AASLD-NASPGHAN-SPLIT COVID-19 & the Liver: Pediatric Perspective

July 23, 2020

5:00pm – 6:00pm EDT

Joint Webinar

Society of Pediatric Liver Transplantation

The Transplantation Society

AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

NASPGHAN

Moderated by:

Emily J. Rothbaum Perito, MD

Nadia Ovchinsky, MD, MBA

Presenters:

Jaime Chu, MD

Noelle Ebel, MD

Mohit Kehar, MBBS, DNB

Burnett “Beau” S. Kelly, MD

Panelists:

Vicky Lee Ng, MD, FRCPC

Mercedes Martinez, MD

Webinar Agenda

- Housekeeping Items – Dr. Nadia Ovchinsky
- Presenter Introductions – Dr. Nadia Ovchinsky
- Webinar Introduction – Dr. Nadia Ovchinsky / Dr. Emily Perito
- Liver manifestations of pediatric COVID-19 infection and MIS-C – Dr. Jaime Chu
- COVID-19 Registry: Outcomes in Pediatric Liver Transplant Recipients – Dr. Mohit Kehar & Dr. Noelle Ebel
- Re-Entry into Clinical Transplantation during a COVID Pandemic – Dr. Beau Kelly
- Panel Discussion / Q&A

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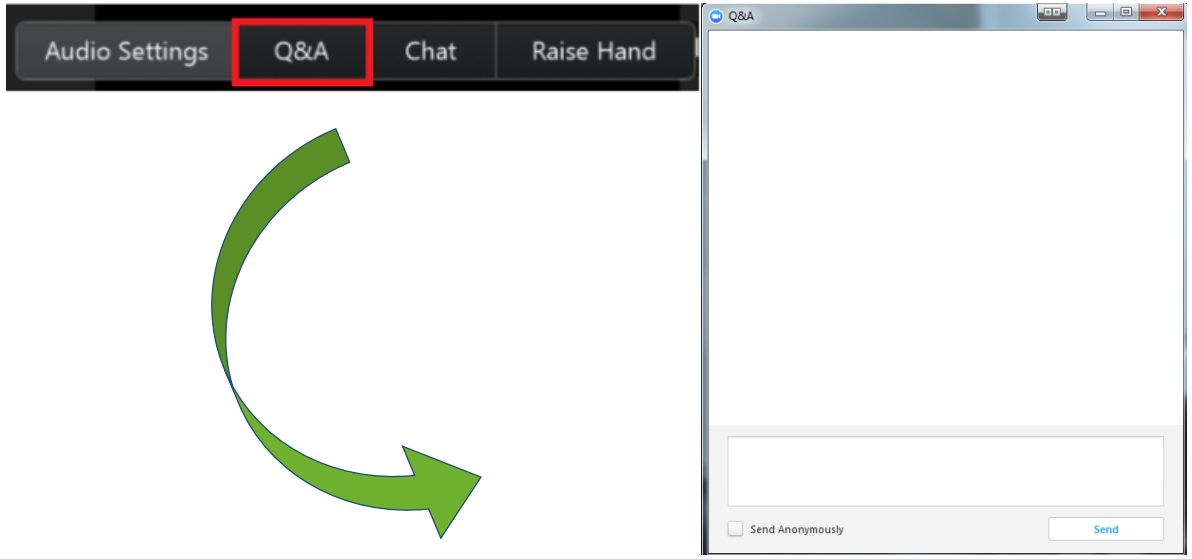
Webinar Q&A

Submit your questions in the Q&A box at the top or bottom of your screen.



Questions will be answered at the end of the presentation.

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Webinar Moderator

Nadia Ovchinsky, MD, MBA

Director, Pediatric Hepatology
Medical Director, Pediatric Liver Transplant

Associate Professor of Pediatrics,
Children's Hospital at Montefiore – Albert Einstein College of Medicine

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Webinar Moderator

Emily Perito, MD

Associate Medical Director of
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Associate Professor of Pediatrics and
of Epidemiology and Biostatistics

University of California, San Francisco

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Jaime Chu, MD

Associate Chief in the Division of Pediatric Hepatology

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Webinar Presenter

Mohit Kehar, MBBS, DNB

Pediatric Gastroenterologist and Hepatologist – Kingston Health Science Center

Assistant Professor in the Department of Pediatrics – Queens University

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Webinar Presenter

Noelle Ebel, MD

Assistant Professor of Pediatrics

Director the Alagille Syndrome Program

Stanford University

Webinar Presenter

Burnett "Beau" Kelly, MD, MBA, FACS, FAST

Surgical Director and Transplant Surgeon

DCI Donor Services, Inc.

Webinar Panelist

Vicky Lee Ng, MD, FRCPC

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University of Toronto

Medical Director, Pediatric
Liver Transplantation –
Hospital for Sick Children

Webinar Panelist

Mercedes Martinez, MD

Associate Professor of Pediatrics – Columbia University Medical Center

Director, Intestinal Transplant Program – Columbia University College of Physicians and Surgeons

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- Co-chair, Elizabeth C. Verna, MD, MS, Columbia University (New York)
- Kimberly Brown, MD, Henry Ford Health System (Michigan)
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COVID-19 in Children

Kids do get the coronavirus — they just don't get as sick

By Stephanie Pappas - Live Science Contributor March 06, 2020

A new study suggests that kids are as likely as adults to be infected with the new coronavirus, but their symptoms tend to be mild.

Comments (18)

The NEW ENGLAND JOURNAL of MEDICINE

CORRESPONDENCE

SARS-CoV-2 Infection in Children

TO THE EDITOR: As of March 10, 2020, the 2019 novel coronavirus (SARS-CoV-2) has been responsible for more than 110,000 infections and 4000 deaths worldwide, but data regarding the epidemiologic characteristics and clinical features of infected children are limited.[1-3] A recent review of 72,314 cases by the Chinese Center for Disease Control and Prevention showed that less than 1% of the cases were in children younger than 10 years of age.[2] In order to determine the spectrum of disease in children, we evaluated children infected with SARS-CoV-2 and treated at the Wuhan Children's Hospital, the only center assigned by the central government for treating infected children under 16 years of age in Wuhan. Both symptomatic and asymptomatic children with known contact with persons having confirmed or suspected SARS-CoV-2 infection were evaluated. Nasopharyngeal or throat swabs were obtained for detection of SARS-CoV-2 RNA by established methods.[4] The clinical outcomes were monitored up to March 8, 2020.

Of the 1391 children assessed and tested from January 28 through February 26, 2020, a total of 171 (12.3%) were confirmed to have SARS-CoV-2 infection. Demographic data and clinical features are summarized in Table 1. (Details of the laboratory and radiologic findings are provided in the Supplementary Appendix, available with the full text of this letter at NEJM.org.) The median age of the infected children was 6.7 years. Fever was present in 41.5% of the children at any time during the illness. Other common signs and symptoms included cough and pharyngeal erythema. A total of 27 patients (15.8%) did not have any symptoms of infection or radiologic features of pneumonia. A total of 12 patients had radiologic features of pneumonia but did not have any symptoms of infection. During the course of hospitalization, 3 patients required intensive care support and invasive mechanical ventilation; all had coexisting conditions (hydronephrosis, leukemia [for which the patient was receiving maintenance chemotherapy], and intussusception). Lymphopenia (lymphocyte count, $<1.2\times10^9$ per liter) was present in 6 patients (3.5%). The most

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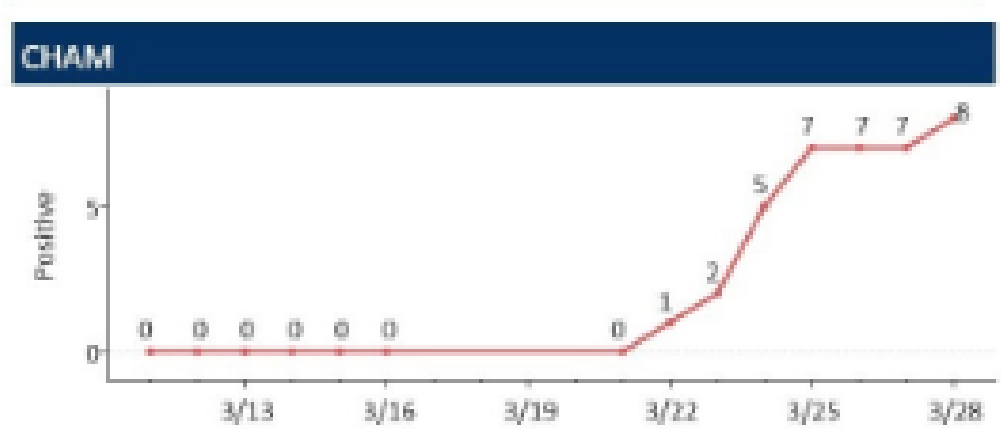
COVID-19 in Children

COVID-19 Pediatrics Daily Update: March 20, 2020

- **RECENT CHAM NUMBERS & STATISTICS**
  - As of the morning of March 20, 2020, the Department of Pediatrics has tested 22 children at the Children's Hospital at Montefiore (CHAM). Of the total 22 tests
    - 1 test positive
    - 8 tests negative
    - 13 tests pending
- **FIRST COVID-19 CASE**
  - On Thursday, March 19, we confirmed our first COVID-19 positive patient at CHAM. The teams from Pediatric Emergency Medicine (PEM) to our inpatient services did an excellent job screening the patient and appropriately isolating the patient in the emergency department (ED) and throughout her admission until the testing results were available. **Thank you for the great teamwork in maintaining a safe environment for our patients and staff**.



Nadia Ovchinsky @D... · 3/28/20
Admitting my first liver transplant #covidpositive baby

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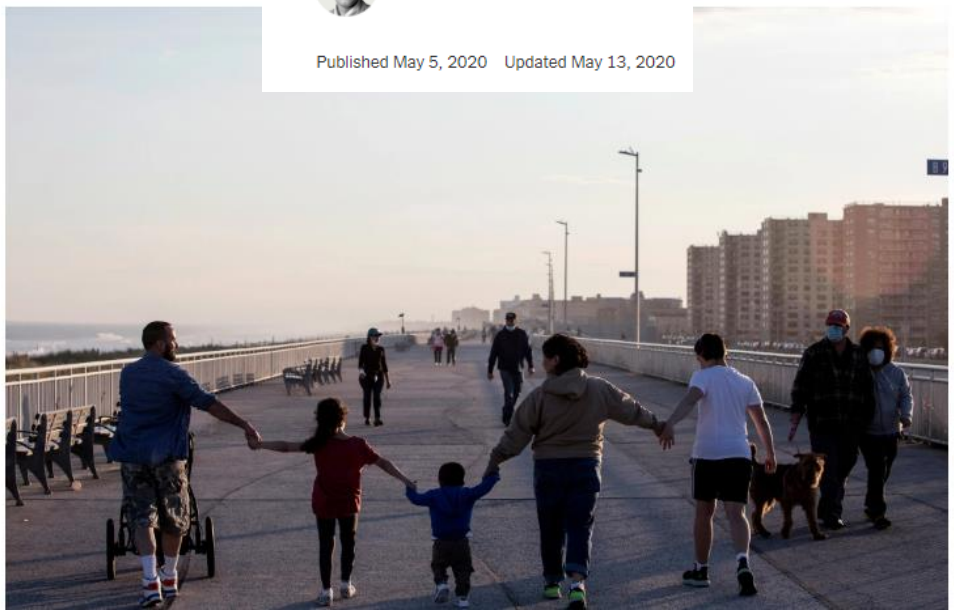
COVID-19 in Children

15 Children Are Hospitalized With Mysterious Illness Possibly Tied to Covid-19

The health authorities in New York City issued an alert saying that the children had a syndrome that doctors do not yet fully understand.

By Joseph Goldstein

Published May 5, 2020 Updated May 13, 2020



An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study

Lucio Verdoni, Angelo Mazza, Annalisa Gervasoni, Laura Martelli, Maurizio Ruggeri, Matteo Ciuffreda, Ezio Bonanomi, Lorenzo D'Antiga

Summary

Background The Bergamo province, which is extensively affected by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) epidemic, is a natural observatory of virus manifestations in the general population. In the past month we recorded an outbreak of Kawasaki disease; we aimed to evaluate incidence and features of patients with Kawasaki-like disease diagnosed during the SARS-CoV-2 epidemic.

Methods All patients diagnosed with a Kawasaki-like disease at our centre in the past 5 years were divided according to symptomatic presentation before (group 1) or after (group 2) the beginning of the SARS-CoV-2 epidemic. Kawasaki-like presentations were managed as Kawasaki disease according to the American Heart Association indications. Kawasaki disease shock syndrome (KDSS) was defined by presence of circulatory dysfunction, and macrophage activation syndrome (MAS) by the Paediatric Rheumatology International Trials Organisation criteria. Current or previous infection was sought by reverse-transcriptase quantitative PCR in nasopharyngeal and oropharyngeal swabs, and by serological qualitative test detecting SARS-CoV-2 IgM and IgG, respectively.

Findings Group 1 comprised 19 patients (seven boys, 12 girls; aged 3·0 years [SD 2·5]) diagnosed between Jan 1, 2015, and Feb 17, 2020. Group 2 included ten patients (seven boys, three girls; aged 7·5 years [SD 3·5]) diagnosed between Feb 18 and April 20, 2020; eight of ten were positive for IgG or IgM, or both. The two groups differed in disease incidence (group 1 *vs* group 2, 0·3 *vs* ten per month), mean age (3·0 *vs* 7·5 years), cardiac involvement (two of 19 *vs* six of ten), KDSS (zero of 19 *vs* five of ten), MAS (zero of 19 *vs* five of ten), and need for adjunctive steroid treatment (three of 19 *vs* eight of ten; all p<0·01).

Interpretation In the past month we found a 30-fold increased incidence of Kawasaki-like disease. Children diagnosed after the SARS-CoV-2 epidemic began showed evidence of immune response to the virus, were older, had a higher rate of cardiac involvement, and features of MAS. The SARS-CoV-2 epidemic was associated with high incidence of a severe form of Kawasaki disease. A similar outbreak of Kawasaki-like disease is expected in countries involved in the SARS-CoV-2 epidemic.

Lancet 2020; 395: 1771–78

Published Online May 13, 2020 https://doi.org/10.1016/S0140-6736(20)31103-X

See Comment page 1741

Paediatric Department (L Verdoni MD, A Mazza MD, A Gervasoni MD, L Martelli MD, M Ruggeri MD, L D'Antiga MD), **Paediatric Cardiology** (M Ciuffreda MD), **and Paediatric Intensive Care Unit** (E Bonanomi MD), **Hospital Papa Giovanni XXIII, Bergamo, Italy**

Correspondence to: Dr Lorenzo D'Antiga, Paediatric Department, Hospital Papa Giovanni XXIII, 24127 Bergamo, Italy **ldantiga@asst-pg23.it**

Liver manifestations of pediatric COVID-19 infection and MIS-C

Jaime Chu, MD

Associate Chief in the Division of Pediatric Hepatology

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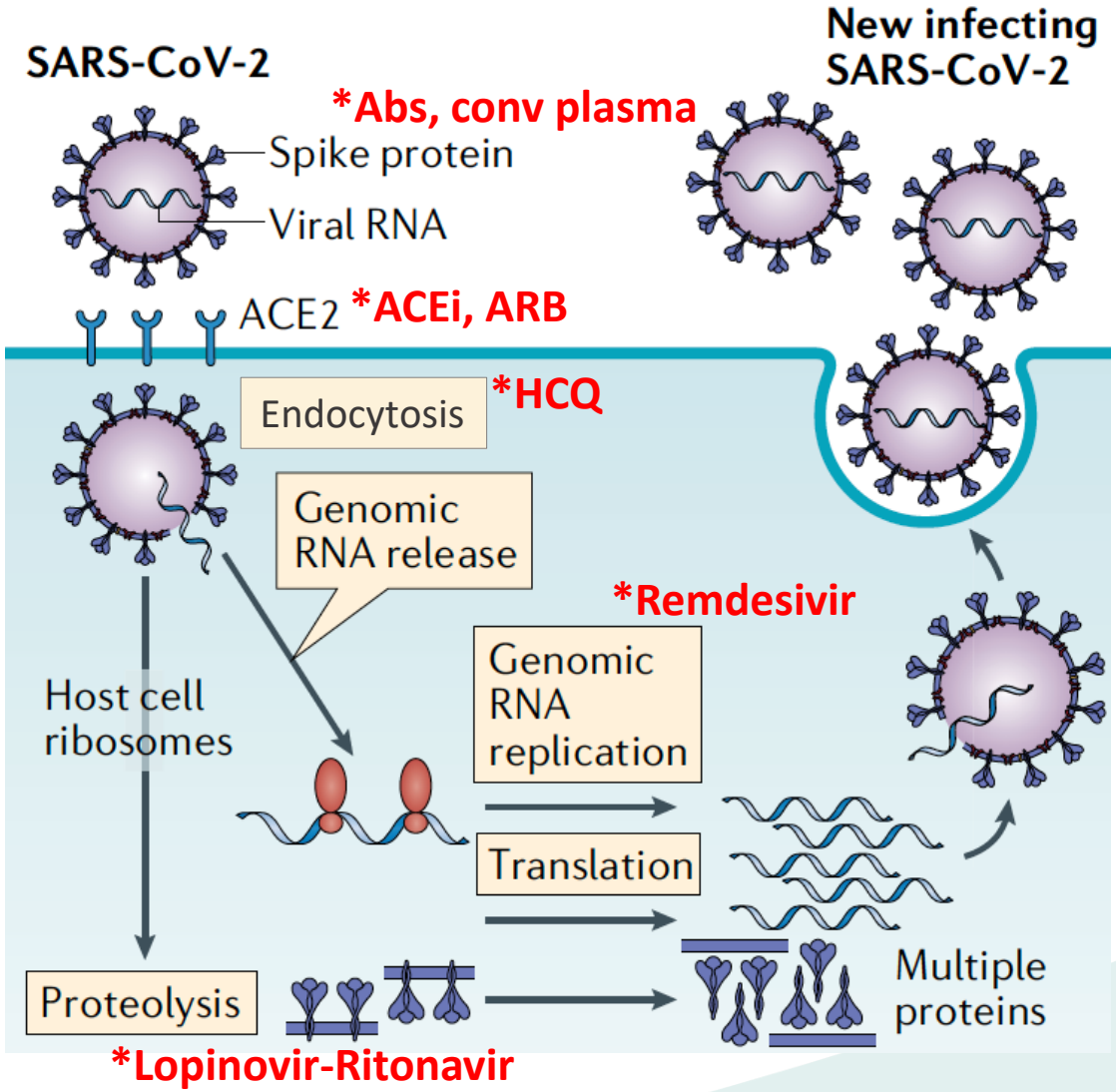
Overview

