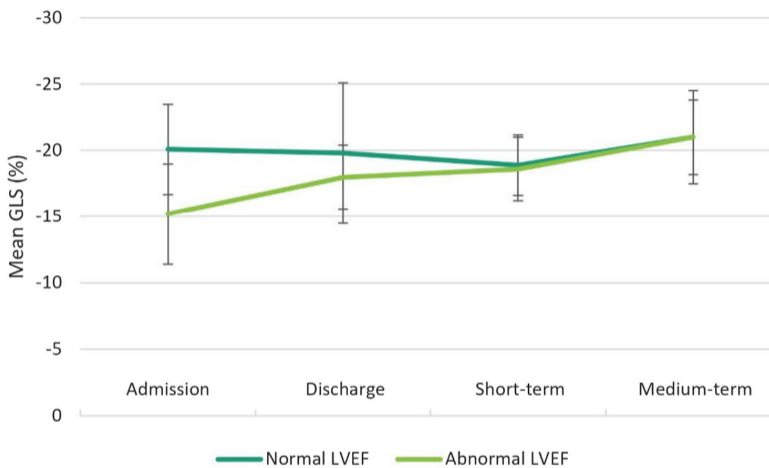
- all patients returned to functional baseline with normal LV systolic function and resolution of coronary abnormalities
- no evidence of myocardial edema or fibrosis

# MIS-C, cardiac outcomes

**A** Resolution of decreased left ventricular ejection fraction



Feldstein, JAMA 2021



Matsubara, JACC 2020

# vaccines prevent COVID and complications

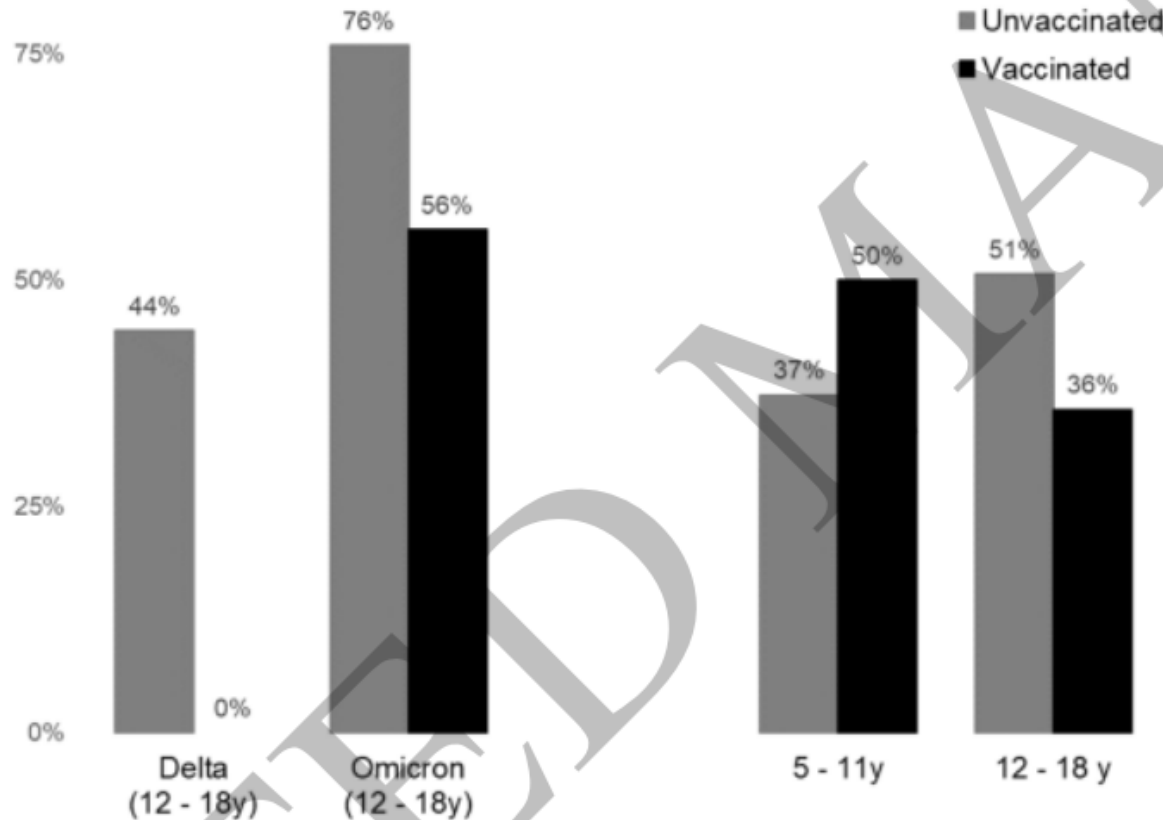
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in the USA, from Dec 1, 2020 to Sept 30, 2021 vaccination prevented ~

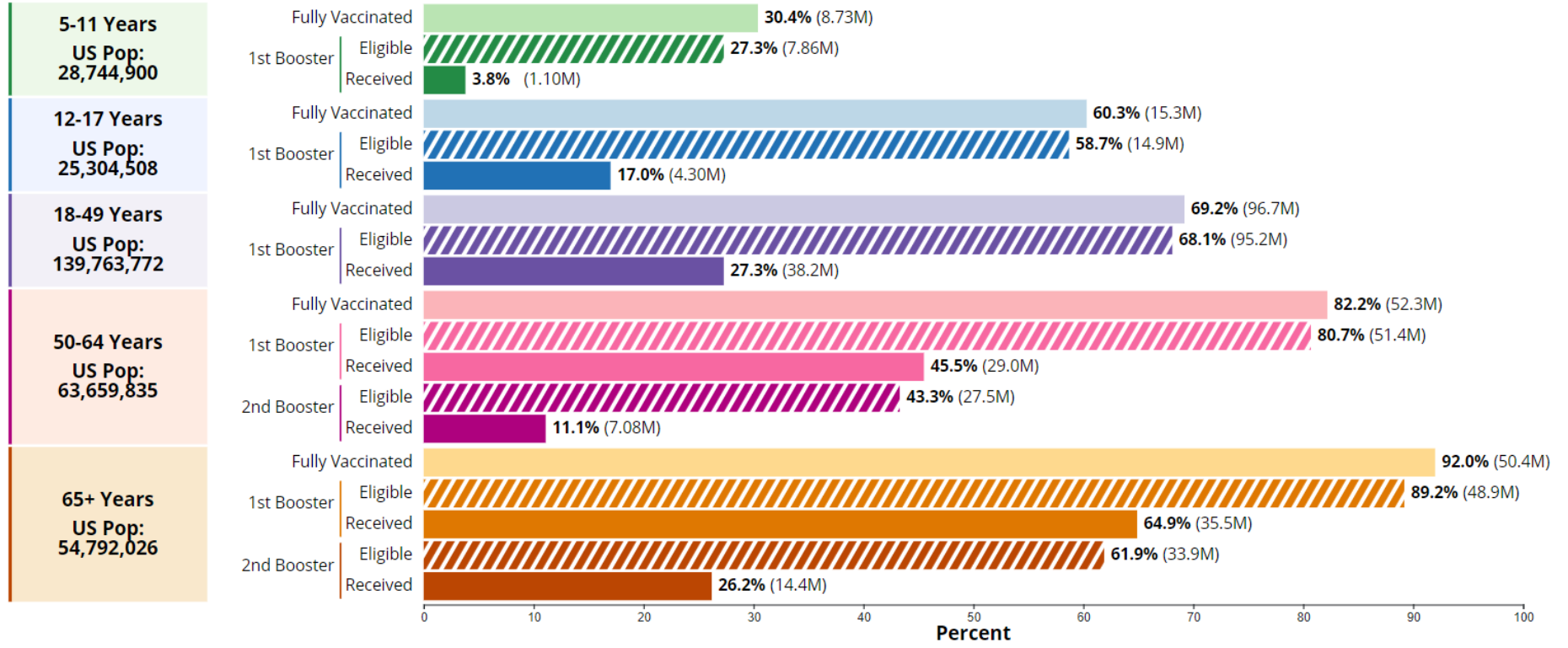
- 27 million infections (52% of expected)
- 1.6 million hospitalizations (56% of expected)
- 235 000 (95% UI, 175 000–305 000) deaths (58% of expected)

# vaccines prevent MIS-C

**B. Comparison of MIS-C cases resulting in life support or death between vaccinated and unvaccinated patients, by period of variant predominance and by age group.**