Focus on liver manifestations in COVID-19 and MIS-C in **children without known chronic liver disease or transplantation**

1. Pathogenesis of liver injury in COVID-19
2. Liver injury in COVID-19
3. Liver injury in Multisystem Inflammatory Syndrome in Children (MIS-C)

Viral pathogenesis of SARS-CoV-2

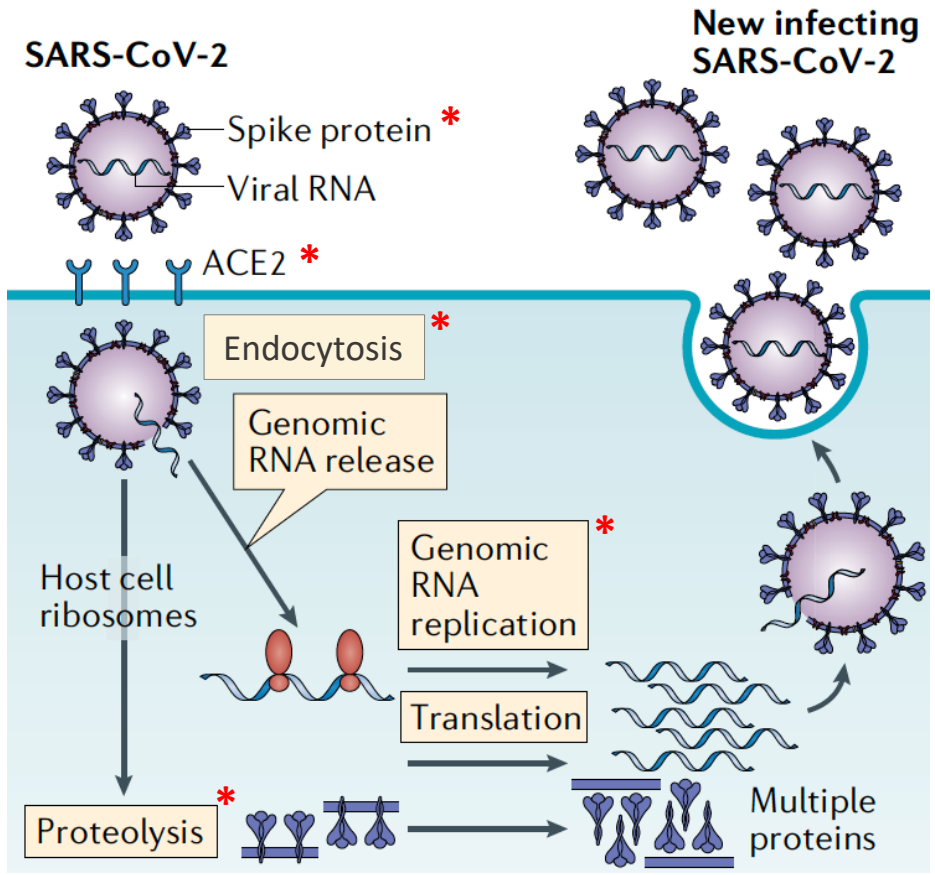


Adapted from Risitano et al., Nat Rev Immunol, June 2020.

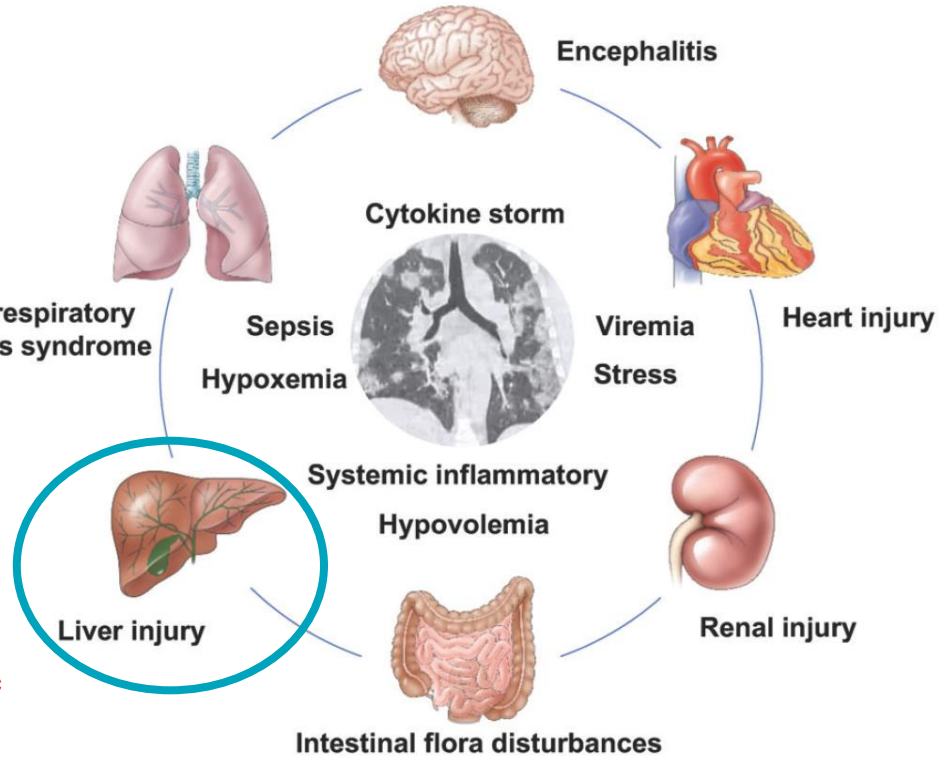
Viral pathogenesis of SARS-CoV-2

1. Viral Entry

2. Viral Replication



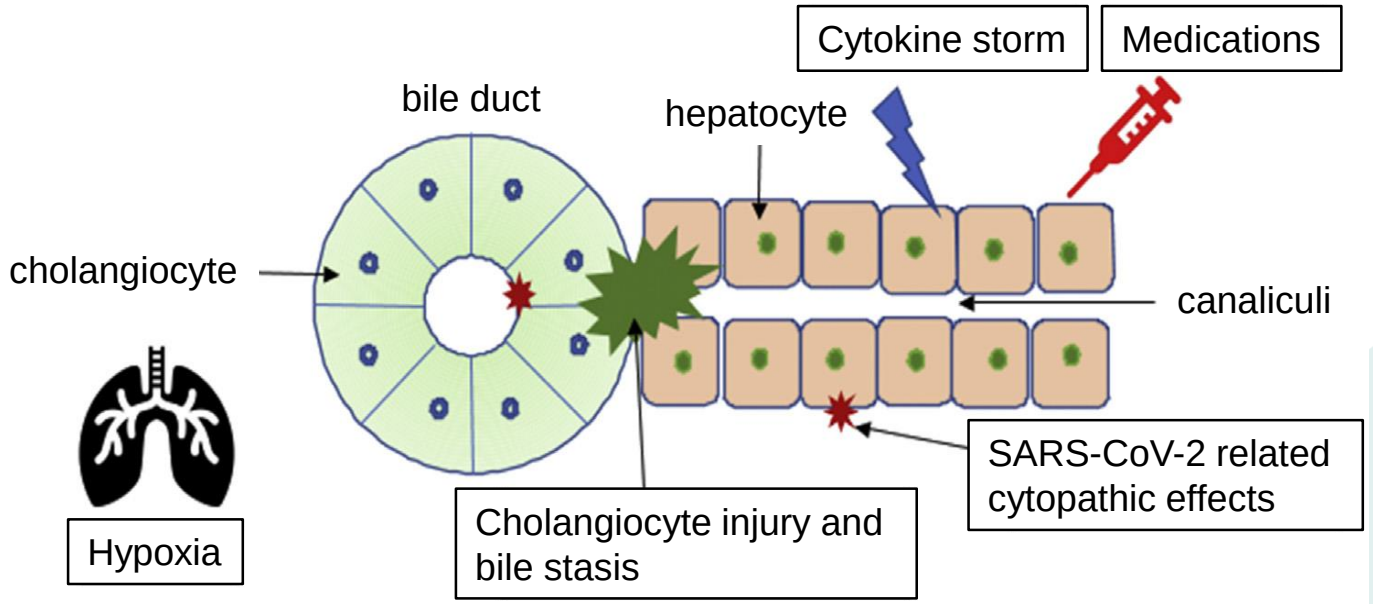
3. Inflammation and Immune Dysregulation*



Li and Fan, *J Clin Transl Hepatol*, March 2020.
Adapted from Risitano et al., Nat Rev Immunol, June 2020.

Multiple etiologies of liver injury in COVID-19

- Direct injury to liver cells
  - Limited data regarding ACE2 expression in cholangiocytes > hepatocytes
- Secondary to COVID-19 complications:
  - myositis (AST > ALT)
  - cardiac injury
  - ischemia/hypotension
  - cytokine release syndrome
- Drug-induced liver injury
- Multisystem Inflammatory Syndrome in Children (MIS-C)



Kumar et al., *J Clin Exp Hepatol*., 2020.

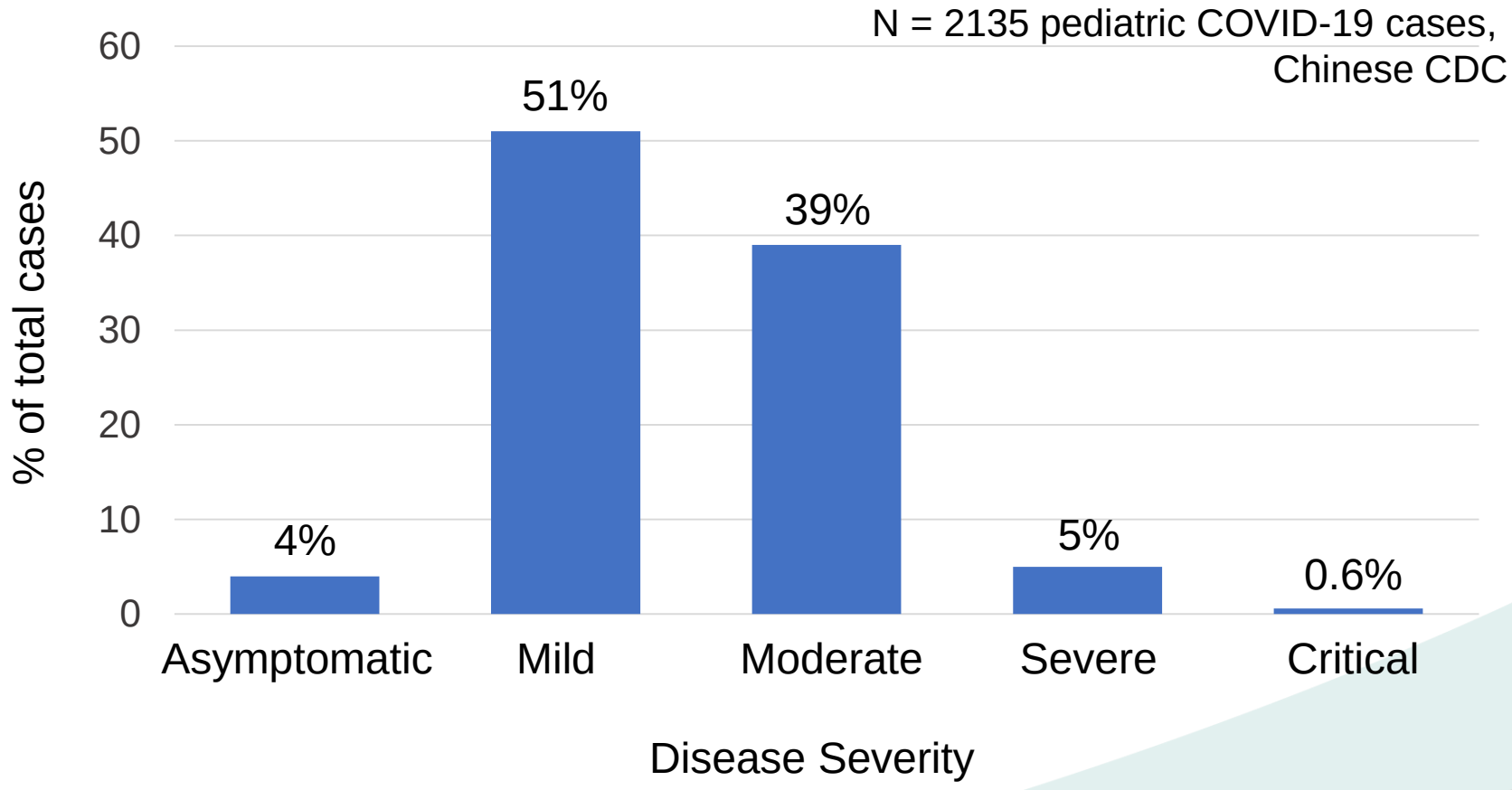
Burden of COVID-19 in children

Relatively fewer cases of COVID-19 among children compared to cases among adult patients:

- **United States**: 2% of confirmed cases of COVID-19 were <18 years
- **China**: 2.2% were pediatric COVID-19 cases
- **Italy**: 1.2% were pediatric COVID-19 cases
- **Spain**: 0.8% were pediatric COVID-19 cases

https://www.cdc.gov/coronavirus/2019-ncov/hcp/pediatric-hcp.html

COVID-19 clinical course is less severe in children



Dong et al., *Pediatrics,* March 2020.

The majority of adult COVID-19 with mild liver injury

Abnormal liver biochemistries in the first 30 days of +COVID test

	SARS-CoV-2 (n=816)
Peak ALT	
<ULN	445 (54.5)
≥1× to <2×ULN	190 (23.3)
≥2× to <5×ULN	141 (17.3)
≥5× to <10×ULN	32 (3.9)
≥10×ULN	8 (1.0)
Peak ALP	
<ULN	747 (91.5)
≥1× to <2×ULN	65 (8.0)
≥2× to <5×ULN	4 (0.5)
≥5× to <10×ULN	0 (0)
≥10×ULN	0 (0)
Peak total bilirubin	
<ULN	391 (47.9)
≥1× to <2×ULN	339 (41.5)
≥2× to <5×ULN	79 (9.7)
≥5× to <10×ULN	6 (0.7)
≥10×ULN	1 (0.1)

Yip TC-F et al., *Gut*, June 2020

Pediatric COVID-19 and mild liver injury

Table 2. Difference of Laboratory Findings of Pediatric Patients With Coronavirus Disease 2019 on Admission to Hospital

Biomarker	Median (IQR) Total (N = 148)	Mild (n = 60)	Moderate (n = 88)	*P* value[a]
Coagulation function				
Prothrombin time, s	10.9 (10.5-11.3)	10.9 (10.6-11.4)	10.8 (10.5-11.1)	.24
Fibrinogen, g/L	207 (177-252)	199 (176-231)	214 (178-267)	.26
Activated partial thromboplastin time, s	30.8 (28.7-33.8)	30.3 (27.8-33.5)	30.9 (28.8-34.2)	.28
Thrombin time, s	18.4 (17.7-19.4)	18.6 (18.0-19.2)	18.4 (17.5-19.6)	.84
D-dimer, μg/mL	0.20 (0.14-0.35)	0.16 (0.13-0.26)	0.24 (0.15-0.36)	.02
Liver function				
Total bilirubin, mg/dL	0.44 (0.32-0.61)	0.51 (0.36-0.67)	0.43 (0.29-0.58)	.04
Direct bilirubin, mg/dL	0.14 (0.10-0.19)	0.15 (0.10-0.20)	0.13 (0.09-0.19)	.12
Albumin, g/dL	4.54 (4.32-4.77)	4.56 (43.4-48.2)	4.54 (4.31-4.75)	.27
Globulin, mean (SD), g/dL	2.30 (0.48)	2.34 (0.37)	2.27 (0.54)	.48
Alanine aminotransferase, U/L	16.0 (12.0-26.0)	13.0 (11.0-18.8)	18.0 (12.3-33.8)	.001
γ-glutamyltransferase, U/L	11.0 (9.0-16.0)	10.0 (8.0-13.0)	12.0 (10.0-19.0)	.005
Aspartate aminotransferase				
Level, U/L	30.0 (23.0-41.8)	25.0 (20.3-34.5)	33.0 (24.0-46.8)	<.001
Increased, No. (%)	25 (16.9)	4 (6.7)	21 (23.9)	.007

Mao et al., *Lancet Gastroenterol Hepatol,* May 2020.
Wu et al., *JAMA Netw Open,* June 2020.