# Primary Series Completion, Booster Dose Eligibility, and Booster Dose Receipt by Age, United States



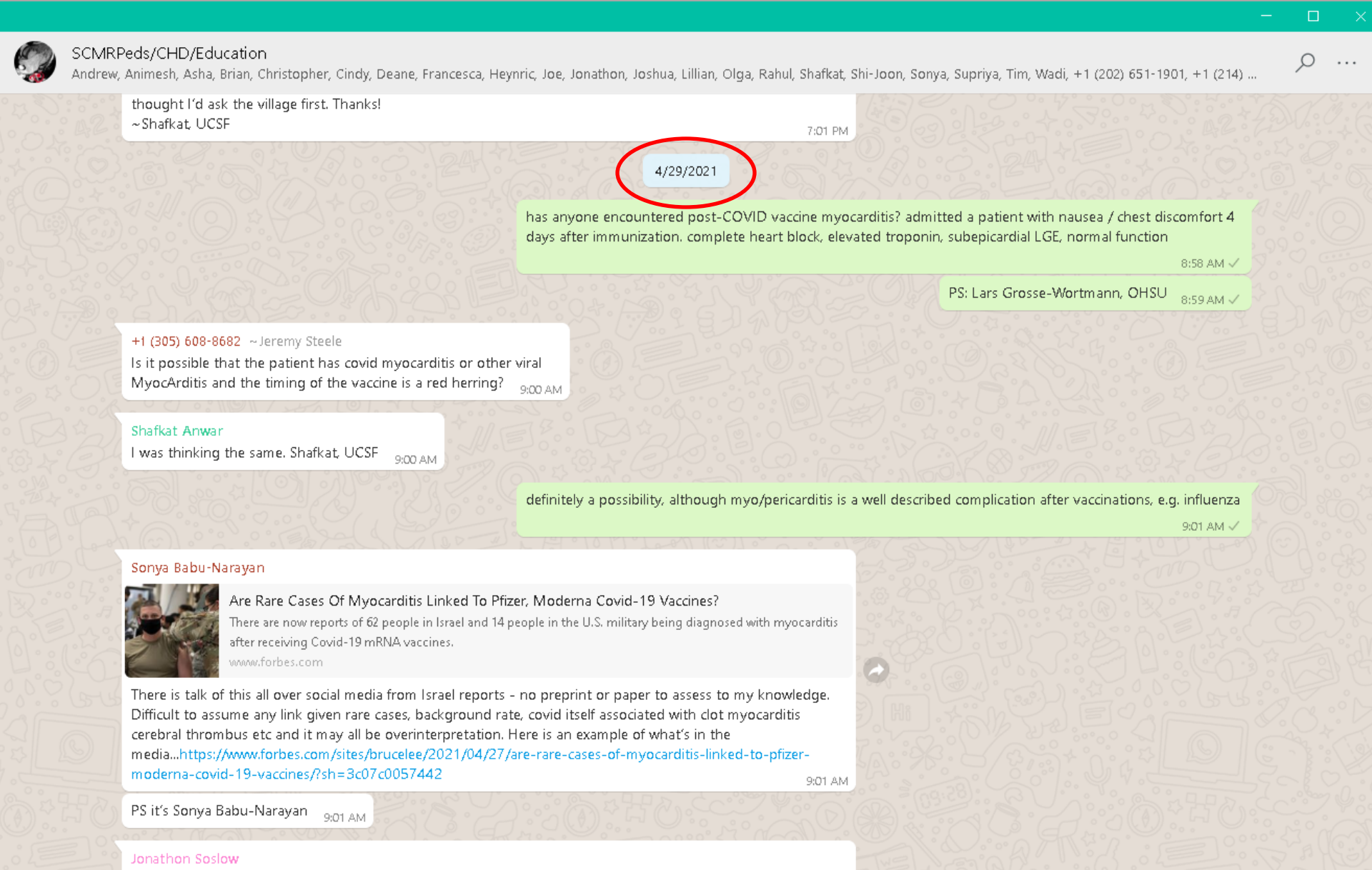
- COVID19 and the heart

- MIS-C

- vaccine associated myocarditis

- long-COVID

# the power of community



SCMRPeds/CHD/Education

Andrew, Animesh, Asha, Brian, Christopher, Cindy, Deane, Francesca, Heynric, Joe, Jonathon, Joshua, Lillian, Olga, Rahul, Shafkat, Shi-Joon, Sonya, Supriya, Tim, Wadi, +1 (202) 651-1901, +1 (214) ...

thought I'd ask the village first. Thanks!  
~Shafkat, UCSF

7:01 PM

4/29/2021

has anyone encountered post-COVID vaccine myocarditis? admitted a patient with nausea / chest discomfort 4 days after immunization. complete heart block, elevated troponin, subepicardial LGE, normal function

8:58 AM ✓

PS: Lars Grosse-Wortmann, OHSU

8:59 AM ✓

+1 (305) 608-8682 ~ Jeremy Steele

Is it possible that the patient has covid myocarditis or other viral Myocarditis and the timing of the vaccine is a red herring?

9:00 AM

Shafkat Anwar

I was thinking the same. Shafkat, UCSF

9:00 AM

definitely a possibility, although myo/pericarditis is a well described complication after vaccinations, e.g. influenza

9:01 AM ✓

Sonya Babu-Narayan



Are Rare Cases Of Myocarditis Linked To Pfizer, Moderna Covid-19 Vaccines?

There are now reports of 62 people in Israel and 14 people in the U.S. military being diagnosed with myocarditis after receiving Covid-19 mRNA vaccines.

[www.forbes.com](http://www.forbes.com)

There is talk of this all over social media from Israel reports - no preprint or paper to assess to my knowledge. Difficult to assume any link given rare cases, background rate, covid itself associated with clot myocarditis cerebral thrombus etc and it may all be overinterpretation. Here is an example of what's in the media...<https://www.forbes.com/sites/brucelee/2021/04/27/are-rare-cases-of-myocarditis-linked-to-pfizer-moderna-covid-19-vaccines/?sh=3c07c0057442>

9:01 AM

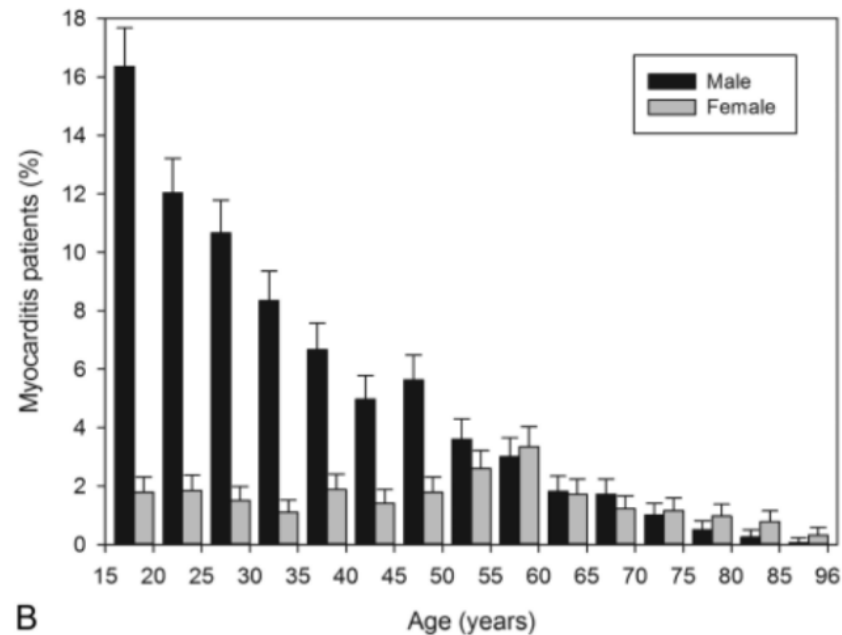
PS it's Sonya Babu-Narayan

9:01 AM

Jonathon Soslow



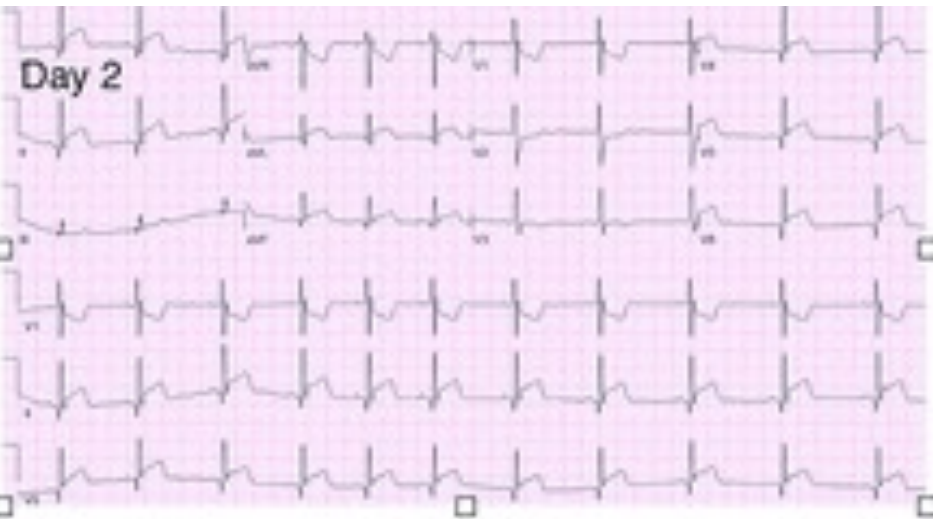
- 63 patients with myocarditis after mRNA vaccine
- 12-15yrs, n=31; 16-20yrs, n=32
- 92% male
- All except 1 after 2<sup>nd</sup> dose
- 2.1±1.3 days (0–7) between vaccine and symptom onset
  - 68% white
  - 14% Hispanic
  - 5% Asian American
  - 3% other, 10% unreported
- all post mRNA vaccine