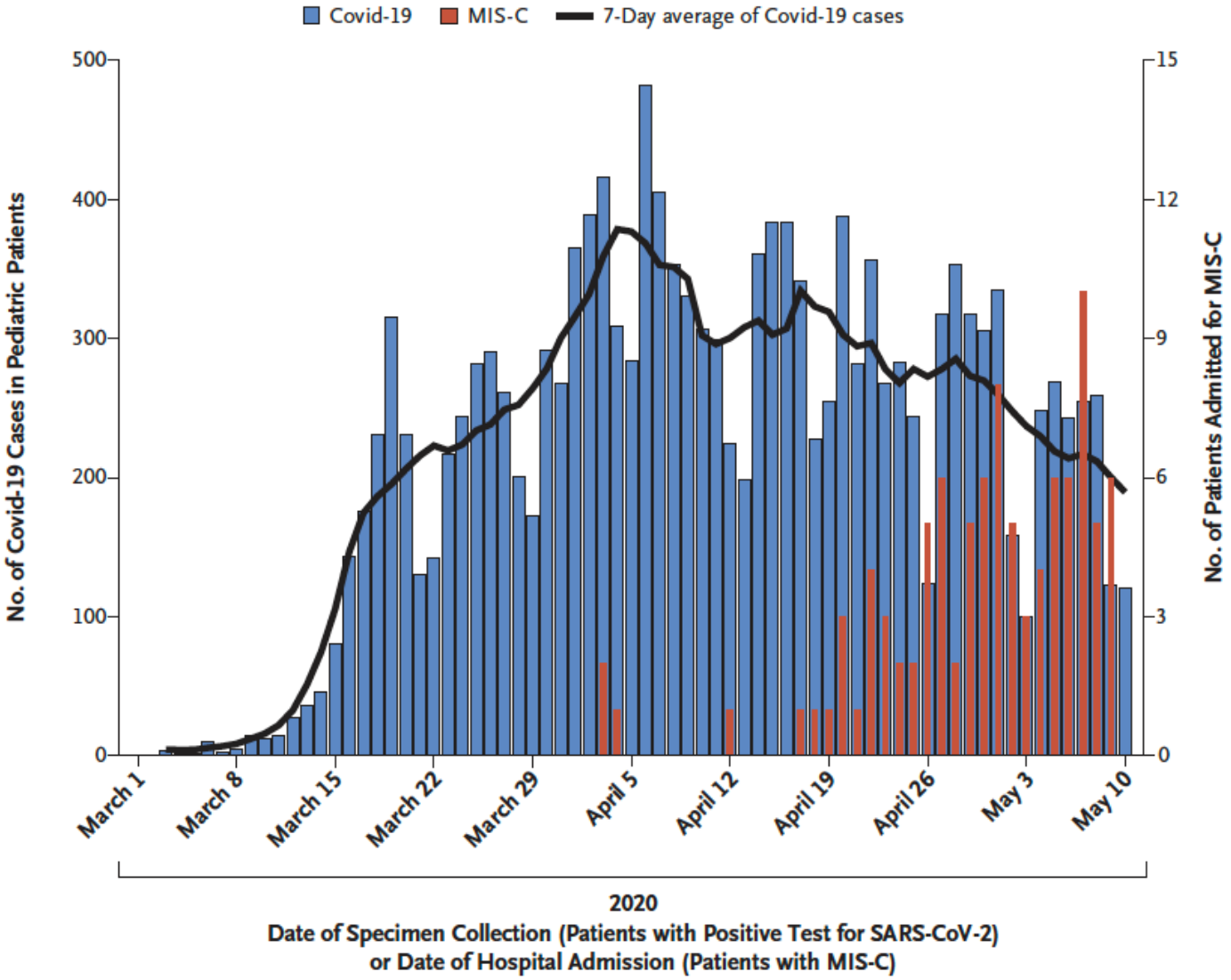
Emerging evidence suggests increased ALT is associated with more severe COVID-19

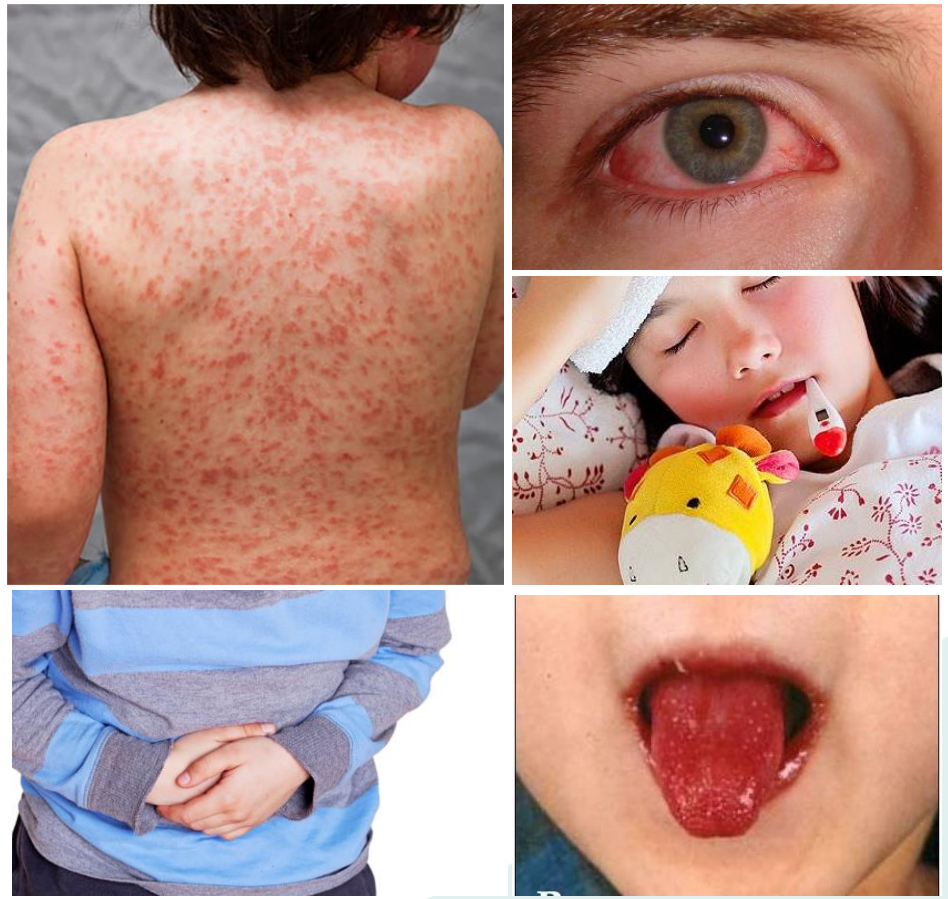
- Increased ALT or abnormal liver function on admission is associated with more severe COVID-19
- COVID-19 patients with elevated liver chemistries had increased risk of adverse clinical outcomes and mortality compared to patients without elevated liver chemistries
- Difficult to determine whether the liver injury is directly modulating disease or whether the injury is secondary to COVID-19-related pathologies, DILI, or immune dysregulation

Yip TC-F et al., *Gut*, June 2020
Mao et al., *Lancet Gastroenterol Hepatol,* May 2020
Kulkarni et al., *Aliment Pharmacol Ther*, July 2020
Fan et al., *Clin Gastroenterol Hepatol*, April 2020

Multisystem Inflammatory Syndrome in Children (MIS-C)

Pediatric Cases of COVID-19 and MIS-C in New York State

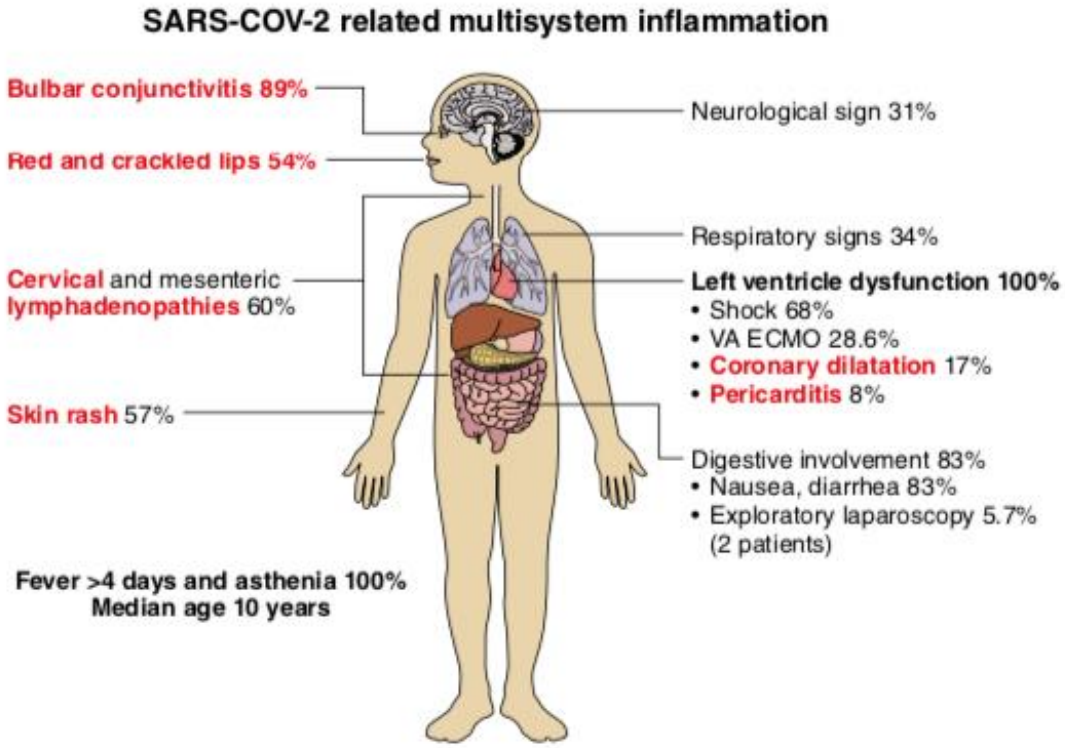




Dufort et al., *N Engl J Med*, June 2020.

MIS-C: CDC definition, 5 criteria

1. Hospitalized patient < 21 years
2. Fever ≥ 24 hours
3. Laboratory evidence of inflammation (CRP, ESR, fibrinogen, procalcitonin, d-dimer, ferritin, LDH, or IL-6, elevated neutrophils, reduced lymphocytes and low albumin)
4. Multisystem (≥ 2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurological)
5. Evidence of SARS-CoV-2 infection by RT-PCR, antibody, antigen test; or exposure to a suspected or confirmed COVID-19 case within the last 4 weeks of symptom onset



https://www.dicardiology.com/article/kawasaki-inflammatory-disease-affects-children-covid-19

Riphagen et al., *Lancet*, May 2020. (U.K.)

https://www.cdc.gov/mis-c/hcp/

THE JOURNAL OF PEDIATRICS • www.jpeds.com

ORIGINAL ARTICLES

Multisystem Inflammatory Syndrome in Children Associated with Severe Acute Respiratory Syndrome Coronavirus 2 Infection: A Multi-institutional Study from New York City

Shubhi Kaushik, MBBS[1,*], Scott I. Aydin, MD[1,2,*], Kim R. Derespina, MD[3], Prerna B. Bansal, MD[2], Shanna Kowalsky, DO[4], Rebecca Trachtman, MD[5], Jennifer K. Gillen, MD[1], Michelle M. Perez, MD[3], Sara H. Soshnick, DO, MS[3], Edward E. Conway, Jr., MD[6], Asher Bercow, MD[6], Howard S. Seiden, MD[2], Robert H. Pass, MD[2], Henry M. Ushay, MD, PhD[3], George Ofori-Amanfo, MD[1,2], and Shivanand S. Medar, MD[3,7]

June 2020

- Children with MIS-C admitted to pediatric ICUs in New York City between April 23 and May 23, 2020
- In contrast with the infantile age distribution of Kawasaki disease, MIS-C is predominantly a disease of older children and adolescents (median age 10 years) and is consistent with other centers.

Table I. Demographic and clinical characteristics of patients (n = 33) with MIS-C

Characteristics	Values
Age, y	10 (6-13)
Male sex	20 (61)
Weight, kg	33.4 (20.7-60.0)
BMI, kg/m^2	18.6 (15.9-22.9)
Race	
Hispanic or Latino	15 (45)
Black	13 (39)
White	3 (9)
Asian	1 (3)
Other	1 (3)
Comorbid conditions	16 (48)
Asthma	5 (15)
Allergic rhinitis/eczema	3 (9)
Obesity (BMI >30 kg/m^2)	2 (6)
Cardiac	2 (6)
Hematologic	2 (6)
Others	3 (9)
Symptoms	
Duration of symptoms before admission, d (n = 35)	4.5 (3-6)
Maximum temperature (n = 31)	39.4 (38.8-40.0)
Fever	31 (93)
Mucocutaneous involvement	7 (21)
Conjunctivitis	12 (36)
Rash	14 (42)
Abdominal pain	21 (63)
Nausea/vomiting	23 (69)
Diarrhea	16 (48)
Shortness of breath	11 (33)
Dizziness	3 (9)
Hypotension	21 (63)
Neurologic involvement	4 (12)
Ill contact	8 (24)
Known COVID+ contact	5 (15)

Liver injury is mild in MIS-C

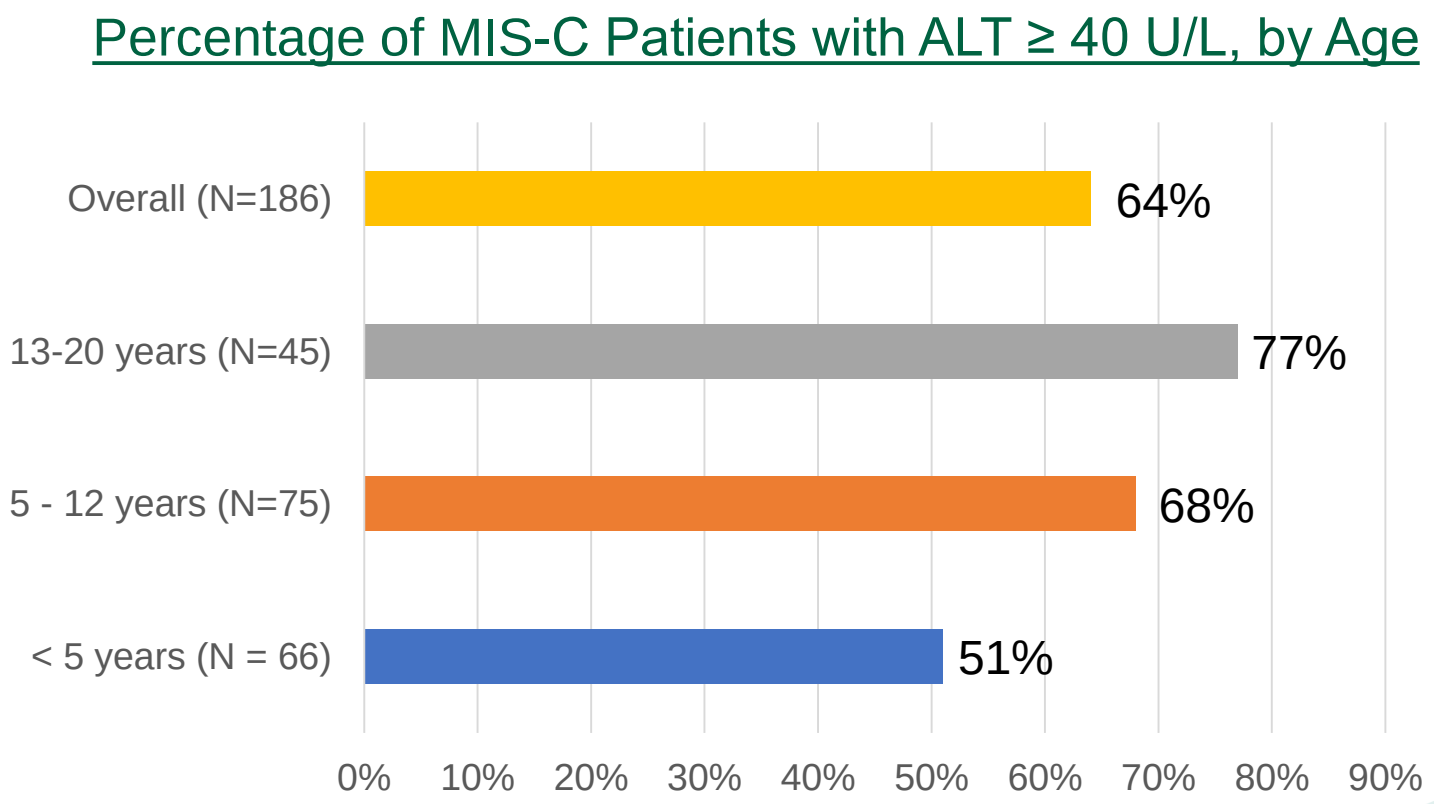
Table II. Admission laboratory test results of all patients with MIS-C

Tests	Value	Reference normal range
SARS-CoV-2 PCR positive	11 (33)	–
SARS-CoV-2 antibody positive	27 (81)	–
SARs CoV-2 PCR and antibody positive	6 (18)	–
WBC, cells/μL	11 000 (8450-14 400)	4000-11 000/μL
Hemoglobin, g/dL	11.3 (9.55-12.5)	10.5-14 g/dL
Platelets, thousands/μL	176 (130.5-282)	150-300 K/μL
Absolute lymphocyte count, thousands/μL	1.1 (0.6-1.3)	1.0-4.0 K/μL
ESR, mm/h	53 (28.2-77.2)	0-10 mm/h
Serum sodium, mEq/L	136 (135-139)	135-145 mEq/L
Albumin, g/dL	3.5 (2.6-3.9)	3.5-4.9 g/dL
BUN, mg/dL	12 (9-16)	6-23 mg/dL
Serum creatinine, mg/dL	0.6 (0.4-1.1)	0.7-1.3 mg/dL
AST, U/L	48 (27-69)	1-35 U/L
ALT, U/L	36 (28-53)	1-45 U/L
Total bilirubin, mg/dL	0.7 (0.4-1.3)	0.1-1.2 mg/dL
C-reactive protein, mg/L	250 (156-302)	0.0-5.0 mg/L
C-reactive protein at peak, mg/L	255 (181-310)	0.0-5.0 mg/L
Procalcitonin, ng/mL	5.4 (1.8-16.7)	<0.1 ng/mL
Procalcitonin peak, ng/mL	6 (2.7-16.5)	<0.1 ng/mL
Fibrinogen, mg/dL	627 (455-782)	162-378 mg/dL
Ferritin, ng/mL	568 (340-954)	80-500 ng/mL
BNP at admission, pg/mL	388 (75-1086)	0-100 pg/mL

- PICU LOS = 4.7 days
- Hospital LOS 7.8 days
- Mortality 3%
- Rapid, complete clinical and myocardial recovery was almost universal

Kaushik et al., *J Pediatr*, June 2020.

Liver injury is more common in MIS-C than in acute COVID-19



186 MIS-C Cases, 26 states
March 15-May 20, 2020

https://www.cdc.gov/coronavirus/2019-ncov/covid-data/infographic-mis-c.html

MIS-C ICU cases: persistent but mild liver injury (U.K)

N = 78	Reference ranges	Day 1 (n=78)	Day 2 (n=44)	Day 3 (n=43)	Day 4 (n=36)
Neutrophil count (×10⁹ cells per L)	2·0–7·5	12·3 (10·7–22·9)	13·2 (9·2–17·6)	13·0 (8·9–19·4)	11·9 (7·2–20·0)
Lymphocyte count (×10⁹ cells per L)	1·5–4·0	0·7 (0·4–1·1)	0·9 (0·7–1·6)	1·2 (0·9–1·7)	1·8 (1·0–2·3)
Platelet count (×10⁹ cells per L)	150–400	125 (75–178)	179 (115–272)	187 (109–293)	201 (100–358)
C-reactive protein (mg/L)	<5	264 (192–316)	233 (143–308)	191 (77–283)	96 (39–197)
D-dimer (µg/L)	<500	4030 (2349–7422)	2293 (1319–4638)	3503 (1902–5291)	1659 (646–3792)
Ferritin (µg/L)	12–200	1042 (538–1746)	1152 (473–1529)	842 (495–1422)	757 (484–1198)
Troponin (ng/L)	<10	157 (43–810)	232 (70–829)	355 (66–2252)	358 (30–3015)
Creatinine (µmol/L)	60–120	75 (46–103)	54 (41–77)	48 (34–67)	49 (32–64)
ALT (IU/L)	10–50	50 (30–93)	51 (27–77)	43 (30–68)	51 (35–71)

Data are median (IQR). PICU=paediatric intensive care unit. ALT=alanine aminotransferase.

Table 2: **Laboratory results for the first 4 days of PICU admission**

Davies et al., *Lancet Child Adolesc Health,* July 2020.

Summary and Recommendations

- Liver injury is common but mild in most pediatric COVID-19 and MIS-C cases
- Etiologies of abnormal liver biochemistries include myositis, ischemia, cardiac injury, DILI, MIS-C
- Monitor for interval change of liver tests, especially in pediatric patients receiving investigational treatments such as remdesivir and tocilizumab
- Longitudinal studies are needed to determine the long-term effects of COVID-19 in children

https://www.aasld.org/sites/default/files/2020-06/AASLD-COVID19-ExpertPanelConsensusStatement-June252020-v2-FINAL.pdf

AASLD-NASPGHAN-SPLIT
COVID-19 & the Liver: Pediatric Perspective

Mohit Kehar, MBBS,DNB

Assistant Professor of Pediatrics
Queen's University, Canada

Joint Webinar

Society of Pediatric Liver Transplantation

The Transplantation Society

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Outline

- Introduction
- NASPGHAN-SPLIT COVID-19 Registry
- Review course, treatment and outcome in children with liver disease (native liver) presenting with COVID-19 infection:
  - Demographics
  - Etiology and comorbid conditions
  - Presenting symptoms
  - Laboratory trends
  - Management
  - Outcome

Introduction

- COVID 19: Elevated AST/ALT/Bilirubin
- Information is limited regarding the effects of COVID-19 infection in patients with chronic liver disease
- Few adult studies
- **No Pediatric Data**

ORIGINAL RESEARCH

Comparison of mortality risk in patients with cirrhosis and COVID-19 compared with patients with cirrhosis alone and COVID-19 alone: multicentre matched cohort

- **37** patients with cirrhosis+COVID-19
- Matched with **108** patients with COVID-19 and **127** patients with cirrhosis
- Seven sites in USA, Median age 61yrs.
- Mortality
  - Cirrhosis+COVID-19 vs. COVID-19 (30% vs. 13%, p=0.03)
  - Cirrhosis +COVID-19 vs. Cirrhosis (30% vs. 20%, p=0.16)

Gut . 2020 Jul 13;gutjnl-2020-322118.

JOURNAL OF HEPATOLOGY

High mortality rates for SARS-CoV-2 infection in patients with pre-existing chronic liver disease and cirrhosis: Preliminary results from an international registry

- N= 152 (103 patients with cirrhosis and 49 with non-cirrhotic CLD)
- Median age 61 yrs.
- Most Common diagnosis : NAFLD
- Death (N=47)
  - COVID-19 lung disease: 78.7%
  - Cardiac-related: 4.3%
  - Liver-related: **12.2%**

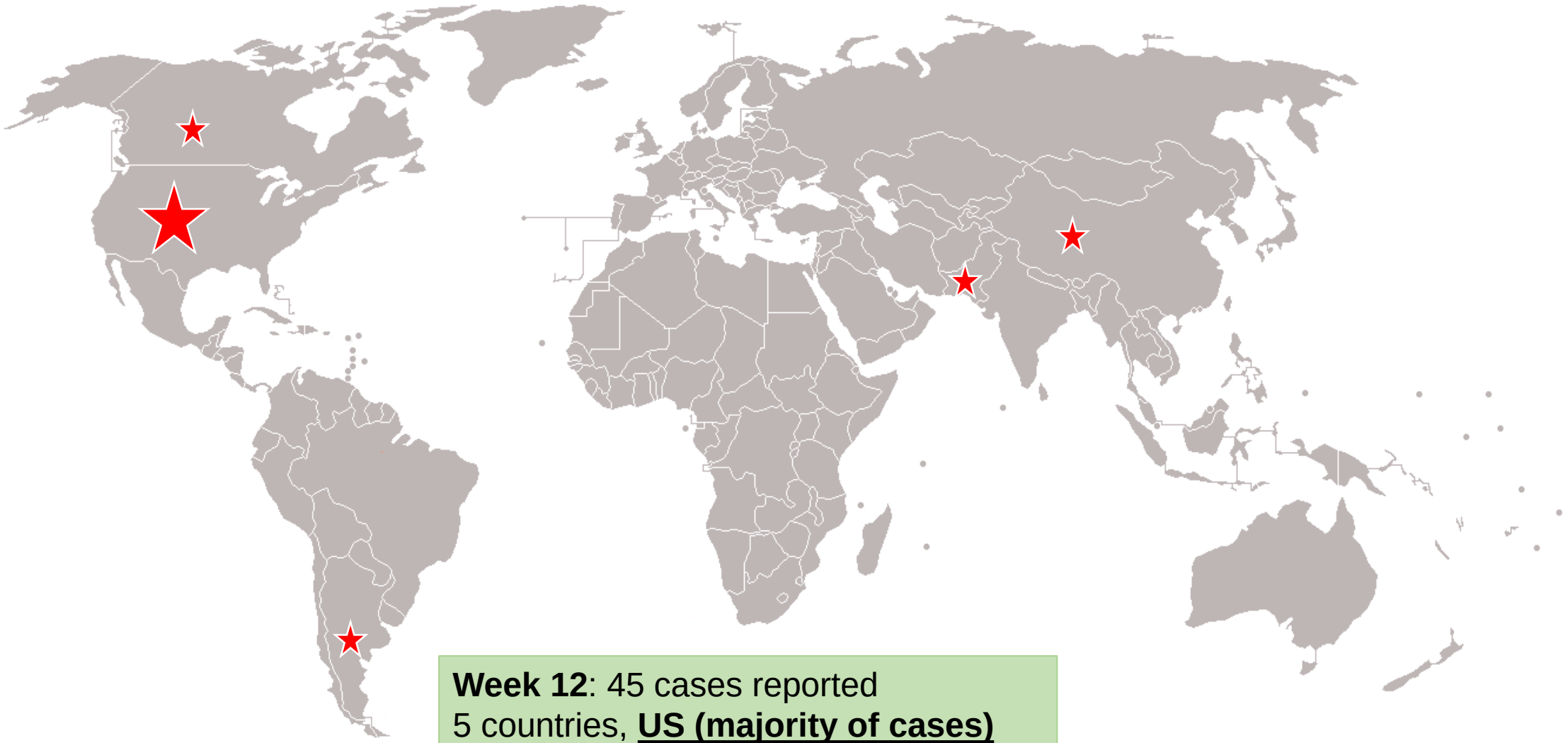
J Hepatol . 2020 May 21;S0168-8278(20)30305-6.

NASPGHAN-SPLIT COVID-19 registry

- Joint collaborative effort: NASPGHAN Hepatology committee and Society of Pediatric Liver Transplantation
- Course and outcome of COVID-19 in children with liver disease and recipients of liver transplantation
- **Patient Population:** Less than 21 years of age
- **Inclusion Criteria**: All cases of chronic liver disease, recipients of pediatric liver transplantation ± intestinal transplant/MVT/Other solid organs

NASPGHAN-SPLIT COVID-19 registry

- **Launched**: April 2020
- Weekly report shared through the NASPGHAN GI listserv, the SPLIT COVID listserv and the NASPGHAN website
- Week 12 report shared last week
- International RED cap registry
- Data collection ongoing



Week 12: 45 cases reported
5 countries, **US (majority of cases)**

THE UNIVERSITY OF CHICAGO MEDICINE

Atrium Health
Levine Children's

The Children's Hospital of Philadelphia®

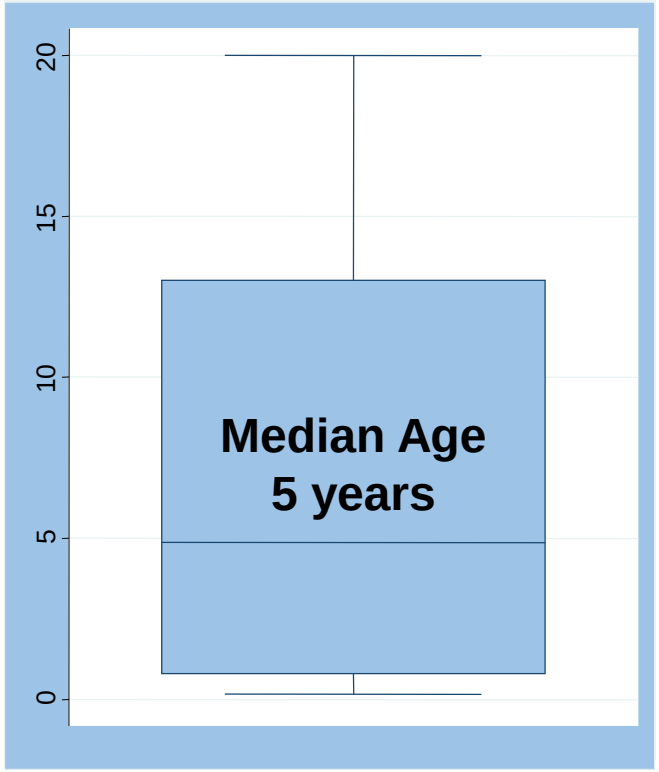
Ann & Robert H. Lurie
Children's Hospital of Chicago℠

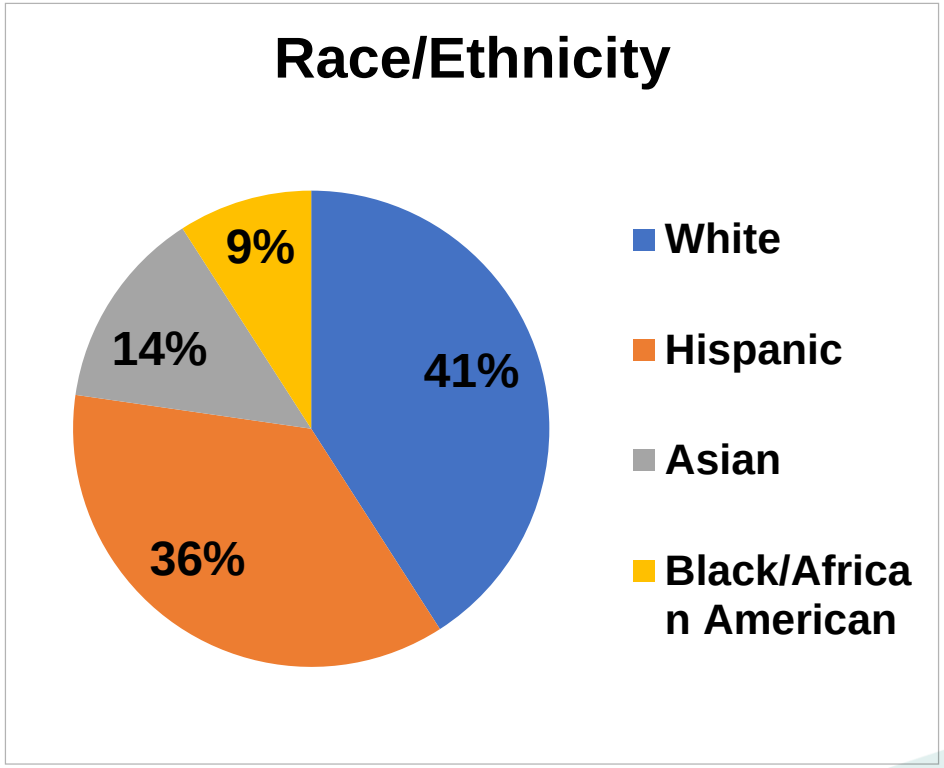
UNIVERSITY of MARYLAND
SCHOOL OF MEDICINE

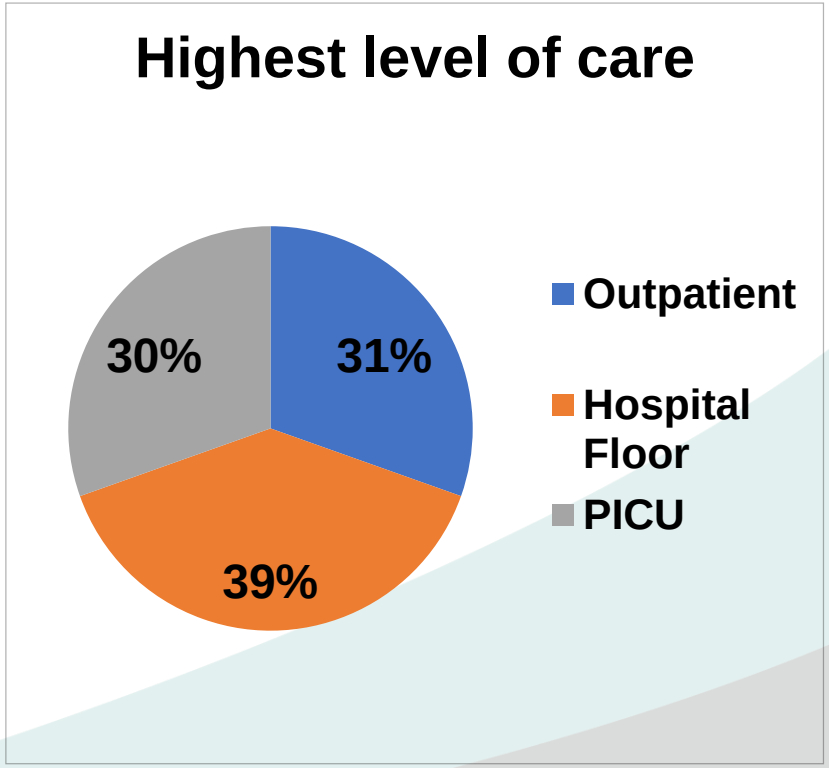
9 States
21 centers

Demographics of Children: COVID+ Liver Disease (Native Liver)

N=23 of 45
M/F = 13/10





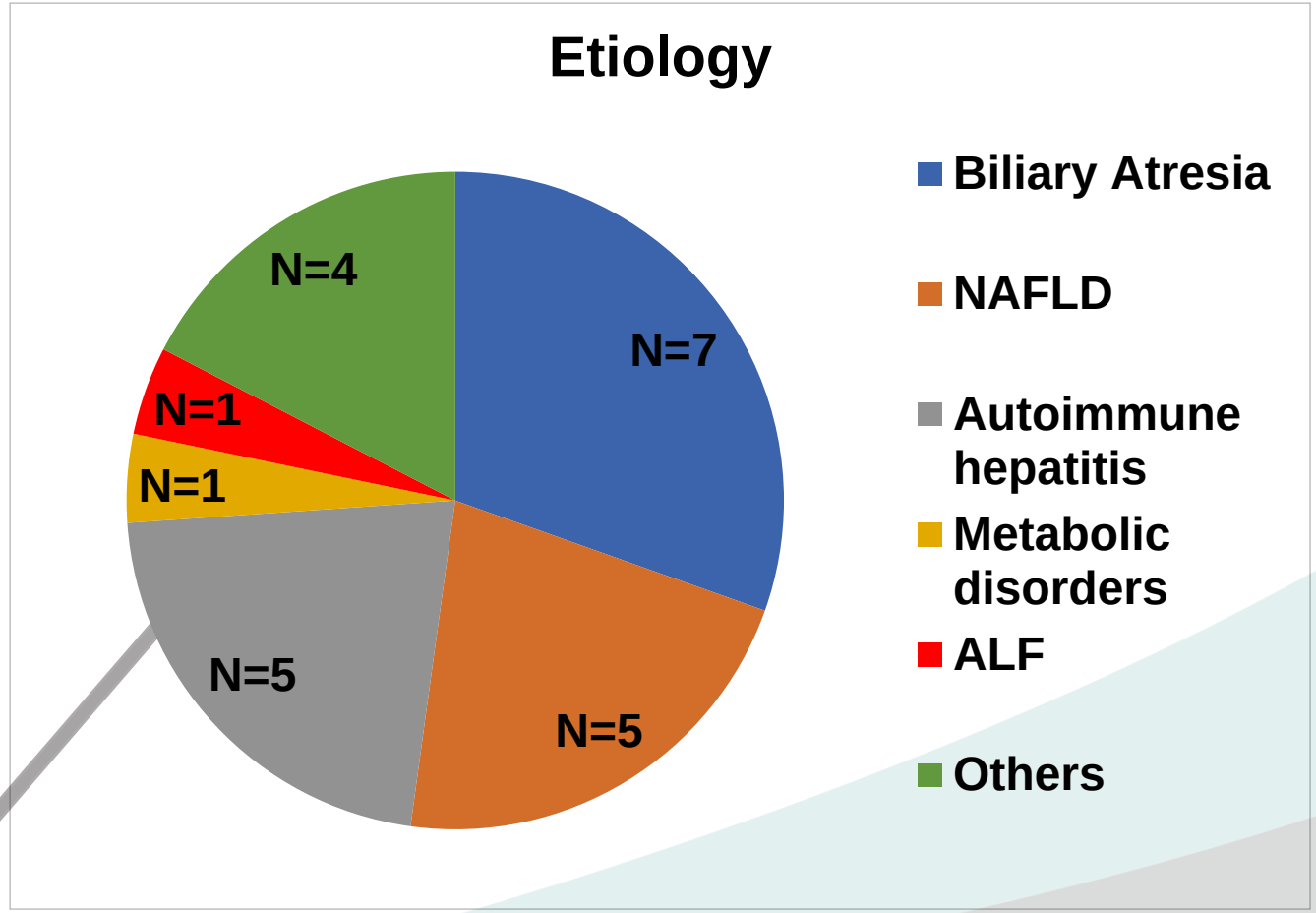


Etiology and Comorbid Conditions: COVID+ Liver Disease (Native liver)