Day 1



Day 2

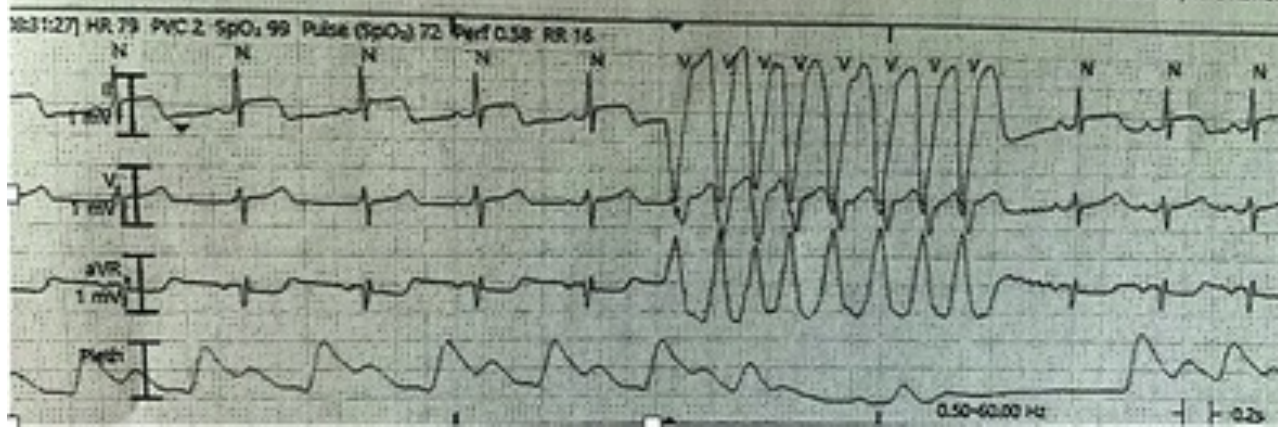
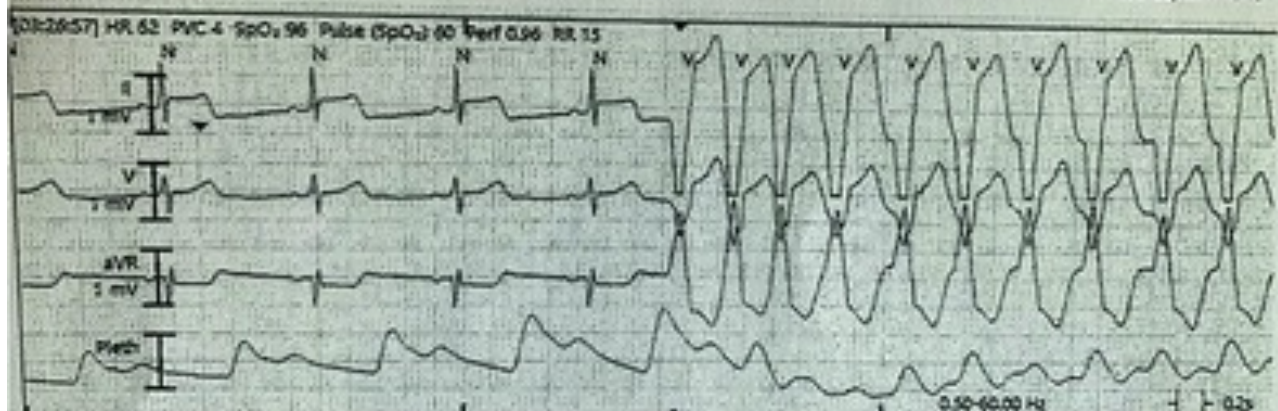
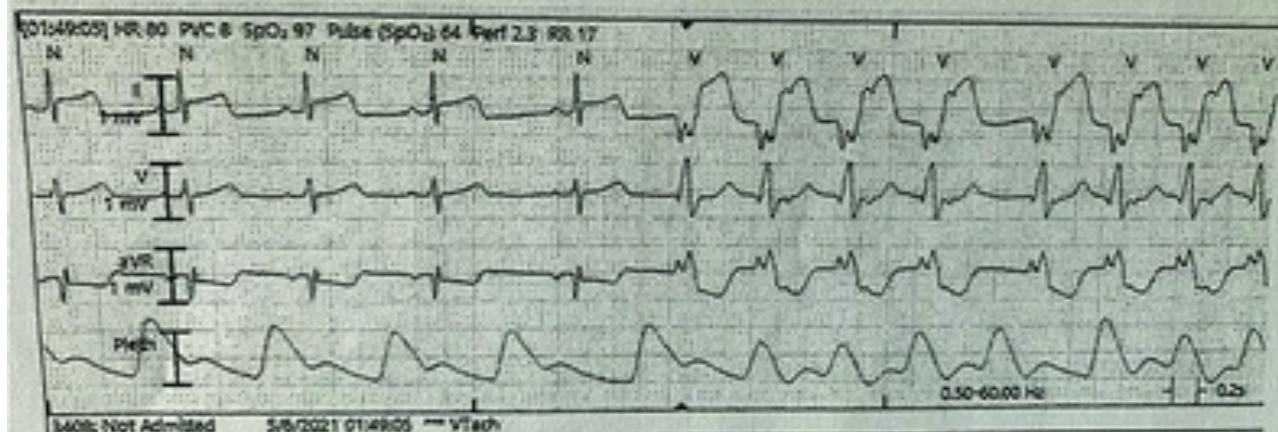


Day 4



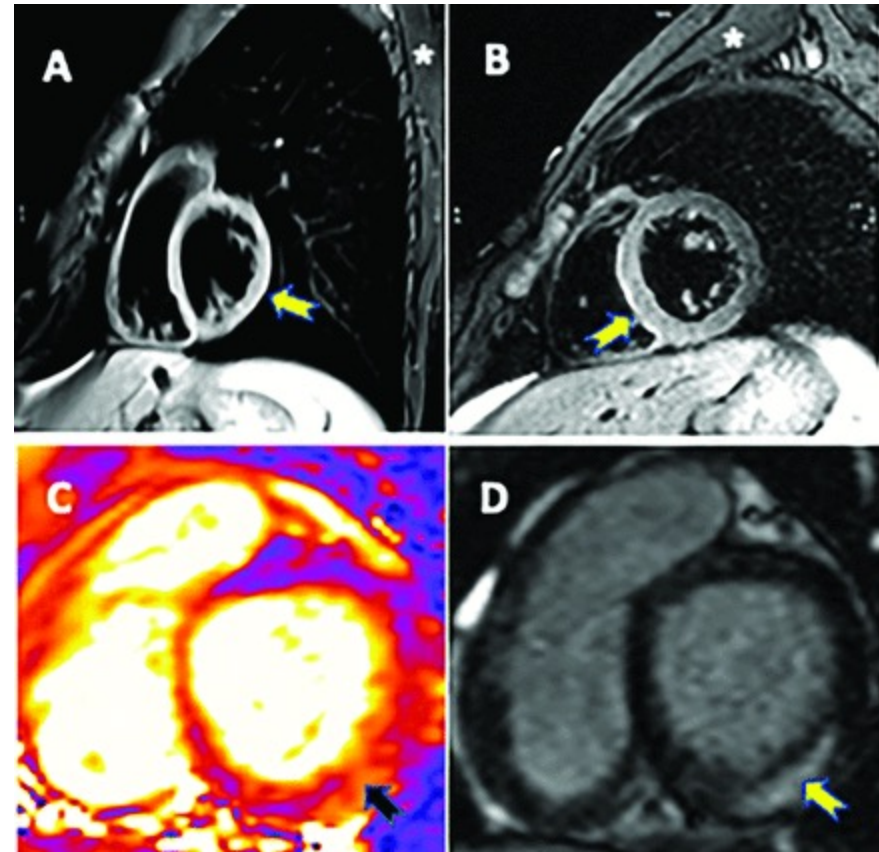
Day 10

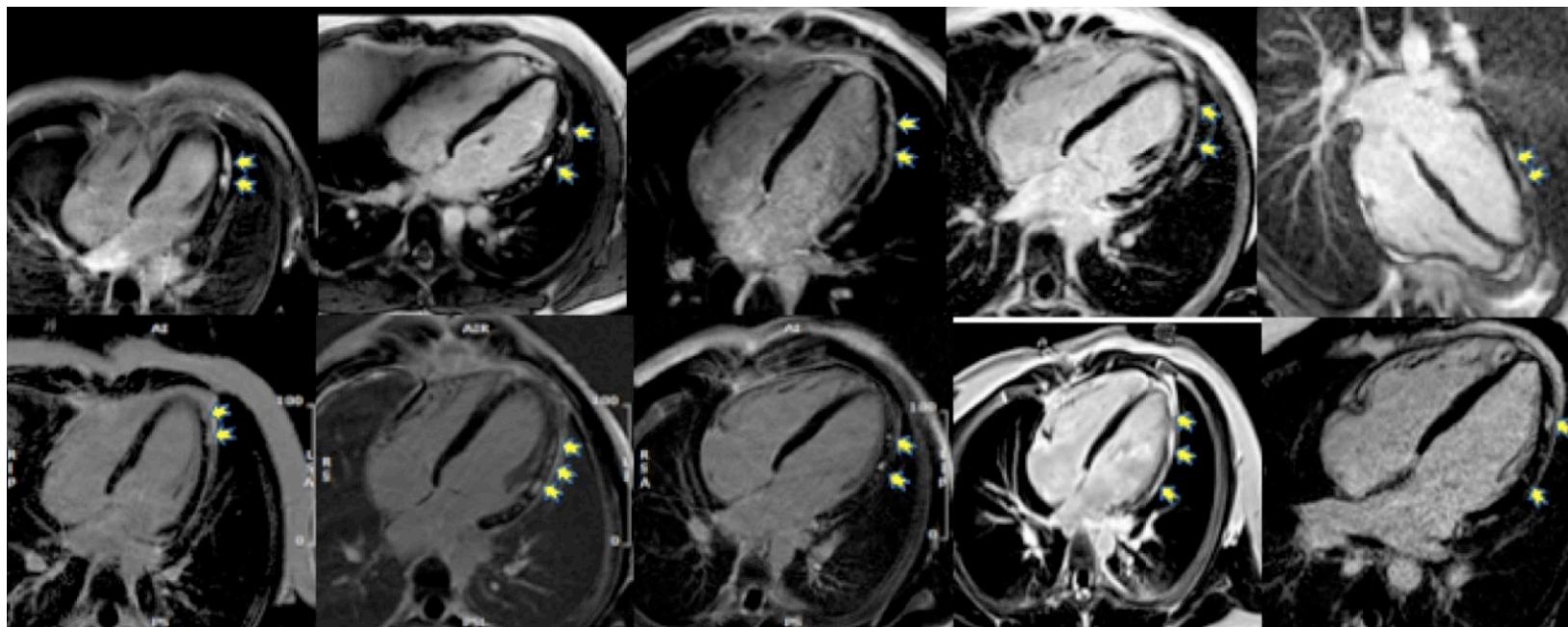
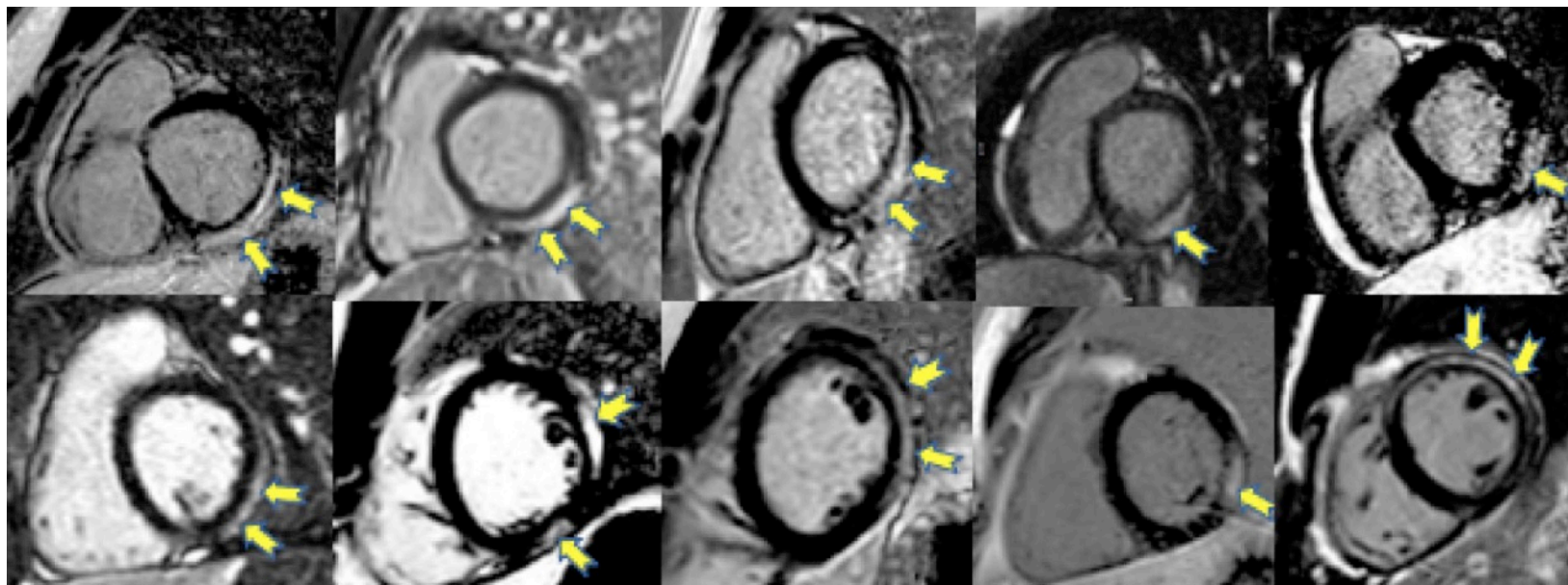