Comorbid conditions	
Obesity	5
Failure to thrive	3
Gastrointestinal	3
Genetic	2
Cardiac	2
Renal/CKD	1
Endocrine	1
Pulmo	
Others	

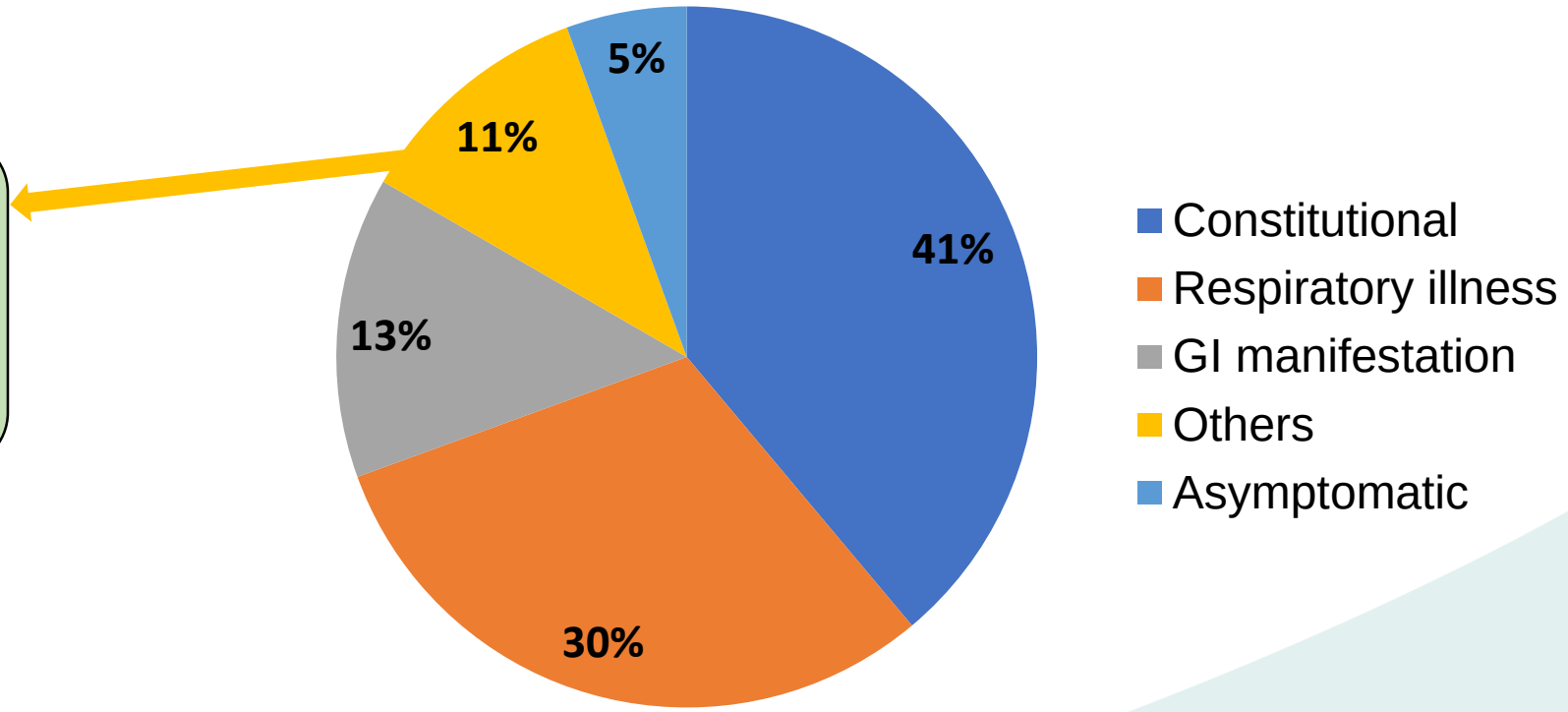
Azathioprine : 5
Steroids : 3

Dose reduced : 1
No changes : 4



Presenting Symptoms: COVID+ Liver Disease (Native liver)

Anorexia, malaise
headache
MIS-C (N=2)



Constitutional : fever, myalgia, fatigue, sore throat, loss of smell/taste

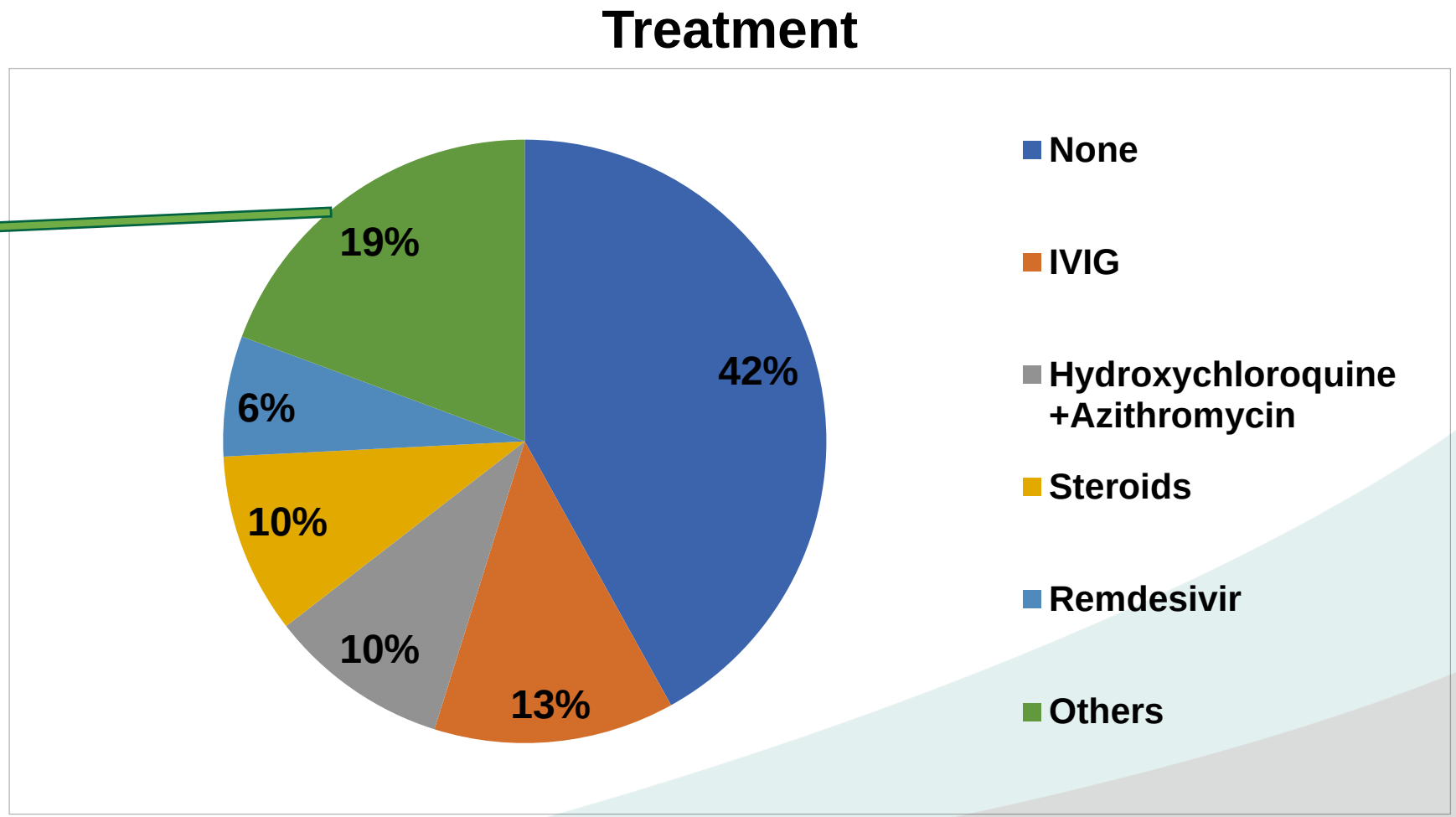
Laboratory Trends: COVID+ Liver disease (Native liver)

Laboratory Variable	Baseline value Median (IQR)	Peak value Median (IQR)	P value
WBC count (10X9 cells/L)	10.9 (5.3-14.7)	14.4 (7.9-20.43)	0.002
ALT (IU/L)	74 (41-143)	146 (53-227)	<0.001
Total Bilirubin (mg/dl)	0.85 (0.52-6.4)	3.25 (1-8.5)	<0.001
INR	1.12 (1-1.2)	1.2 (1.18-1.5)	0.002
Laboratory Variable	**Baseline value Median (IQR)**	**Nadir value Median (IQR)**	**P value**
WBC count (10X9 cells/L)	10.9 (5.3-14.7)	7.35 (4.1-11.1)	0.008
Albumin (g/dl)	3.8 (3.4-4.35)	3.1 (2.6-3.4)	<0.001

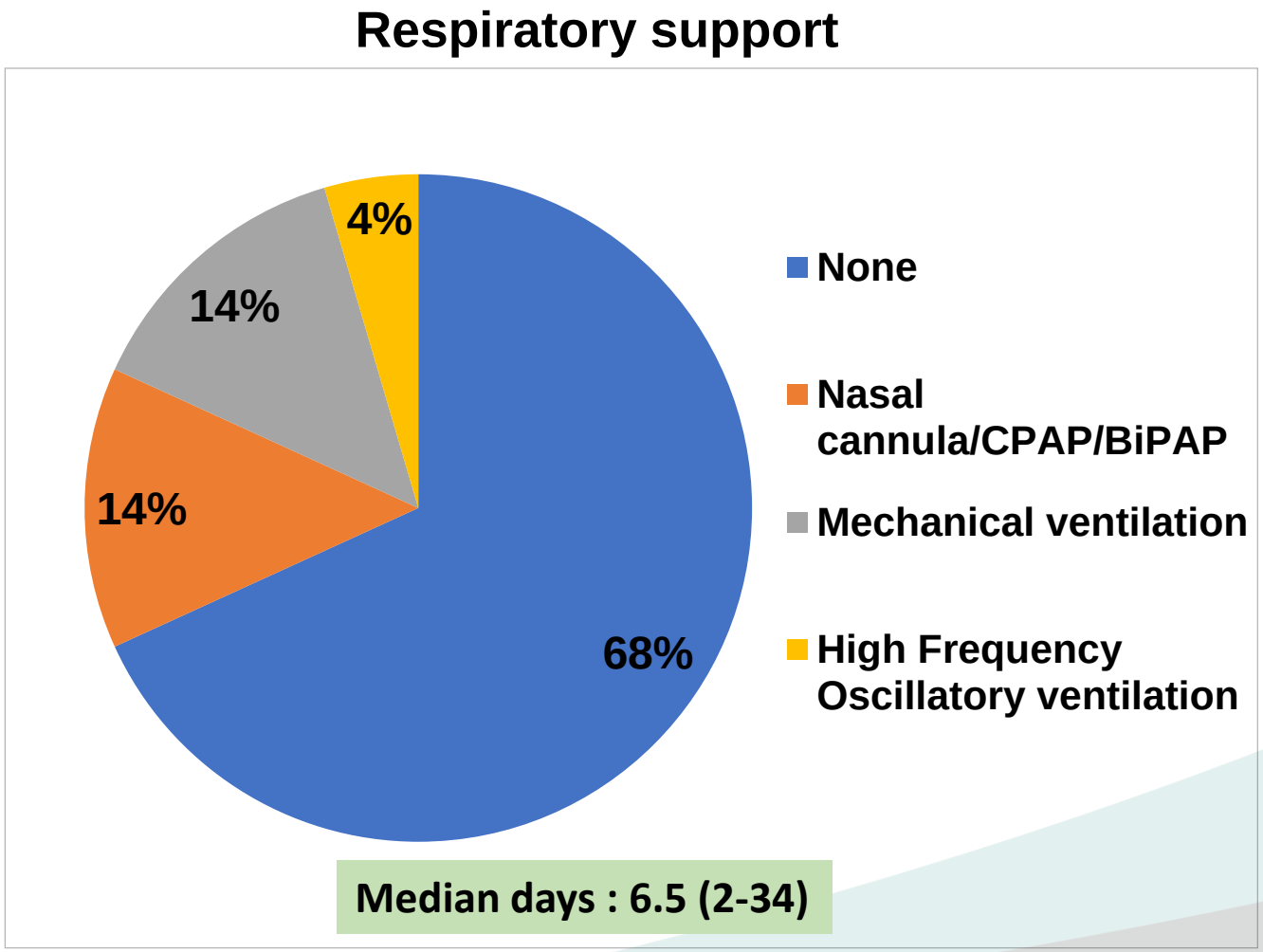
Median ALC: 2.48 (0.76-7)k/ul

Management: COVID+ Liver disease (Native liver)

Others:
Tocilizumab + Sarilumab (N=2)
Azithromycin (N=1)
Convalescent Plasma (N=1)
Anakinra (N=1)
Eculizimab (N=1)

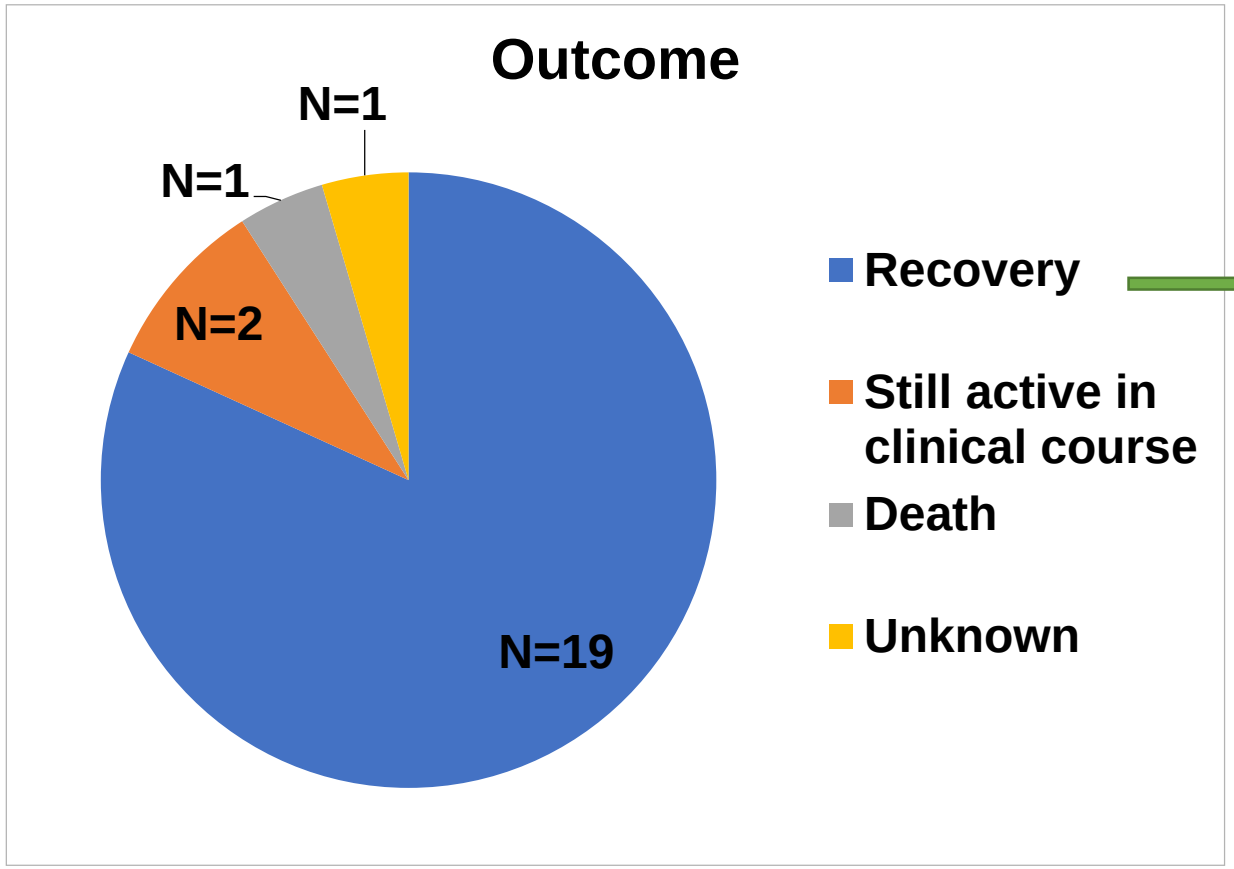


Management: COVID+ Liver disease (Native liver)

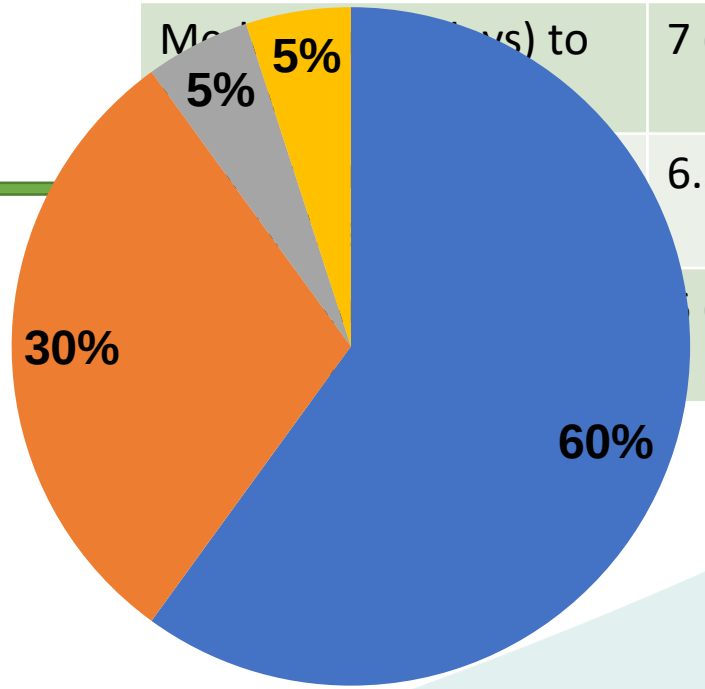


Need for vasoactive agents: 4
Need for RRT: 2

Outcome: COVID+ Liver disease (Native liver)



Variable	Median (range)
Ma[illegible]ys) to	7 (2-37)
	6.5 (1-37)
	[illegible] (4-34)



Summary

- First Pediatric specific registry assessing outcome of COVID-19 on liver disease and liver transplantation recipient
- Hospitalization was needed in majority (70%) of children with liver disease (native liver) +COVID 19
- Majority of patients did not receive any specific treatment for COVID-19 or respiratory support
- Over 80% recovered with only one death reported till date in cohort of children with liver disease (native liver) +COVID 19

COVID-19 Registry: Outcomes in Pediatric Liver Transplant Recipients

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Director, Alagille Syndrome Program
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Joint Webinar

Society of Pediatric Liver Transplantation

The Transplantation Society

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Background: COVID+ post-transplant recipients

SECURE-Cirrhosis REGISTRY
Surveillance Epidemiology of Coronavirus (COVID-19) Under Research Exclusion

EASL The Home of Hepatology | COVID-HEP REGISTRY
COVID-19 in Patients with Liver Disease or Transplantation

Median age 59 years, 63% male

Liver transplant (n = 160)

Major outcomes

Hospitalised	129	81%
Intensive care admission	47	29%
Invasive ventilation	31	19%
Death	30	19%

COVID-19 in an international European liver transplant recipient cohort

- 57 patients, 70% male, aged 57-70 years
- Co-morbidities: 37% cardiovasc disease, 37% diabetes, 28% renal disease, 23% respiratory disease
- 28% outpatient
- 72% inpatient
  - 10% ICU, intubated
  - 19% ARDS
  - 12% died

https://doi.org/10.1016/S2468-1253(20)30125-4
doi:10.1136/gutjnl-2020-321923

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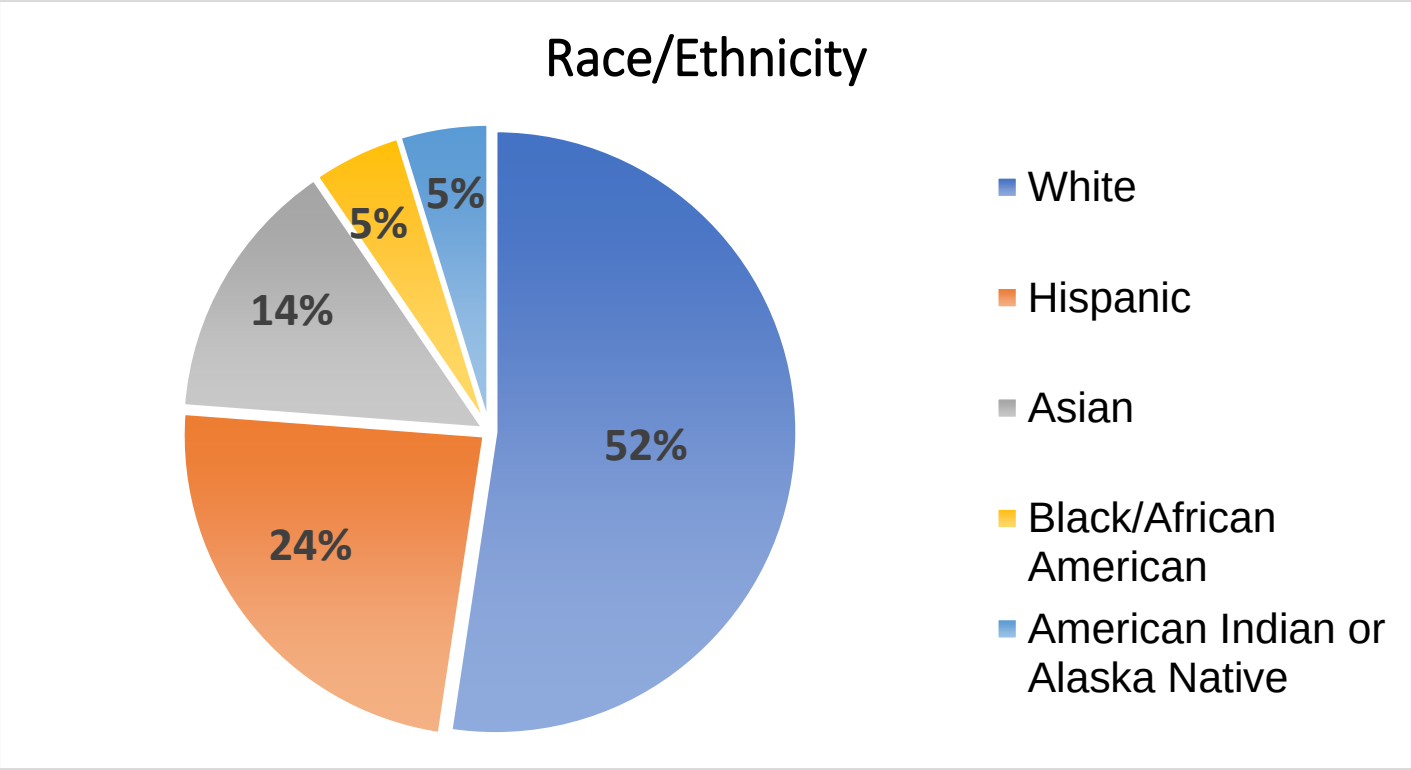
Demographics of COVID+ post-transplant recipients

22 post-liver transplant recipients in the registry

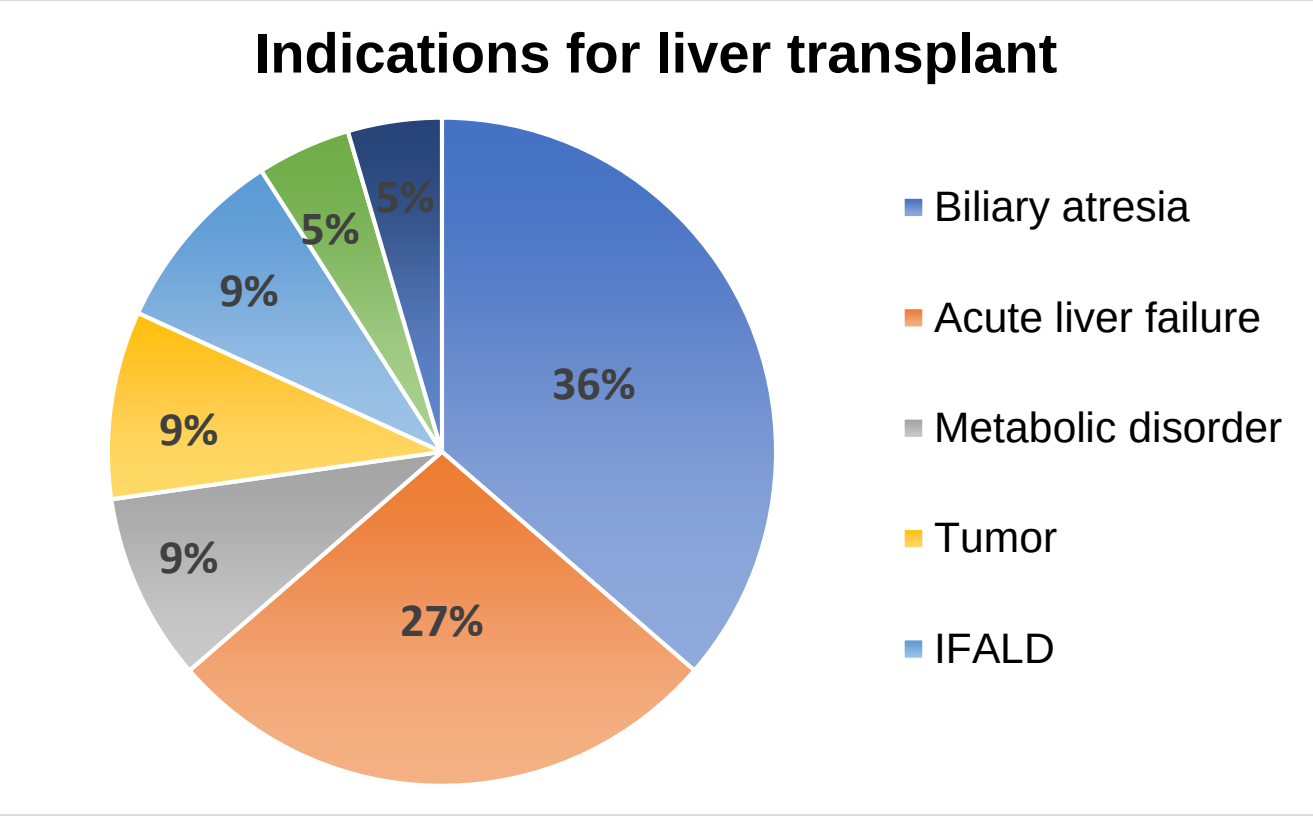
- 45% female (n=10)
- Aged 6 months – 21 years (median 13.5 years old)
- Time out from transplant: 1 week – 19 years (median 4.6 years)

Race of COVID+ post-transplant recipients

22 post-liver transplant recipients in the registry



Indications for liver transplantation

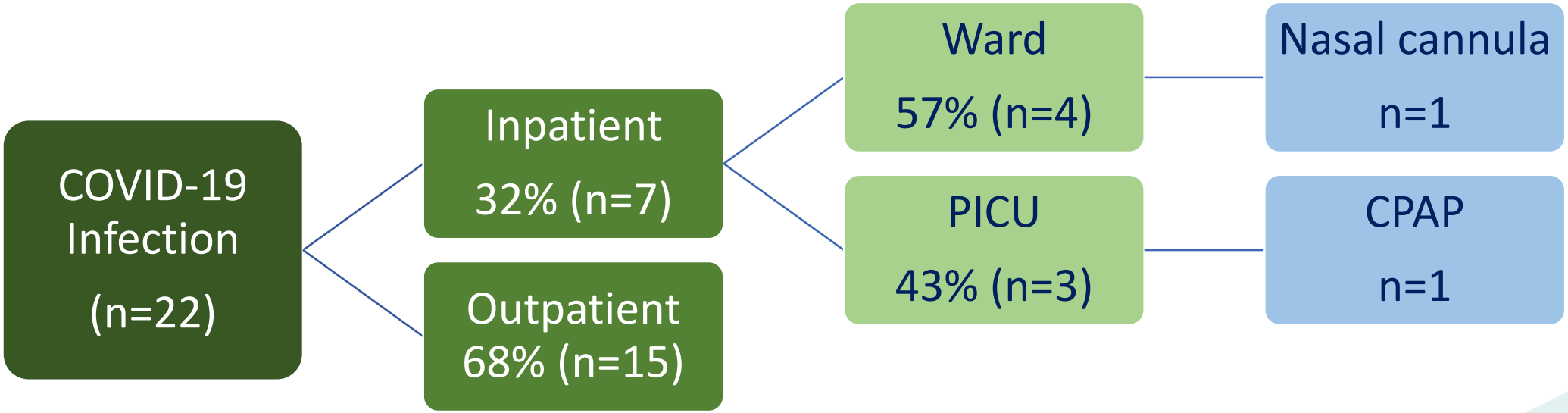


Comorbidities at time of diagnosis	
Autoimmune	1 - de novo AIH 1 - lupus
Gastrointestinal	1 - IBD
Cardiovascular	1 - pacemaker 1 - hypertension
Renal/CKD	1
Endocrine	2 - diabetes

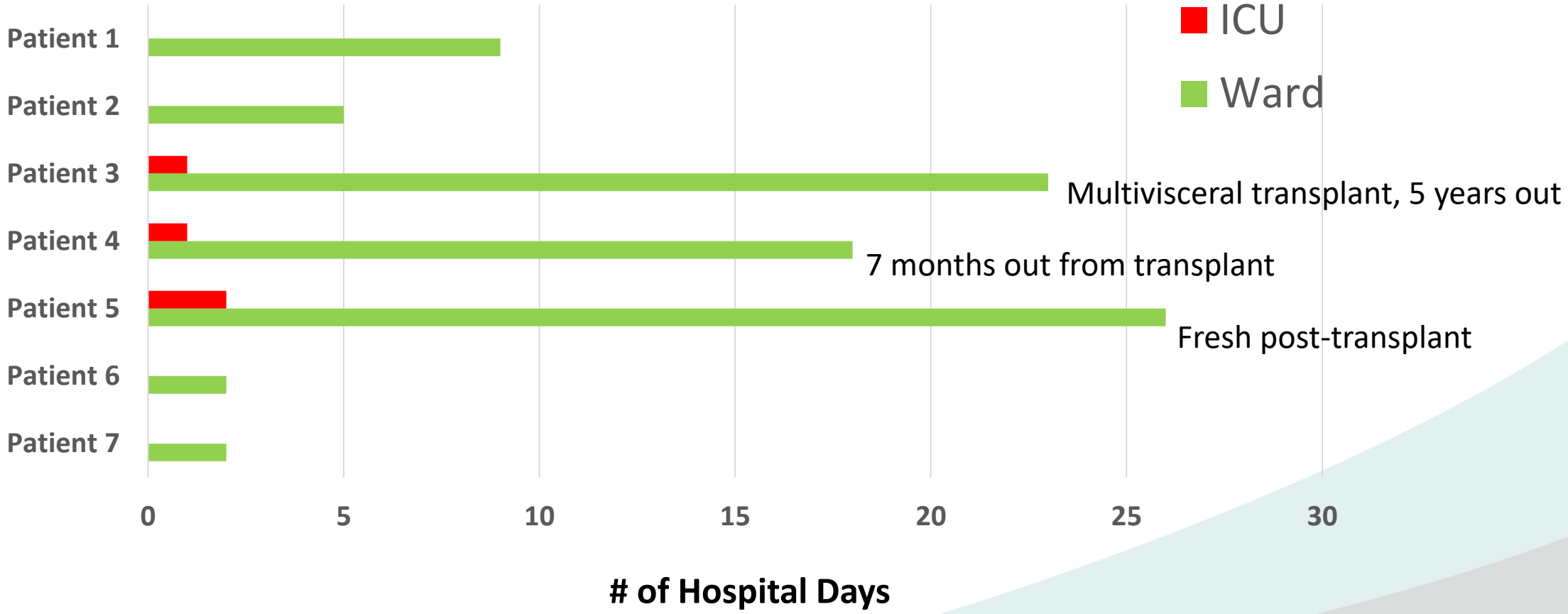
Presenting symptoms of COVID+ post-transplant recipients

	Liver transplant only (includes liver-kidney) (n=20)	Multivisceral transplant (n=2)
Asymptomatic	4 (20%)	0
Fever	10 (50%)	2
Respiratory symptoms	6 (30%)	1
GI symptoms	9 (45%)	1
Constitutional (loss of smell/taste, myalgia, fatigue, sore throat)	6 (30%)	0

Highest level of care for COVID+ post-transplant recipients



Number of hospital days for COVID+ post-transplant recipients



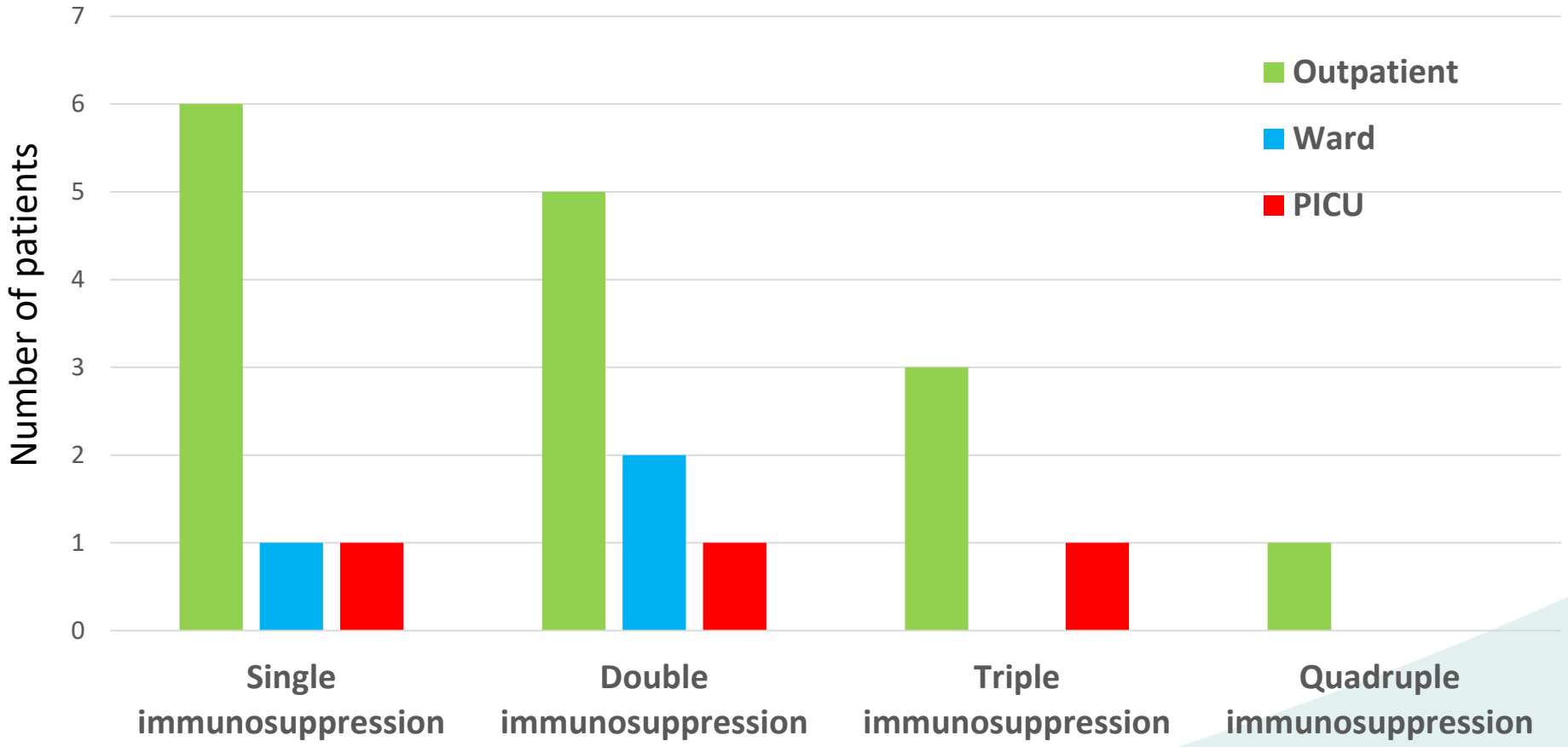
Laboratory trends of COVID+ post-transplant recipients