- LOS  $3.0 \pm 1.4$  days
- no inotropes, ECMO, deaths
- decreased fx in 14%
- CMR in 89%
  - 23% with decreased LVEF
  - 7% with decreased RVEF





ORIGINAL RESEARCH ARTICLE

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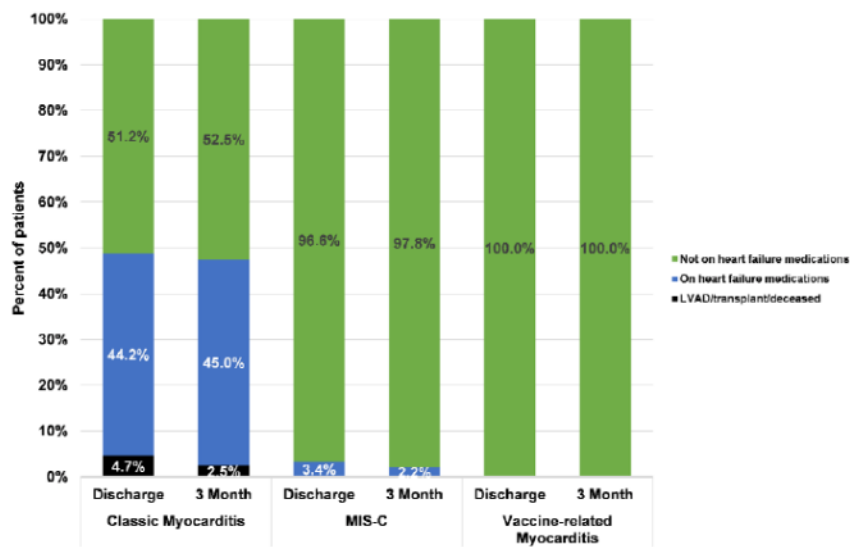
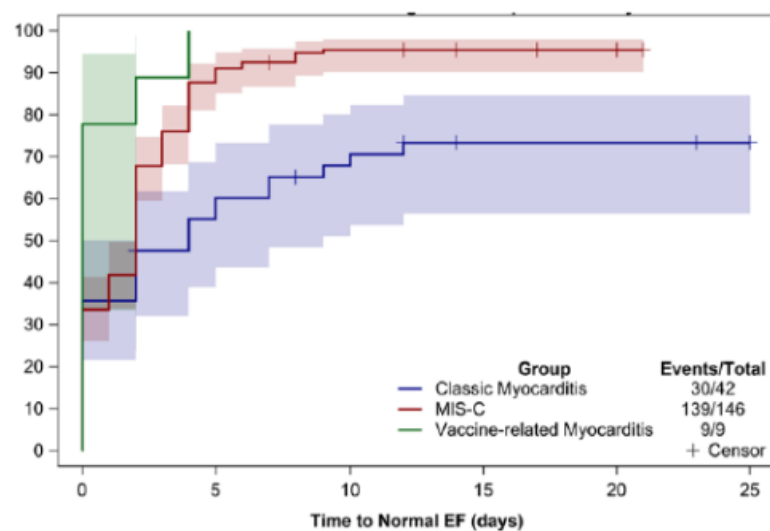
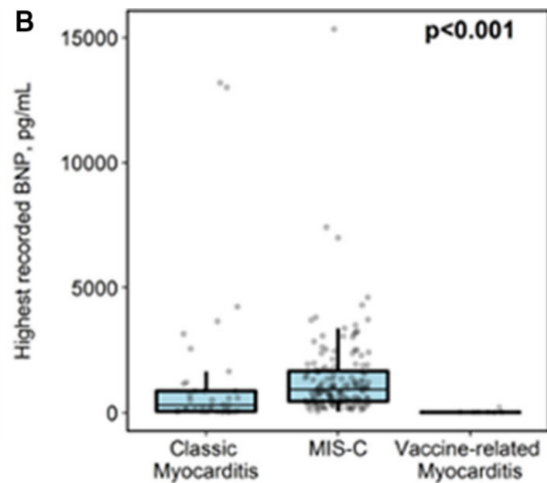
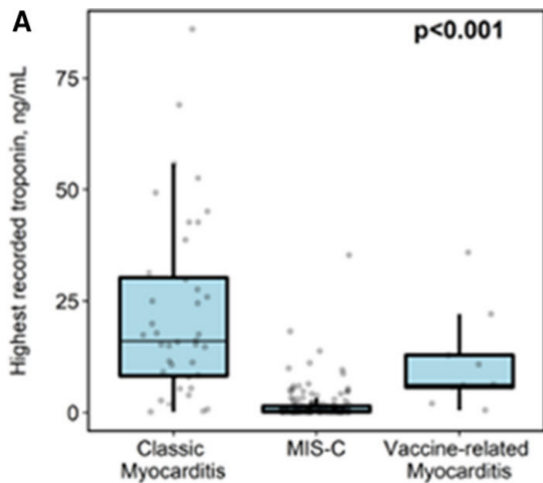
**Clinically Suspected Myocarditis Temporally Related to  
COVID-19 Vaccination in Adolescents and Young Adults:  
Suspected Myocarditis After COVID-19 Vaccination**

Truong

- 139 patients (91 with probable myocarditis)
- 91% male, median age 15.8 years
- Symptom onset 2 days following immunization
- 76 % with LGE, 51% with LLC+
- 26 patients with LVEF<55%, all normalized during f/u

|                                  | <b>VA-M</b> | <b>MIS-C</b> |
|----------------------------------|-------------|--------------|
| time from vaccine / infx         | few days    | weeks        |
| acute illness                    | +/-         | +++          |
| ventricular dysfunction          | +/-         | ++           |
| myocardial injury & inflammation | +++         | +            |
| recovery                         | ++(+)       | ++(+)        |





ORIGINAL ARTICLE

## Myocarditis after Covid-19 Vaccination in a Large Health Care Organization

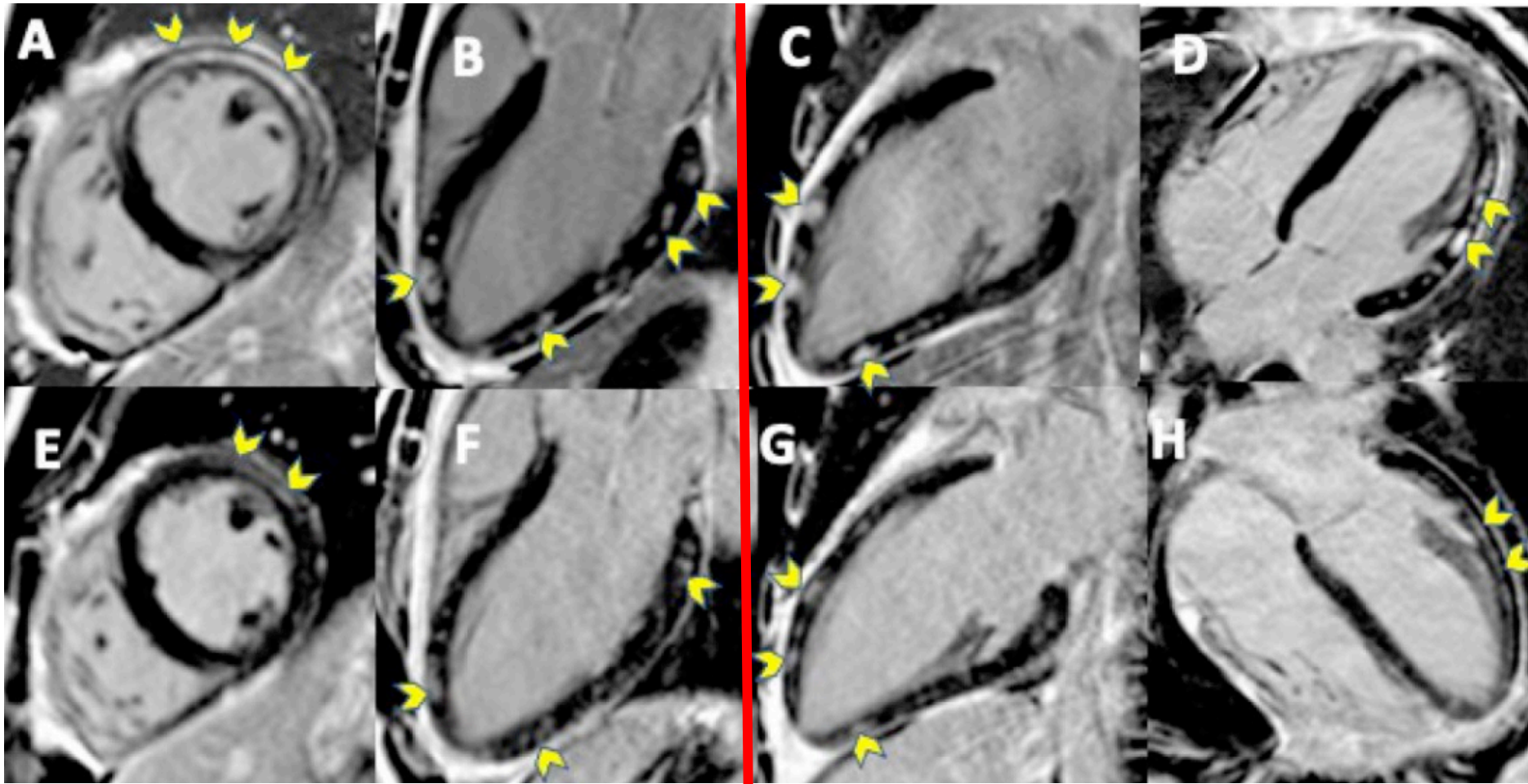
Guy Witberg, M.D., Noam Barda, M.D., Ph.D., Sara Hoss, M.D.,  
Ilan Richter, M.D., M.P.H., Maya Wiessman, M.D., Yaron Aviv, M.D.,  
Tzlil Grinberg, M.D., Oren Auster, M.Sc., Noa Dagan, M.D., Ph.D., M.P.H.,  
Ran D. Balicer, M.D., Ph.D., M.P.H., and Ran Kornowski, M.D.