Elevated ALT (17%)	• ALT 21 -> 174 • ALT 44 -> 424 • ALT baseline 231 (fresh post-transplant) -> 1215
Hypoalbuminemia (11%)	• Albumin baseline 2.5 (fresh post-transplant) -> 2.3 • Albumin 3 -> 1.6
Elevated INR (6%)	• INR baseline 2.3 -> 2.8
Bilirubin	• No reports of significantly elevated bilirubin

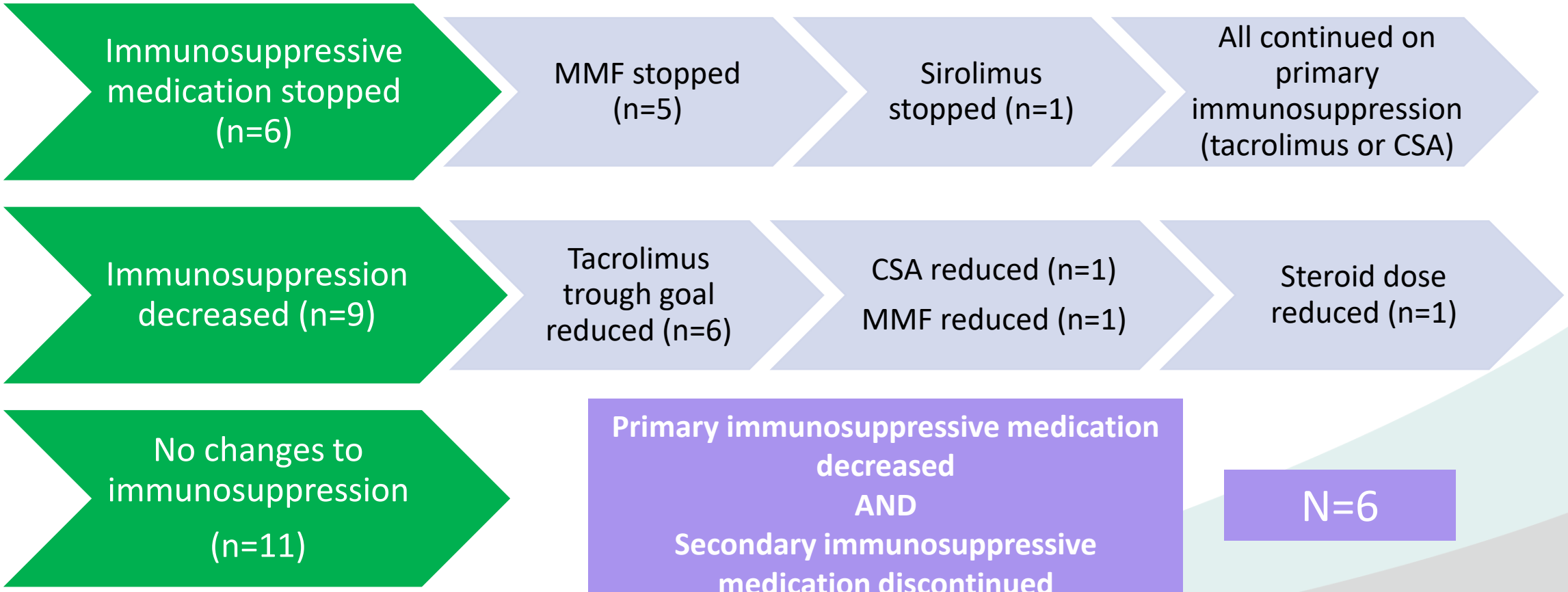
Immunosuppression at time of diagnosis: COVID+ post-transplant recipients

Single immunosuppression (n=8)	• Tacrolimus only (n=6) • Sirolimus only (n=1) • MMF only (n=1)
Dual immunosuppression (n=8)	• Tacrolimus + MMF (n=4) • Tacrolimus + steroids (n=4)
Triple immunosuppression (n=4)	• Tacrolimus + sirolimus + steroids (n=1) • Tacrolimus + MMF + steroids (n=1) • Cyclosporine + MMF + steroids (n=1) • Tacrolimus + azathioprine + steroids (n=1)
Quadruple immunosuppression (n=1)	• Tacrolimus + sirolimus + MMF + steroids

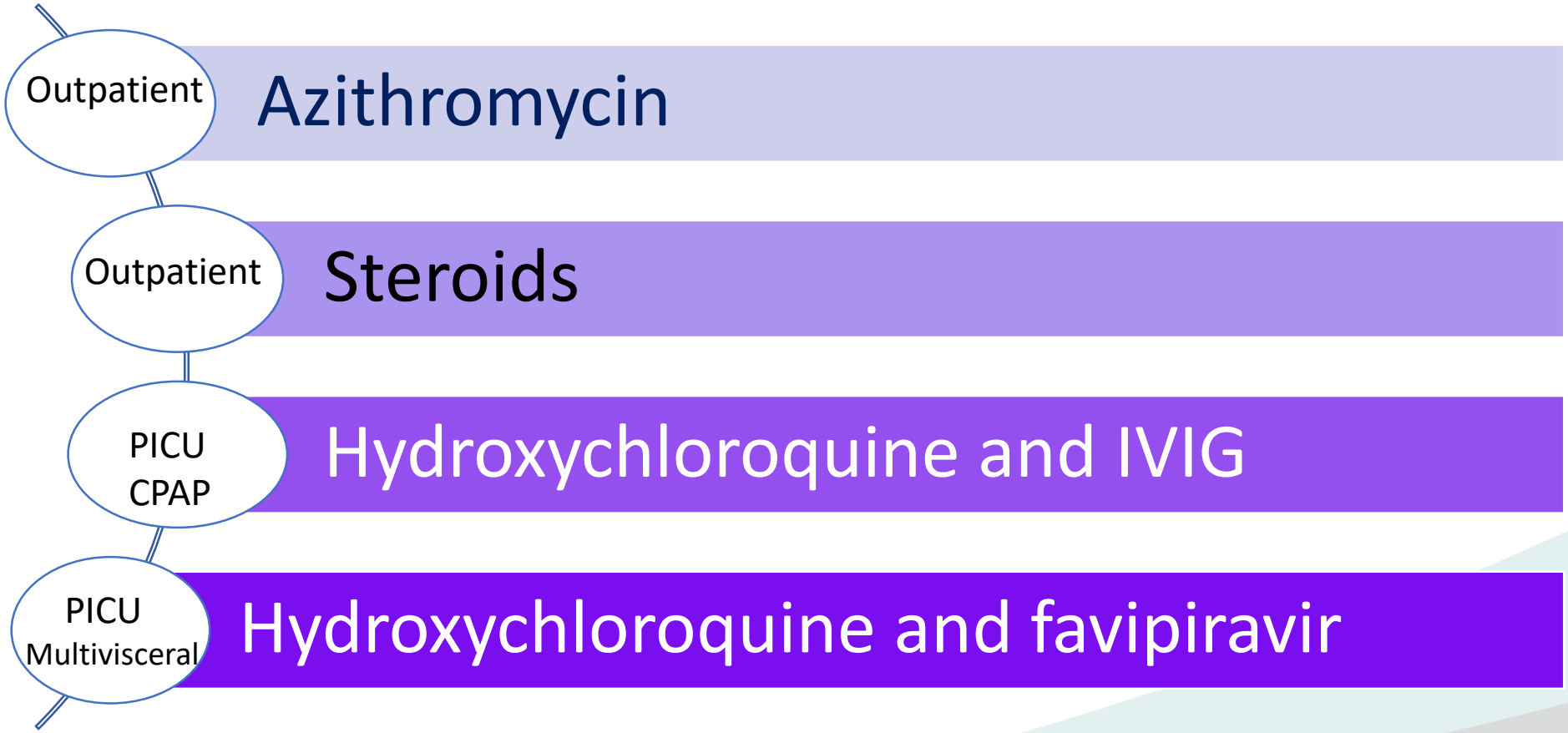
Highest level of care by baseline immunosuppression



Immunosuppression minimization: COVID+ post-transplant recipients



Directed therapies: COVID+ post-transplant recipients



Outcomes: COVID+ post-transplant recipients

Fully recovered (n=17)

Still active in clinical course (n=5)

No reported deaths

Summary: COVID+ post-transplant recipients

- No reported deaths or need for mechanical ventilation
- Higher degrees of immunosuppression didn't necessarily predict more severe COVID courses

Summary: SPLIT and NASPGHAN COVID-19 Registry

Registry link: https://is.gd/naspghansplitliversurvey

SPLIT COVID website: https://tts.org/initiatives/split-covid-19-post-liver-transplantation-data-collection-registry

NASPGHAN COVID website: https://naspghan.org/professional-resources/covid-19/

Re-Entry in Clinical Transplantation during a COVID Pandemic

Beau Kelly MD MBA FACS FAST

Surgical Director and Transplant Surgeon, DCI Donor Services

Joint Webinar

Society of Pediatric Liver Transplantation

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July 2020

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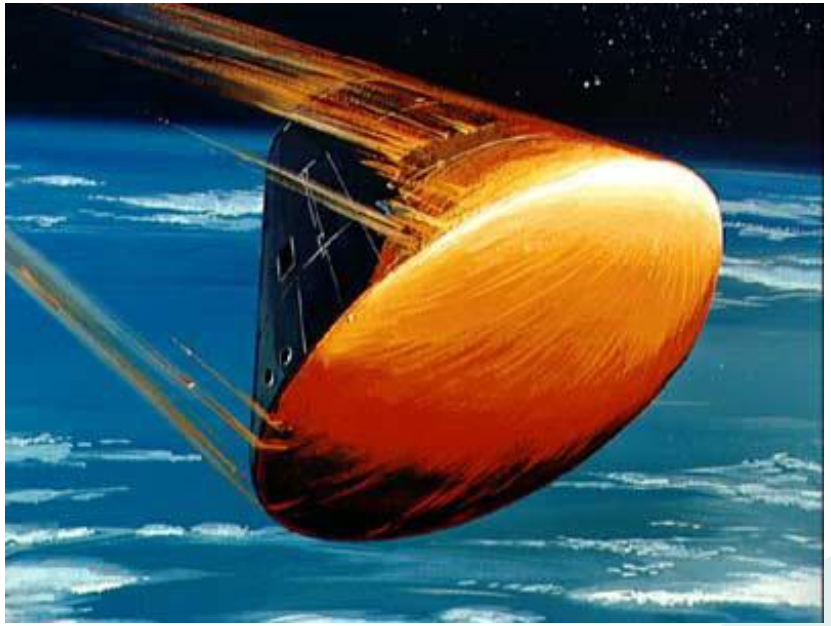
The Problem with Re-Entry



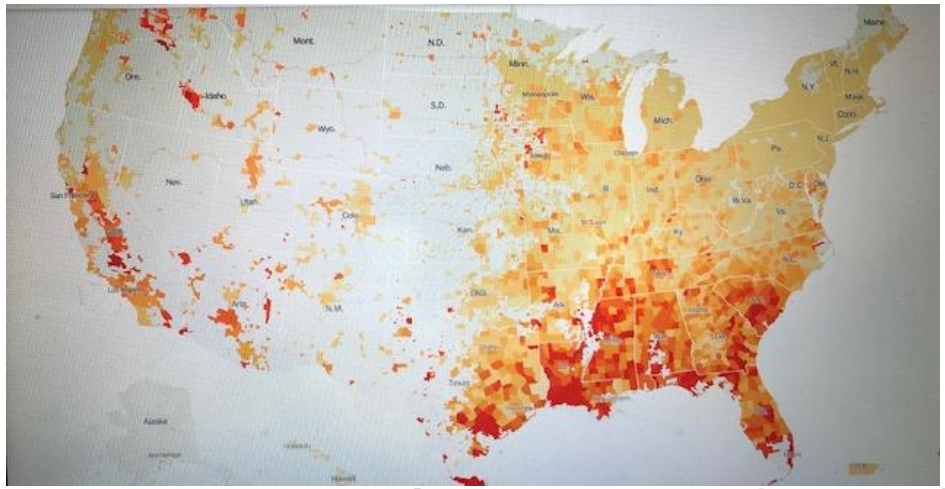
- Accurate triangulation of the present position
  - Separation of Signal from Noise
- The Attack Angle and Attitude
- “Ionization blackout”
  - Poor communication and messaging
- Balancing “G” forces and Environmental pressures
- Faith in developing consensus on a Program and Design

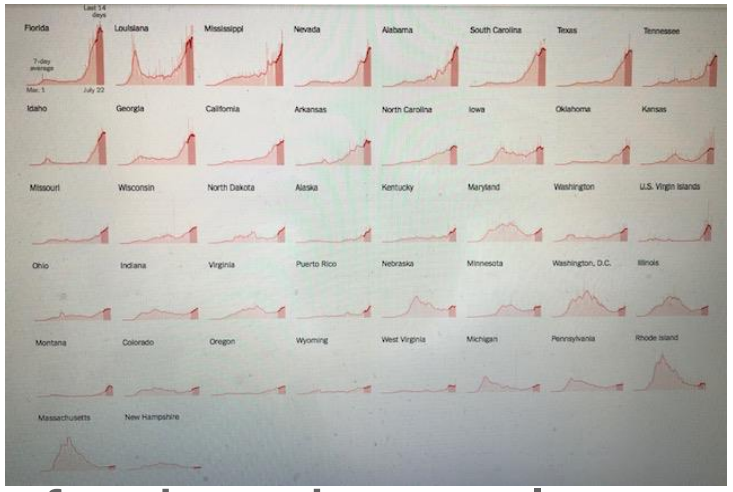
Just want to return to a safe and “normal” life!

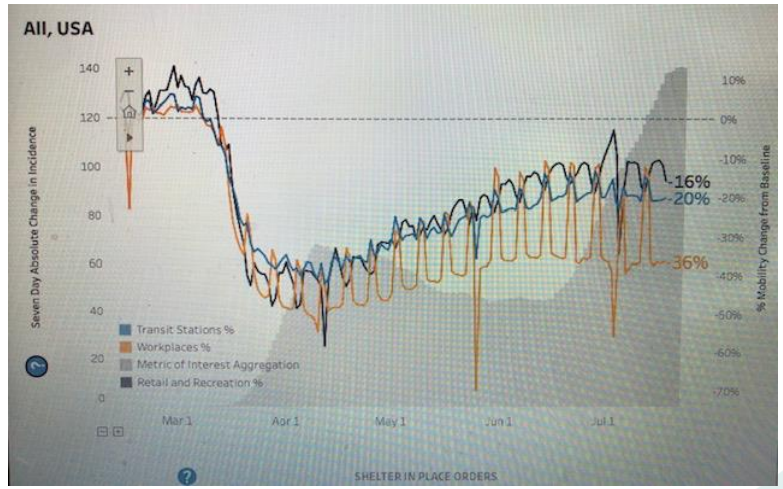
NASA Archives

The Signal and Noise- Nate Silver

Accurate Position and Communication?



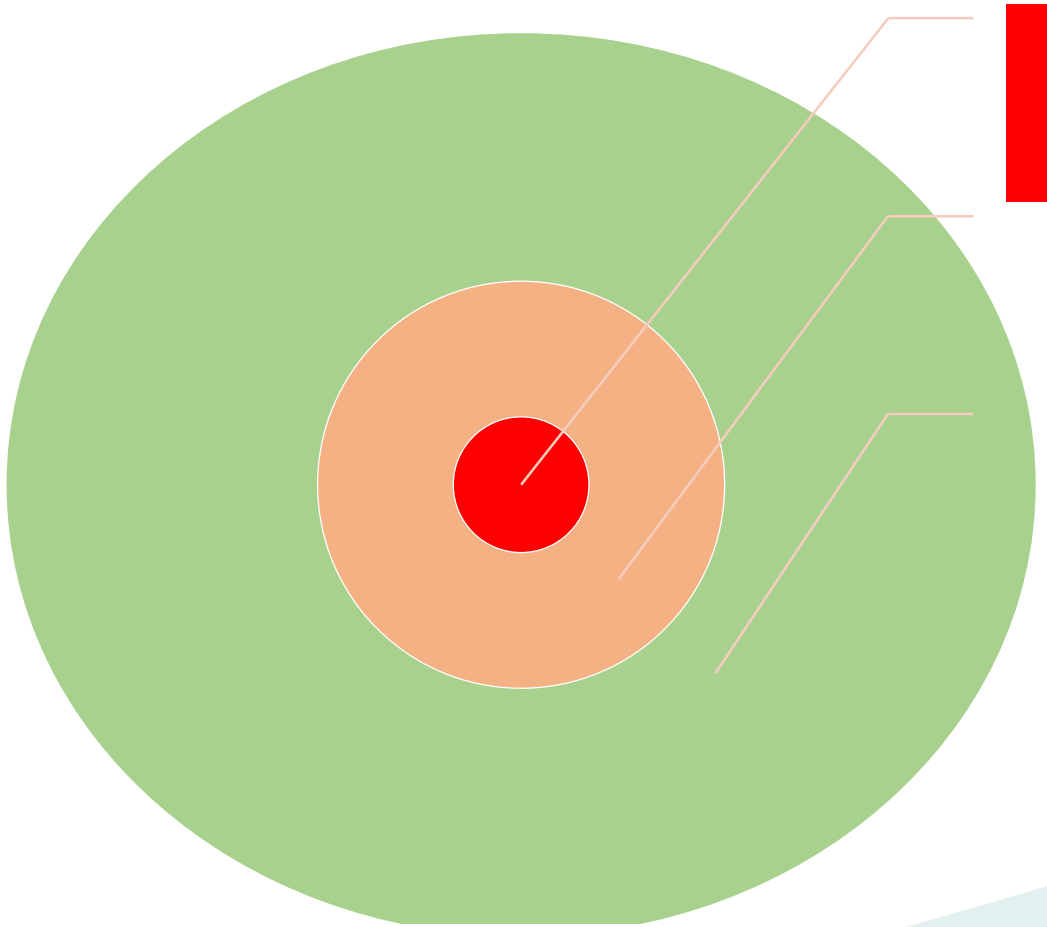




- Increasing rates of new infections in nearly every state!
- Resurgence of cases as mobility increases!
- ~10% Testing COVID +
- Masking, Social distancing, and SIP practices are not uniform

CDC.org

The Result!

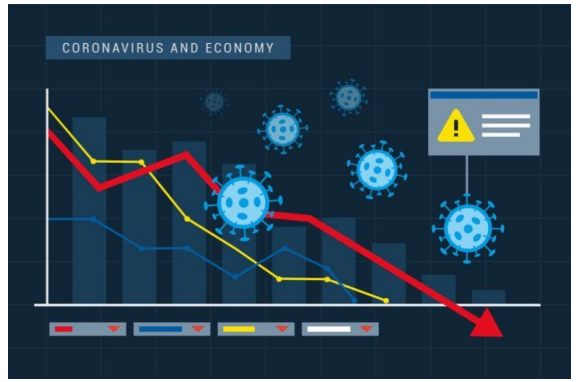


142.8K COVID-related deaths

4.9M COVID +

51.7M COVID tests

The “G” Forces and “Heat”



- Healthcare Economic Impact of COVID (Gravity)
  - GDP decline by 5% for every month of partial closure
  - US Hospital financial losses projected at $323B
  - Unemployment spike to 14.7%
    - Hospital employee layoffs, furloughs, and salary reductions
  - Interruption of Medical Education, Training programs, Hospital credentialing, and Certifications

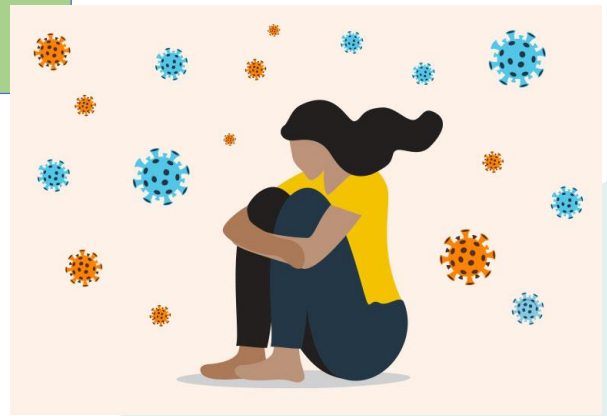
“Adversity introduces us to ourselves!” ~ Albert Einstein

AHA.org
APA.org

The Angle of Attack and Attitude

- Psychosocial Consequences of “Lock-down” and Social Distancing
  - Increased isolation
  - Increased anxiety and depression
  - Disruptions in family structure
  - Food insecurity and
  - Increased ACE’s – predictive determinants of health

- Contracted social programs
- Increased suicide risk



- Profound and Lasting Consequences of COVID
  - Despite a “miracle” COVID vaccine, attitudes will persist that shape how we live!

AHA.org
APA.org
ACE.org

Assumptions and Course Corrections

"When the student is ready, the teacher will appear!"

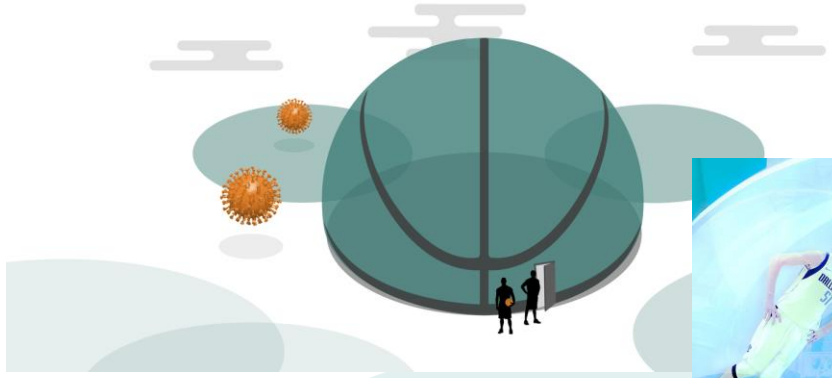
Way back in March we thought…

- Based on past experiences with H1N1, WNV, Influenza, and SARS:
  - Increased infection rates associated with extent of IS
  - Disproportionately high morbidity and mortality in TXP recipients
  - Vaccination yields protective Ab's
    - ?Herd immunity
- Testing will yield too many false positives and should be reserved for symptomatic patients.
  - >150 tests used. ~10 tests are FDA reviewed
- CMS deems transplant as an essential health service- Organ donation and transplantation move forward despite geographic variation in healthcare.

Knowing and Assessing Risk

- Risk of COVID transmission in Organ donation and Transplant across the entire process
  - No NBA “Bubble”
  - The Pro’s and Cons of moving forward with a liver donor and transplant

- Infection Risk Circles and Models
  - Cleveland Clinic Online Risk Calculator
  - CHIME
  - CDC Risk Calculator

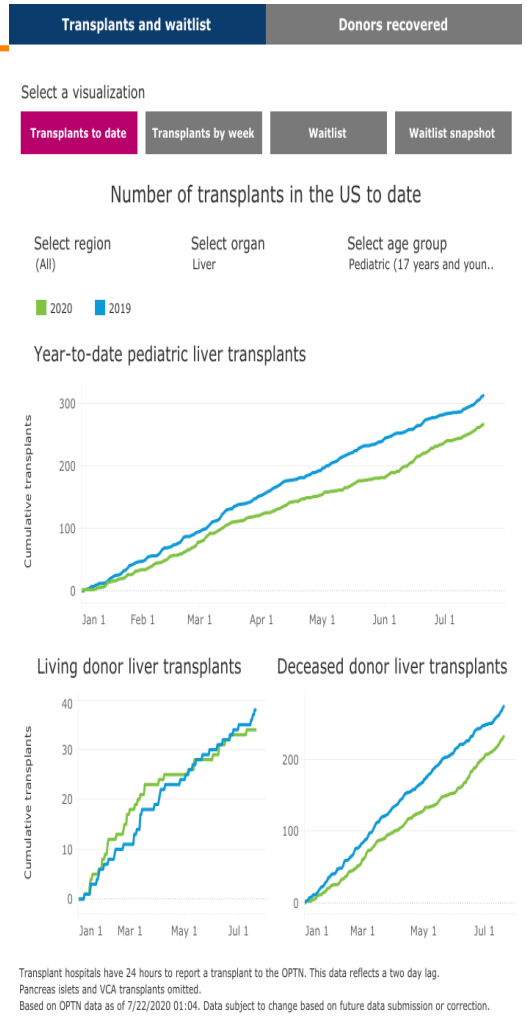


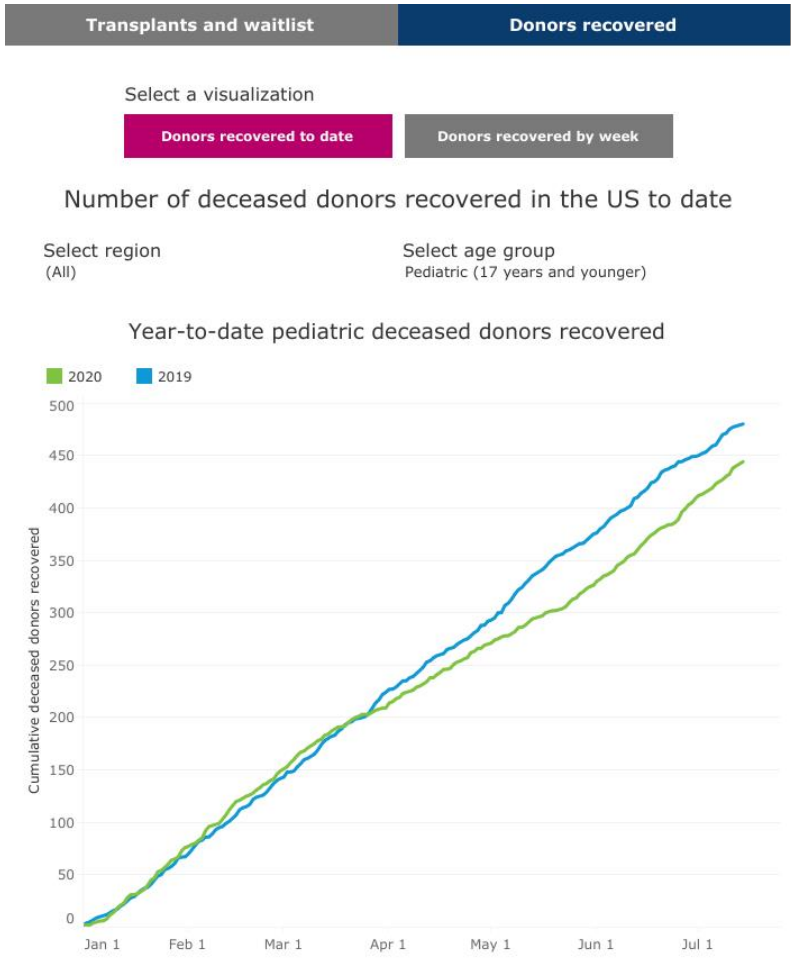
Relative Risk of Returning to Activity

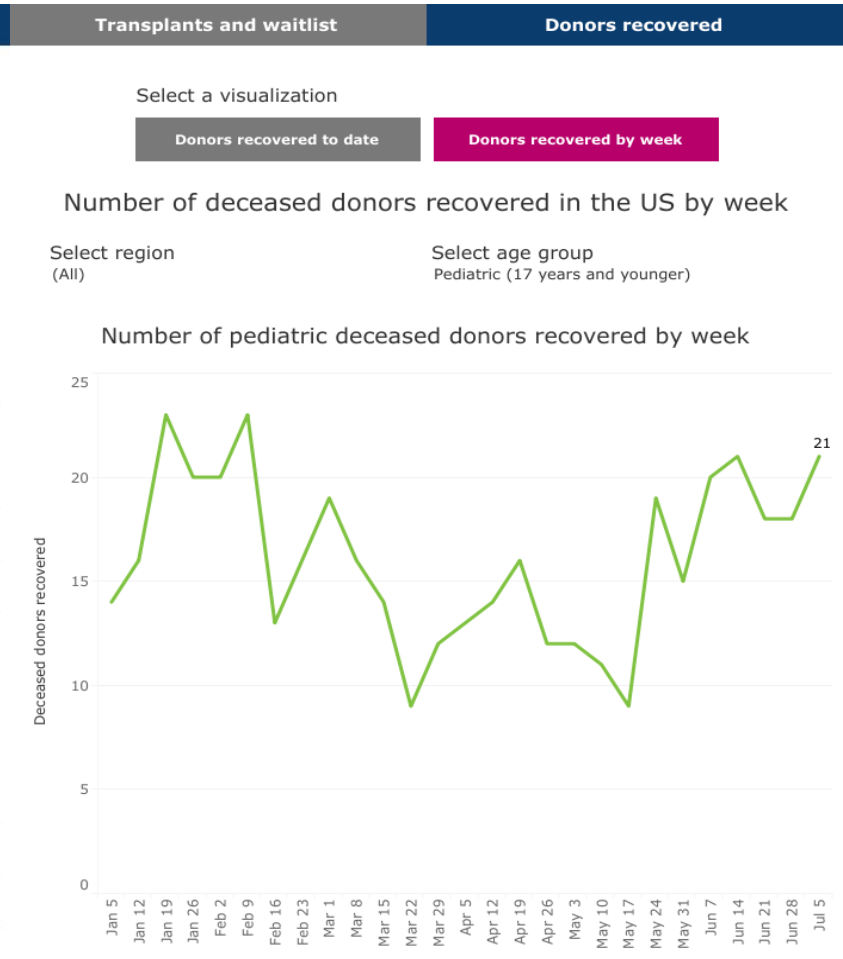
OPO and Liver Program Performance

NorCal
~140 liver donors
Decreased-DCDs, Living-donors

>32 MELD txp'd





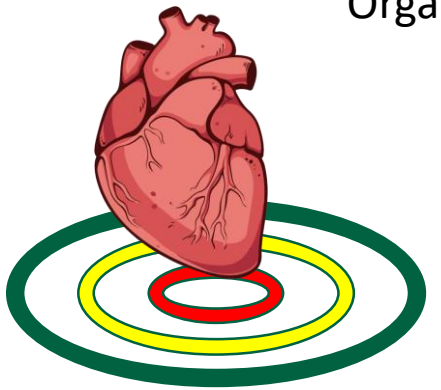


Assessing Aggregate Risk/Benefit

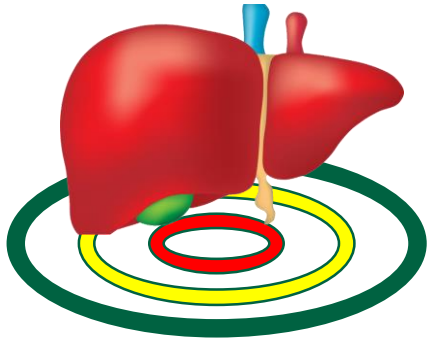
Organ Donor

Procurement Teams

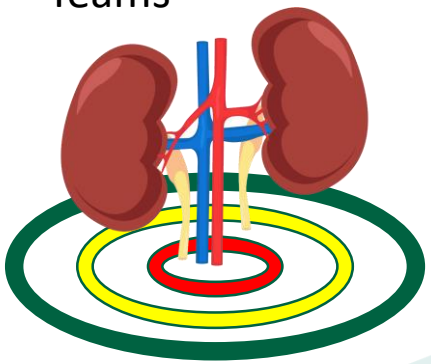
<u>US Measures</u>
Survey
screening
Temp Checks
PCR
IgM/IgG
Surveillance
Quarantine



Heart Recipient



Liver Recipient



Kidney Recipients

<u>Other countries</u>
mandatory serial testing
risk-stratified isolation algorithms

Stratifying Risk of Surgery- MeNTS Score

PROCEDURE SCORE	1	2	3	4	5
OR Time	<30 min	30-60 min	60-120 min	120- 180 min	>180 min
LOS	Outpt	<24 hours	24-48 hours	2-4 days	>4 days
Post-Op ICU Need	Unlikely	<5%	5-10%	10-25%	>25%
EBL	<10cc		0cc		
Surgical Team Size	1				
Intubation Probability	<1%				
Surgical Site	Oth		cal Abd		ic

DISEASE SCORE	1				
Effective Non-Op Option	No Option			Surgery	
Non-Op Option Resource/Exposure Risk	Significant				
Impact on Disease- 2wk Delay	Significant			orse	
Impact on Surgical Outcome- 2wk Delay	Significant			orse	
Impact on Disease- 6wk Delay	Significant			orse	
Impact on Surgical Outcome- 6wk Delay	Significant			orse	

PATIENT SCORE	1				
Age	<20				
Lung Disease (Asthma, COPD, CF)	Nor				
Obstructive Sleep Apnea	None				
CV Disease (HTN, CHF, CAD)	None	Minimal	Mild	Moderate	Severe
Diabetes	None		Mild	Oral Hypoglycemics Meds	On Insulin
Immunocompromised	None			Moderate	Severe
Covid-like Flu Symptoms	None				YES
Exposure to COVID (last 14 days)	None	Probably Not	Probably	More than Likely	YES Definitely

Ethical and Efficient estimation of resource scarcity and provider risk. Review and application of a stratified scoring system for Operations deferred and performed in March 2020

Higher Scores associated with:
Worse Outcomes
Increased Exposure Risk
Higher Resource Utilization

**Organ donation and liver transplant are at the highest end of scores*

Prachand , et. al, JACS, April, 2020

Fundamental Considerations for Re-Entry

- Clear Objectives based on available “data!”
- Clear and transparent risk stratification for every step along the path of the patient
  - Customized step-step plan from organ acceptance to patient discharge
  - Minimize risk of COVID exposure (Distancing, masks, hand hygiene, etc.)
  - Optimize Resources
  - Disaster planning team (administration, multidisciplinary team, community, and PARENTS/PATIENTS)
- Frequent Reassessment and Refinement of the Program and Design beyond financial considerations
- Advocate for government support for families in need
- Ask more Questions!

Return to School Special Considerations

- Liver transplant recipients >6months post-txp.
- Stable/weaning immunosuppression regimens.
- Stable/decreased community COVID incidence (<10% + test rates).
- OK for asymptomatic siblings to return to school.

- Return to athletic programs
- Return to after-school activities
- Return to Colleges
- Siblings living at-home w/ high-risk for exposure

- Recent liver transplant (3-6months)
- High-dose Immunosuppression regimen
- Rapidly increasing COVID+ (Hotspots!)
- Serious medical conditions or actively managed surgical complications
- Any COVID-like symptoms or acute respiratory illness
- School system does not have adequate resources to foster safe participation

*All decisions and options should be discussed with patient-specific transplant professionals!

Acknowledgements

- Special Thanks
- Better _____ is on the other side of this adversity
- Not a “re-entry” into the normal of 2019. Those strategies and practices are inadequate for the weight, challenges and goals of today.

- Rather a Re-emergence!

Panel Discussion Q&A

Please submit any remaining questions to the Q&A Chat at this time!

Joint Webinar

Society of Pediatric Liver Transplantation

The Transplantation Society a Section of

AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

NASPGHAN

Acknowledgements

- Drs. Rohit Kohli & Daniel Leung and the AASLD Pediatric Liver Disorders Special Interest Group
- Dr. Jorge Bezerra and the AASLD COVID-19 Clinical Oversight Subcommittee
- Drs. Karen Murray, Benjamin Gold & Mercedes Martinez and the NASPGHAN Leadership
- Drs. Vicky Ng, Beau Kelly & Steven Lobritto and the SPLIT Leadership
- AASLD Staff that helped in the organization and production of this webinar