- 54 patients with myocarditis
- 2.13 / 100,000
- Males 16-29 years: 1 / 9,355
- Females 16-29 years: 1 / 294,118

# potential pathophysiology

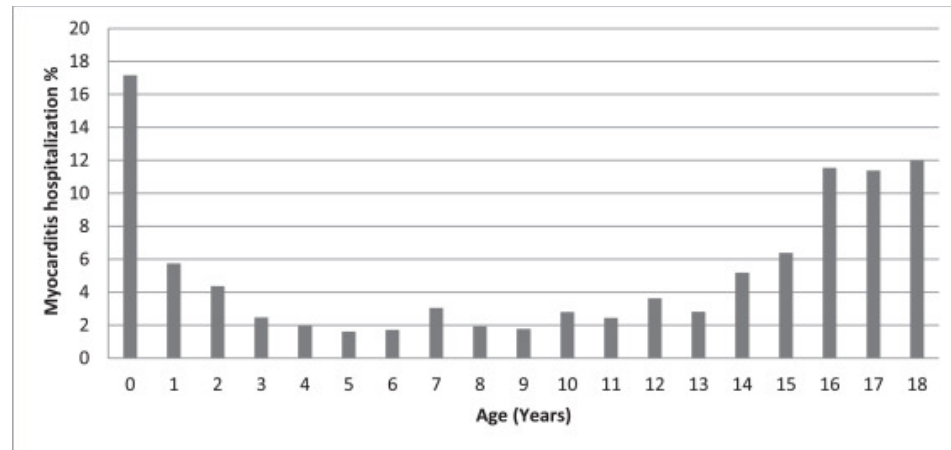
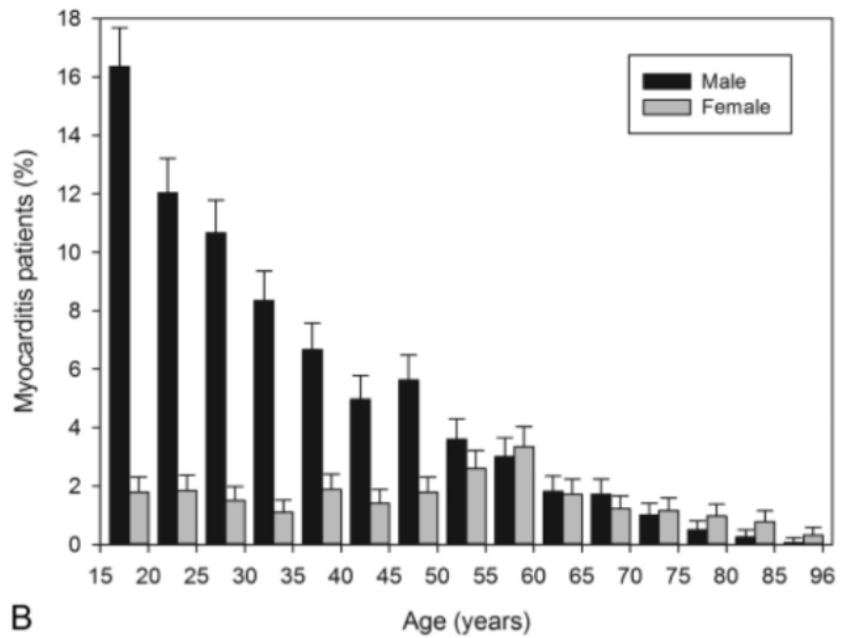
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- molecular mimicry
- spike protein from vaccine may cause myocyte damage (even in the absence of a live virus)
- complex of ACE-2 receptor + spike protein = immunological target
  - estrogen related ACE-2 receptor density
- genetic susceptibility
- racial / ethnic susceptibility



vaccine associated myocarditis

8 weeks post diagnosis



Vasudeva, Am J Cardiol 2021

Kyoto, Heart 2013

# C-VAM outcomes

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- no deaths, significant arrhythmias, re-hospitalization
- non-specific ST segment changes persist
- preserved ventricular function but worse than at initial presentation
- LGE persists in  $\frac{3}{4}$ , but lessens

- COVID19 and the heart

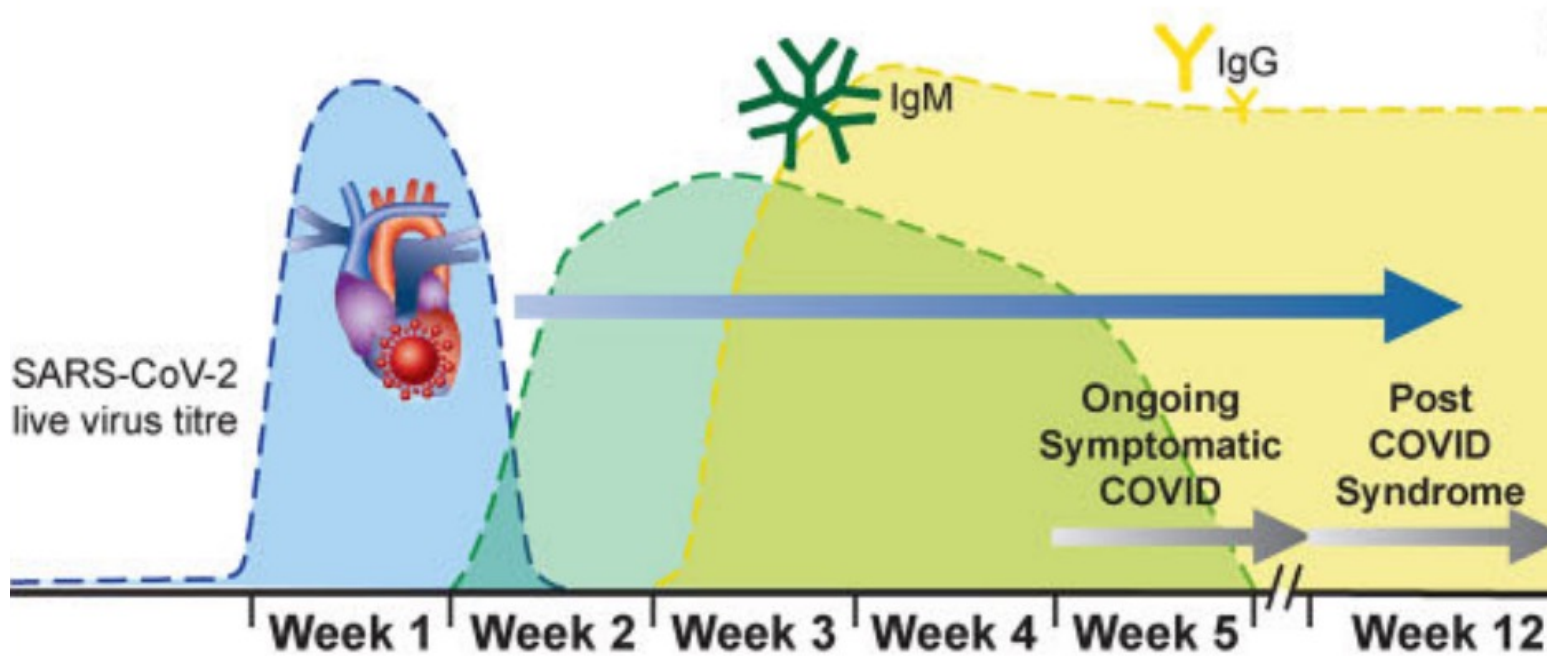
- MIS-C

- vaccine associated myocarditis

- long-COVID



# long COVID, PACS





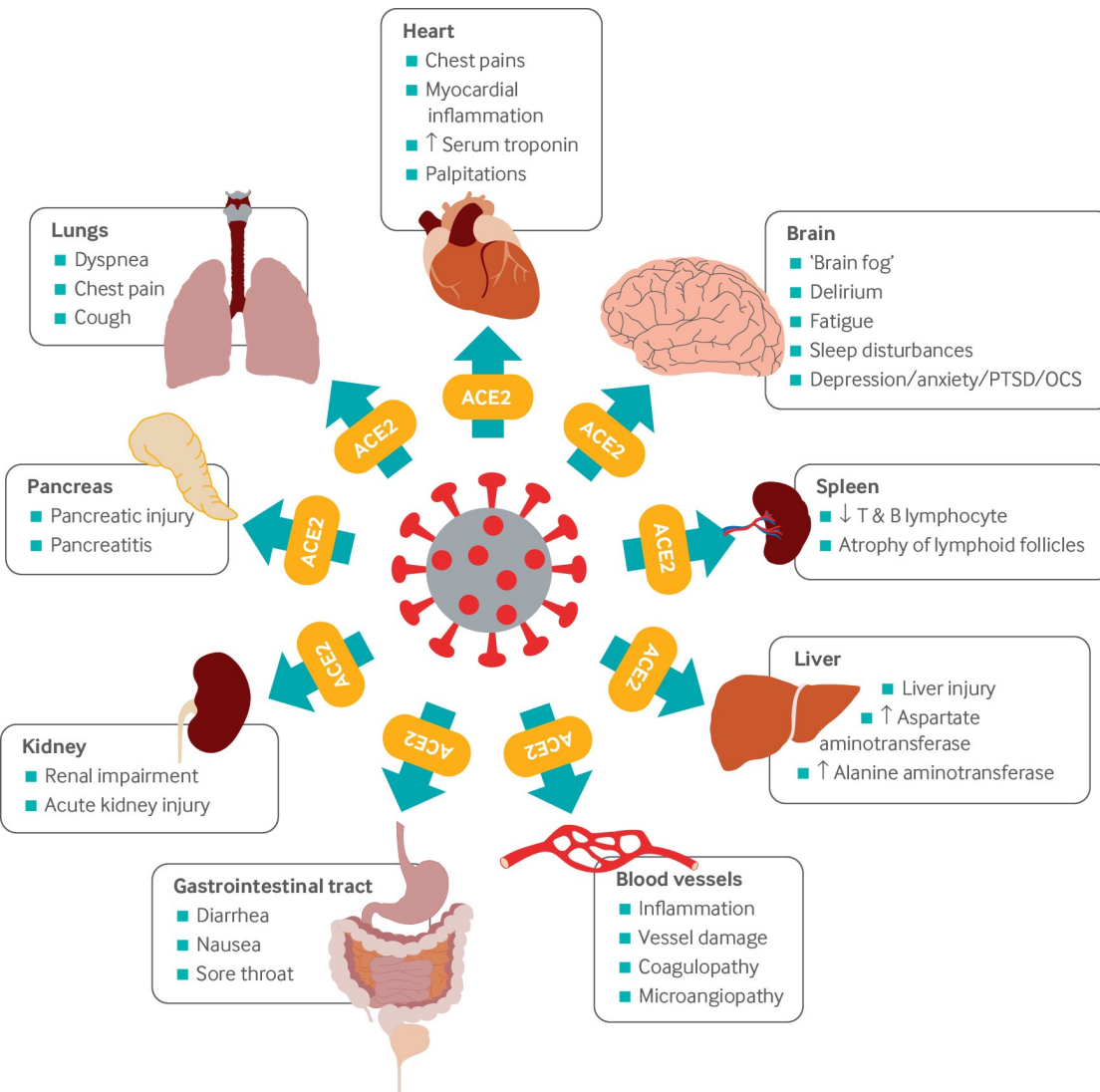
# terminology

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- Subacute or ongoing COVID-19 (PACS, post-acute COVID-19 syndrome):
  - symptoms continuing beyond the 4 weeks of acute infection, up to 12 weeks.
- Post-COVID-19 syndrome / conditions (PCS, PCC):
  - chronic ongoing COVID-19 symptoms beyond 12 weeks from acute infection.
- Post-acute sequelae of COVID-19 (PASC), long-COVID, long-haulers' syndrome:
  - either PACS or PCS



# long COVID, PACS



- Fatigue
- Post-exertional malaise
- Exercise intolerance
- Dyspnoea
- Chest pain
- Palpitations
- Dizziness/syncope

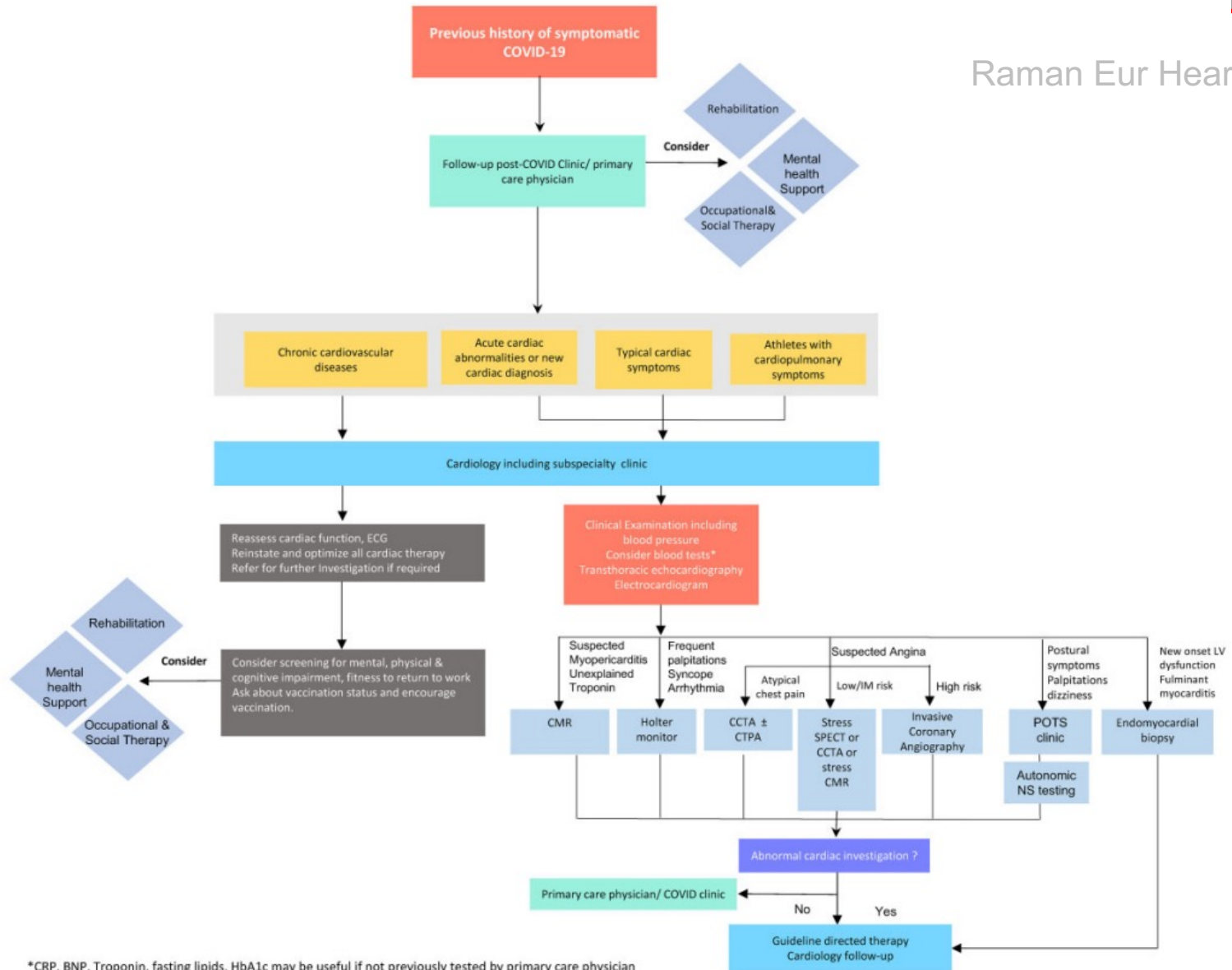
# risk factors

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- female sex
- escalating age
- obesity
- asthma
- poor general health
- poor prepandemic mental health
- poor sociodemographic factors

# Surveillance & work-up

Raman Eur Heart J 2022



# summary

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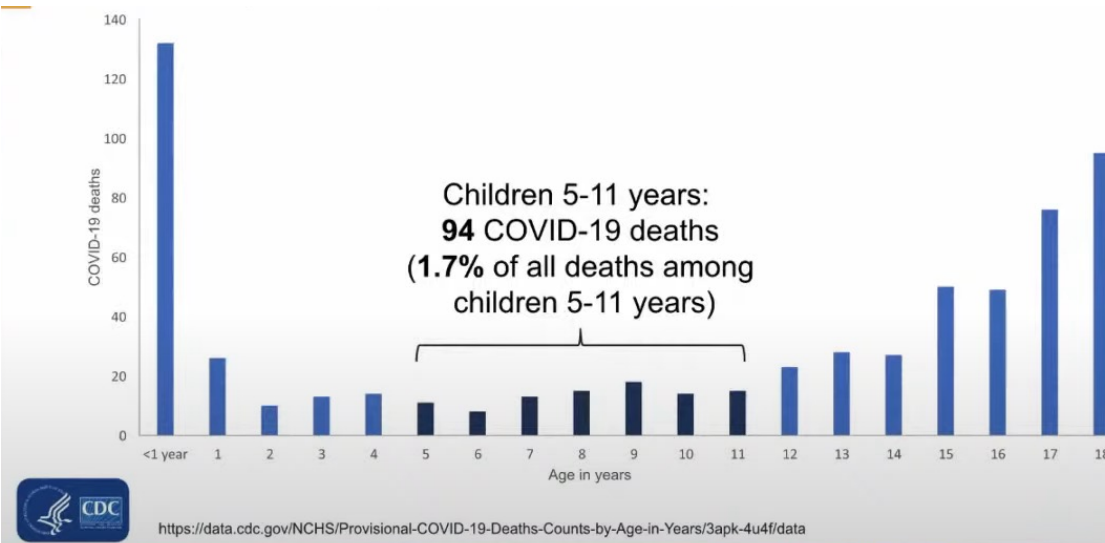
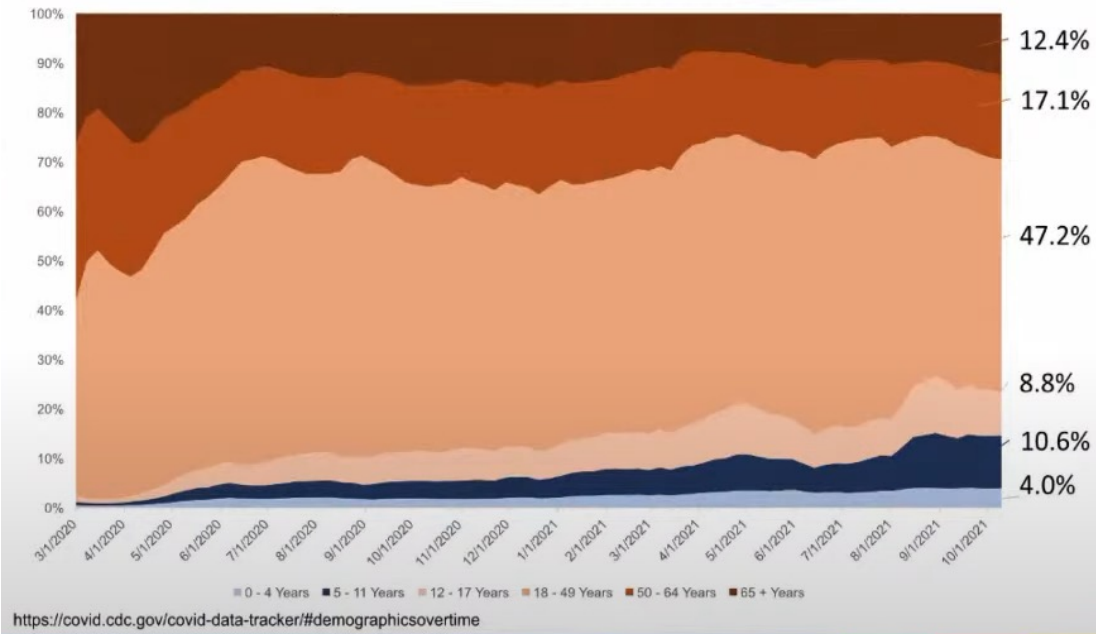
- Acute cardiac manifestations of COVID-19
- Greater risk for patients with pre-existing conditions, including CHD
- COVID-19 is emerging as a risk factor for long-term cardiac health
- MIS-C is a rare, but serious complication
- vaccine associated myocarditis benign, but long-term unclear
- Long COVID moves into focus



Thank you

[grossewo@ohsu.edu](mailto:grossewo@ohsu.edu)







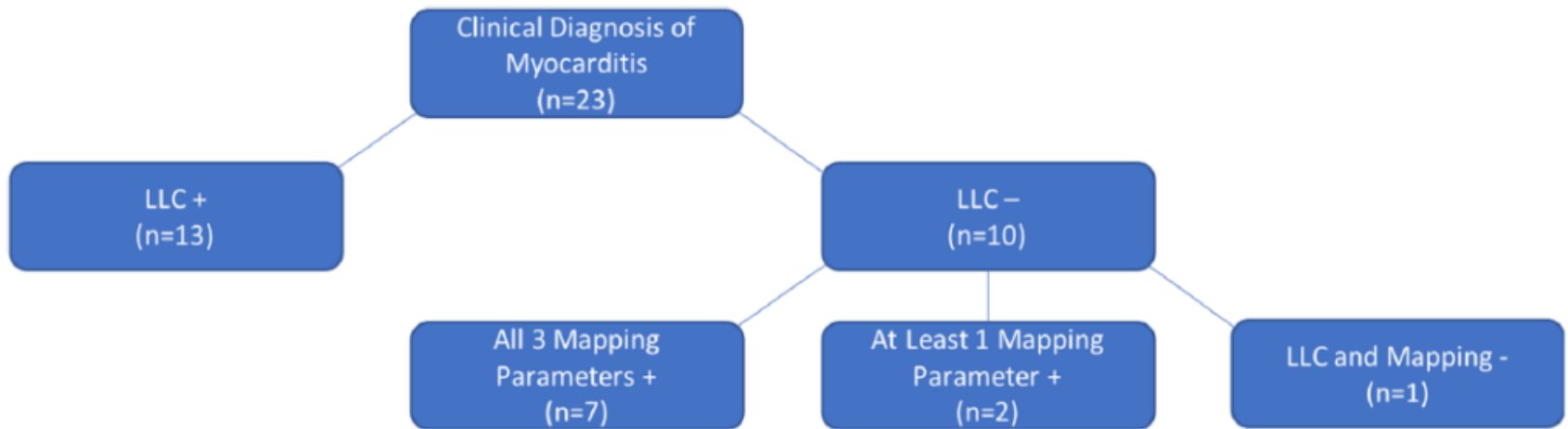
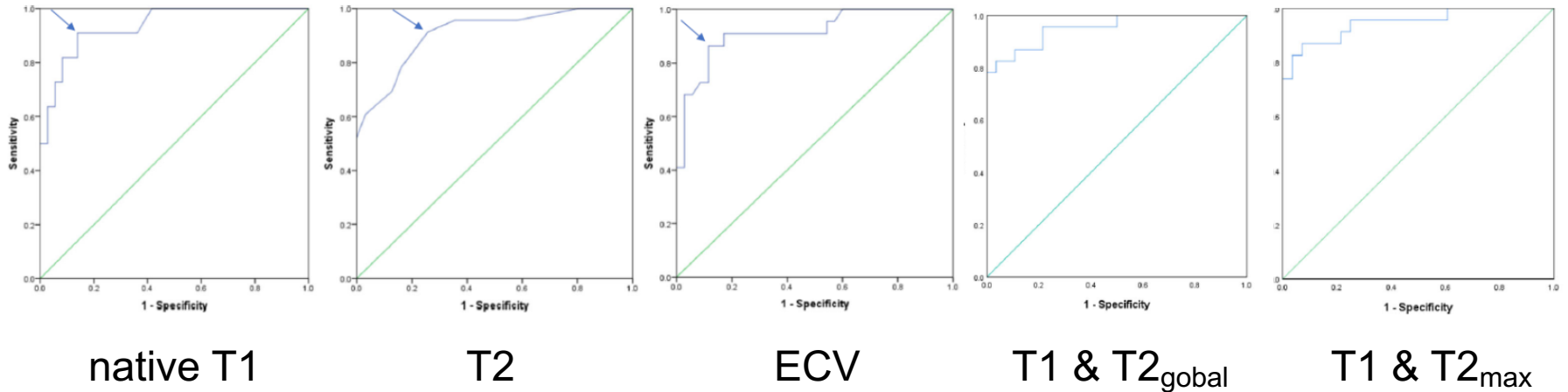
# POTS

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## Comorbidities

- Ehlers-Danlos syndrome
- mast cell activation syndrome
- sensory neuropathy
- autoimmune disorders (e.g., lupus and Sjogren syndrome)

# myocarditis



# OHSU Pediatric Cardiology Evaluation for Myocarditis June 2022

(Not MISC Management)

**History:** Chest pain characteristics, location, duration, associated symptoms, aggravating/alleviating symptoms

- Prior syncopal events, especially since the illness/vaccination
- History of palpitations, racing heart rate, especially since the illness/vaccination
- Recent/remote viral illness
- Time since the viral illnesses
  - Any past COVID infection (test positive or epi link)Recent Exposure to people with COVID-19 infection
- Verify Timing of COVID-19 vaccination (type of vaccine and which dose) and initiation of symptoms.
  - **Vaccine myocarditis usually 2-10 days post vaccine**
- History of drug use
- Cardiac family history, congenital cardiac disease, early myocardial infarction in adults < 50 years of age, arrhythmias, sudden death

**Exam:**

Presence of cardiac murmur, irregular rhythm not related to respiratory cycle, reproducible chest pain on palpation, perfusion, viral exanthem/infectious signs, fever

**Initial Work Up**

- CXR
- EKG
- HS Troponin I (time 0)
- CRP
- COVID-19 PCR

**ED observe or Admit with secondary assessment**

**evaluation:** If patient has continued symptoms and

- ECG concerning for ischemia
- Troponin is **abnormal** for lab reference (**Cut off OHSU lab HS troponin I > 800. Approved by pediatric cardiology consensus Jan 2022.**)
- Chest X ray concerning for pathology

**Secondary Assessment**

- Echocardiogram
- Trend HS troponin I q8hr
- Trend EKG Q24 hours
- NT-pro BNP
- ESR
- Urine drug screen
- SARS-CoV2 nucleocapsid antibody, send-out (ARUP test code: 3002776)
- SARS-CoV2 antibody (in house)
- Viral studies:
  - Nasopharyngeal swab: Respiratory pathogen PCR panel (includes SARS-CoV-2)
  - If febrile or recent illness consider:
    - 1<sup>st</sup> tier: Serum PCR: enterovirus, adenovirus, CMV, EBV
    - 2<sup>nd</sup> tier: Consider HHV6, Parvovirus, HSV
  - If diarrheal illness consider: Stool for bacterial culture, Stool, PCR virus panel
  - If risk factors and compatible illness present consider: Lyme serology, HIV Ab/Ag screening with reflex to confirm, interferon gamma release assay (TB quantiferon gold), Bartonella serology, Hepatitis C serology, HSV

**Discharge from ED or PCP Office:**

- Stable patient, improved pain
- Normal X ray (no concern for pericardial effusion or lung pathology)
- Normal ECG or consistent with pericarditis (cardiology reviewed)
- Troponin reference is WNL or below OHSU HS Troponin I < 800.

**Treatment:**

- Ibuprofen (see below)
- H2 blocker
- Follow up with cardiology if ECG consistent with pericarditis or abnormal Troponin I

**Discharge from ED observation/Admit:**

- Stable patient, improved pain
- Normal echocardiogram
- ECG improvement
- Down trending troponin
- Reassuring secondary assessment
- **Treatment:**
  - Ibuprofen
  - H2 Blocker
  - Follow up with cardiology 2 weeks
  - Exercise restriction until seen
  - Follow up outpatient troponin if not normal at discharge

# Myocarditis: Inpatient Management

## Admit to floor

- Elevated troponins
- Stable blood pressure and heart rates
- Premature atrial contractions
- Normal function on echocardiogram
- **NOTE: ED may not be able to accommodate observation with serial troponins.**

## Admit to PICU

- Patient is hemodynamically unstable with tachycardia, hypotension, and/or poor perfusion
- If patient has an abnormal ECG (ST elevation concerning for ischemia, repolarization abnormalities/T wave inversion in V4-V6, presence of pathologic Q waves, ventricular ectopy or heart block on telemetry).
- Depressed ventricular function on echocardiogram

## Initial Cardiac Management

- Trend troponin I q8hr until value plateaus/down-trends, then space to q12hr
- Daily ECG
- Maintain on telemetry
- If NT-pro BNP abnormal at admit, repeat prior to discharge
- If CRP abnormal at admit (> 10.0 mg/L), repeat q48hrs until normalization/discharge
- For patients with normal ventricular function continue anti-inflammatory treatment:
  - For typically 2 weeks, until normalization of troponin I, CRP, AND resolution of symptoms, or until Cardiology follow-up (2 weeks post discharge)

## Advanced Cardiac Management:

- Low threshold for Cardiac MRI (any of the following):
  - If HS troponin I continues to rise x3 values and/or > 10,000 ng/L
  - Cannot confirm normal coronary anatomy on echocardiogram
  - Ventricular dysfunction on echocardiogram
  - Ventricular ectopy on telemetry
- Consider IVIG and/or steroids if MRI documents myocarditis or suspicion is high based on presentation, lab work, ECG, echocardiogram For patients with fulminant myocarditis, consider other therapies in consultation with transplant center.

## Consults and other To Dos:

- If vaccine associated, fill out VARES on CDC website
- Consider ID consult: if one of the diagnostic tests is positive, if patient has an atypical presentation, or if patient is immunocompromised.
- Consider immunology or rheumatology for unusual cases
- Consider Neurology consult.  
There may be a cardiomyopathy with neurological findings that has gone undiagnosed prior to current illness.

## Therapy

- Consider IVIG for patients with Cardiac MRI consistent with myocarditis OR ventricular dysfunction (echo or MRI) or ventricular ectopy on telemetry
- Consider adding steroids for patients with myocarditis confirmed by Cardiac MRI OR ventricular dysfunction or echocardiogram or significant ectopy
  - Suggested steroid regimen
  - PO prednisone 2mg/kg daily x 3-5 days
  - If echocardiogram does not demonstrate improvement, or persistently elevated troponin I, then consider longer term steroid taper over 2 weeks.
- Avoid oxycodone/morphine use
- For patients with fulminant myocarditis, consider other therapies in consultation with transplant center
- Follow MISC guideline for MISC patients

## Pericardial involvement or post COVID-19 vaccine myocarditis only:

Scheduled NSAIDs (as above if normal ventricular function)

- Ibuprofen dosing:< 10 kg:
  - 10mg/kg/dose q8hr
  - 10 – 20kg: 10mg/kg/dose q8hr
  - 20 – 40kg: 200mg q8hr
  - 40 – 60kg: 400mg q8hr>
  - 60kg: 600mg q8hr
- Add H2 Blocker with NSAIDs
- May use PRN NSAIDs in patients with ventricular dysfunction
- May substitute IV ketorolac dose for moderate to severe pain
- Use Zofran and Benadryl PRN for nausea

**Discharge Criteria:**

- Improvement in symptoms (chest pain, headache, etc)
- Improvement in ECG abnormality or telemetry findings
- HS Troponin I < 2000ng/L AND down trending
- Stabilization or improvement of ventricular function

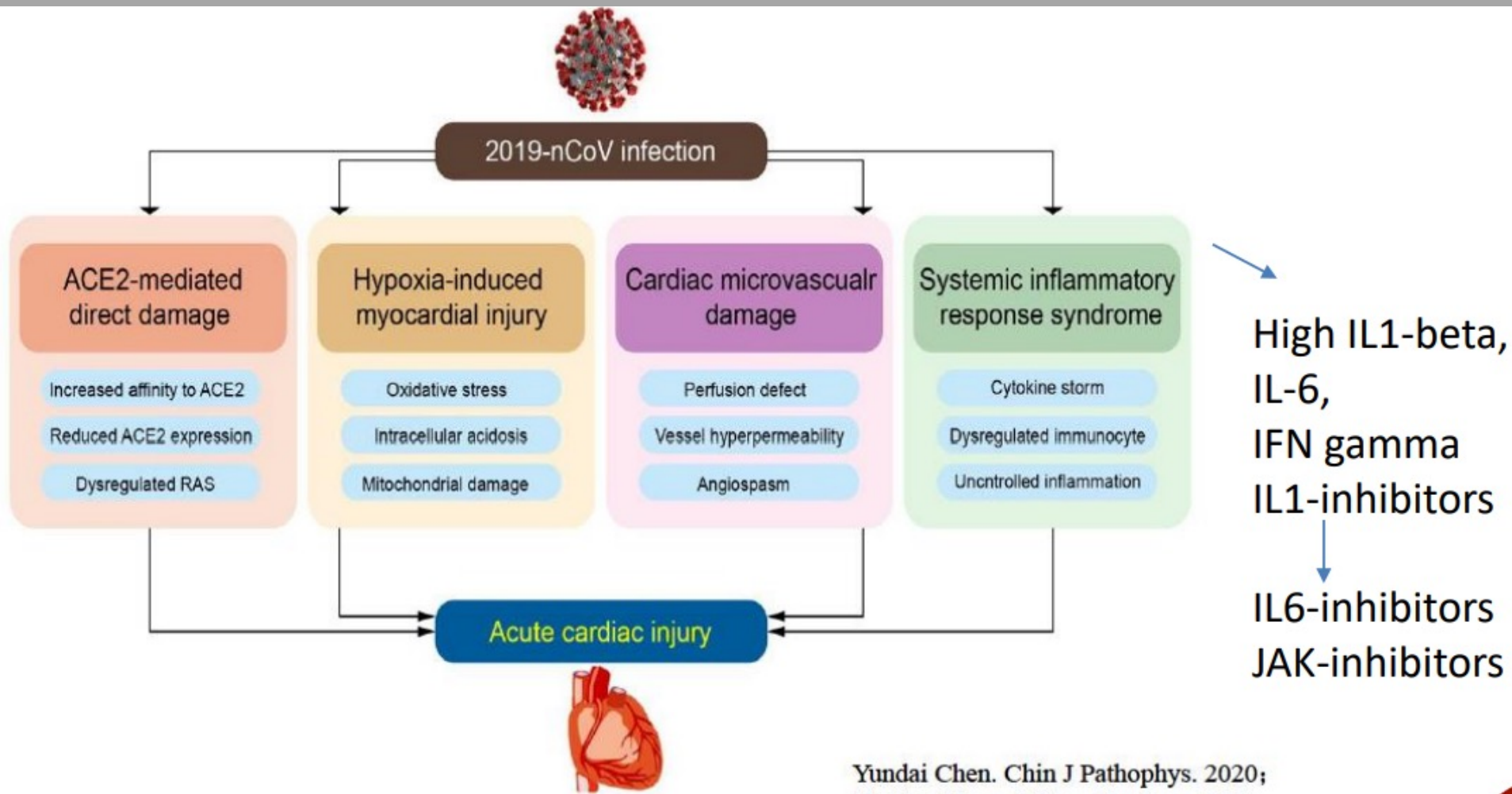
**Follow-up Plan:**

- Activity restrictions: No competitive sports or exertional activities (includes weight lifting, aerobic activity) for 3-6 months duration. Requires Cardiology clearance prior to participation.
- 2 weeks follow up with ECG, MRI (if not done inpatient) or echocardiogram, and labs if values were elevated at the time of discharge (HS troponin I, CRP, NT-pro BNP)
- Follow up in 3-6 months Echocardiogram, ECG, no labs unless otherwise indicated
- Consider Cardiac MRI either as a follow up or baseline
- Activity clearance (normal ventricular function on echocardiogram):
  - Patients < 11 years old (or unable to complete stress test), will need 24hr Holter monitor with activity.
  - Patients > 11 years old, will need 24hr-14day monitor with activity (vs stress ECG or stress echocardiogram)

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# COVID 19 and the heart



Yundai Chen. Chin J Pathophys. 2020;  
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# MIS-C, pathophysiology

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- immune mediated
  - cytokine storm
  - vasculitis
- days to months after COVID19 infection
- 75-100% had IgG antibodies (? Immune mediated)
- socioeconomic status
- ? obesity
- ? ethnicity / race

# Symptomatic Acute Myocarditis in 7 Adolescents After Pfizer-BioNTech COVID-19 Vaccination

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JAMA Cardiology | **Brief Report**

## Association of Myocarditis With BNT162b2 Messenger RNA COVID-19 Vaccine in a Case Series of Children

Audrey Dionne, MD; Francesca Sperotto, MD; Stephanie Chamberlain; Annette L. Baker, MSN, CPNP; Andrew J. Powell, MD; Ashwin Prakash, MD; Daniel A. Castellanos, MD; Susan F. Saleeb, MD; Sarah D. de Ferranti, MD, MPH; Jane W. Newburger, MD, MPH; Kevin G. Friedman, MD



# myocarditis controversies

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- admit vs. ED observation vs. discharge
- acute care vs. PICU
- indication for CMR
- troponin monitoring
- ivlg, Steroids
- discharge criteria
- f/u interval
- exercise restriction

# open questions

- MISC
  - biologic mechanisms
  - management
  - Long-term outcomes
- CVAM
  - Long-term outcomes
- Long COVID

# MIS-C vs. acute COVID-19

| Clinical group by complication                              | No./total No. (%) |                                 | Absolute risk difference, % (95% CI) <sup>b</sup> | Adjusted risk ratio (95% CI) <sup>c</sup> | P value |
|---|-------------------|---------------------------------|---|---|---------|
|   | MIS-C (n = 539)   | Severe acute COVID-19 (n = 577) |   |   |         |
| Respiratory without cardiovascular                          | 130/539 (24.1)    | 408/577 (70.7)                  | -46.6 (-51.8 to -41.4)                            | 1 [Reference]                             |         |
| Cardiorespiratory   | 302/539 (56.0)    | 51/577 (8.8)                    | 47.2 (42.4 to 52.0)                               | 2.99 (2.55 to 3.50)                       | <.001   |
| Cardiovascular without respiratory                          | 57/539 (10.6)     | 17/577 (2.9)                    | 7.7 (4.7 to 10.6)                                 | 2.49 (2.05 to 3.02)                       | <.001   |
| Mucocutaneous without respiratory or cardiovascular         | 38/539 (7.1)      | 13/577 (2.3)                    | 4.8 (2.3 to 7.3)                                  | 2.29 (1.84 to 2.85)                       | <.001   |
| Other without respiratory, cardiovascular, or mucocutaneous | 12/539 (2.2)      | 88/577 (15.3)                   | -13.1 (-16.2 to -9.8)                             | 0.43 (0.25 to 0.74)                       | .002    |
| <b>Laboratory value within first 48 h</b>                   |                   |                                 |   |   |         |
| Neutrophil to lymphocyte ratio >5                           | 321/515 (62.3)    | 154/464 (33.2)                  | 29.1 (23.2 to 35.1)                               | 1.59 (1.40 to 1.80)                       | <.001   |
| Platelets <150 × 10 <sup>3</sup> /μL                        | 212/523 (40.5)    | 84/486 (17.3)                   | 23.2 (17.9 to 28.6)                               | 1.58 (1.43 to 1.75)                       | <.001   |
| C-reactive protein level >100 mg/L                          | 325/491 (66.2)    | 67/285 (23.5)                   | 42.7 (36.2 to 49.1)                               | 1.70 (1.51 to 1.92)                       | <.001   |

