Grand Rounds: Long-Haul COVID-19

Presented at the COVID-19 Clinical Case Conference #24

28 APR 2021
1600 EDT

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- No operational plans specifics
  - No who, what, where, when, or how
  - Carefully aggregate any active duty information
- No names of units, FOBs, or locations
- No names of patients, personnel and/or their families
- No discussion of security or evacuation processes
- No identification of nationalities
- No statements regarding unit morale

➢ HIPAA

- *DO NOT Discuss any PHI or PII*

Objectives

- The objective of the JTS-hosted **DoD COVID-19 Clinical Case Conference** is to establish a recurring venue for bidirectional exchange of information pertaining to the key elements of the ***clinical system*** working to optimize the MHS response to the COVID-19 pandemic, and the survival and recovery of those effected by the virus.
- This conference features updates from military experts in COVID-related clinical care, education and research as well as those experienced in performance improvement processes including development of registries and evidence-based clinical practice guidelines.

Agenda

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Introduction - Kevin Chung

COVID-19 Research Update - CAPT Tim Burgess

COVID-19 Registry Update – Col Stacy Shackelford

Long-Haul COVID - Pulmonary Perspective - Dr Michael Morris

Long-Haul COVID - Cardiac Perspective - MAJ Emilio Fentanes

Long-Haul COVID - Neuro/Psychiatric Perspective - LTC Shannon Ford

Long-Haul COVID – Acute Care Clinic, BAMC – Dr Alison Wiesenthal

Q&A

Resources on JTS Website: www.JTS.amedd.army.mil

Interactive Resources: www.DeployedMedicine.com and Mobile Application

J&J/Janssen COVID-19 vaccine & thrombosis with thrombocytopenia syndrome (TTS)

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Recommendations for Clinicians

- ***Maintain a high index of suspicion*** for symptoms that might represent serious thrombotic events or thrombocytopenia in patients who have recently received the J&J COVID-19 vaccine, including ***severe headache***, ***backache***, ***new neurologic symptoms***, ***severe abdominal pain***, ***shortness of breath***, ***leg swelling***, ***petechiae***, or ***new or easy bruising***. Obtain **platelet counts** and screen for evidence of ITP
- If thrombotic event and thrombocytopenia after J&J COVID-19 vaccine, evaluate initially with screening PF4 ELISA assay as for autoimmune HIT. Consultation with a hematologist is strongly recommended
- ***Do not*** treat patients with TTS following receipt of J&J COVID-19 vaccine with ***heparin***, unless HIT testing is negative
- If HIT testing is positive or unable to be performed in suspected TTS, non-heparin anticoagulants and high-dose IVIG should be strongly considered
- ***Report adverse events to VAERS***

- *DHA Immunization Healthcare Division is lead SME for MHS*
- *CDC HAN: Cases of Cerebral Venous Sinus Thrombosis with Thrombocytopenia after Receipt of the Johnson & Johnson COVID-19 Vaccine* https://emergency.cdc.gov/han/2021/han00442.asp
- *American Society of Hematology recs:* https://www.hematology.org/covid-19/vaccine-induced-immunethrombotic-thrombocytopenia
- *Updated Recommendations from Advisory Committee on Immunization Practices for Use of Janssen (Johnson & Johnson) COVID-19 Vaccine After Reports of Thrombosis with Thrombocytopenia Syndrome Among Vaccine Recipients. MMWR Morb Mortal Wkly Rep. ePub: 27 April 2021. DOI:* http://dx.doi.org/10.15585/mmwr.mm7017e4
- ***DHA has resumed***. *Updated EUA fact sheet (MMQC-21-1256_1)* https://www.fda.gov/media/146305/download

IDCRP COVID-19 Research FY20-FY21

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Interventional studies

- ACTT 1 – 4: Evaluation of remdesivir (EUA) and several immunomodulators (baricitinib, interferon, steroids)
- STORMCHASER: Evaluation of post-exposure prophylaxis intramuscular monoclonal antibody combination

IDCRP COVID-19 Research FY20-FY21

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Observational studies

- CAMP-NYC: Evaluation of SARS-CoV-2 attack rate in NYC COVID-19 field hospital response (published MMWR)
- USNS COMFORT: Evaluation SARS-CoV-2 attack rate in USNS Comfort COVID-19 deployment to NYC (published OFID)
- EPICC: Short and long term COVID-19 outcomes; vaccine and re-infection; breakthrough risks and phenotype; correlates and durability of vaccine and natural immunity; post-acute sequelae; clinical significance of variants of concern; genotype-phenotype associations; mechanisms of severe COVID
- PASS: SARS-CoV-2 seroincidence in MTF HCW; vaccine immune durability/magnitude and correlates thereof
- TOSCANA: Characterized risk and risk factors of SARS-CoV-2 seroconversion at USNA
- PISCES: SARS-CoV-2 and other ARI epidemiology in USUHS affiliates in a time of vaccine roll-out
- Modeling and simulation: non-pharmaceutical intervention effectiveness; recombination emergence risk

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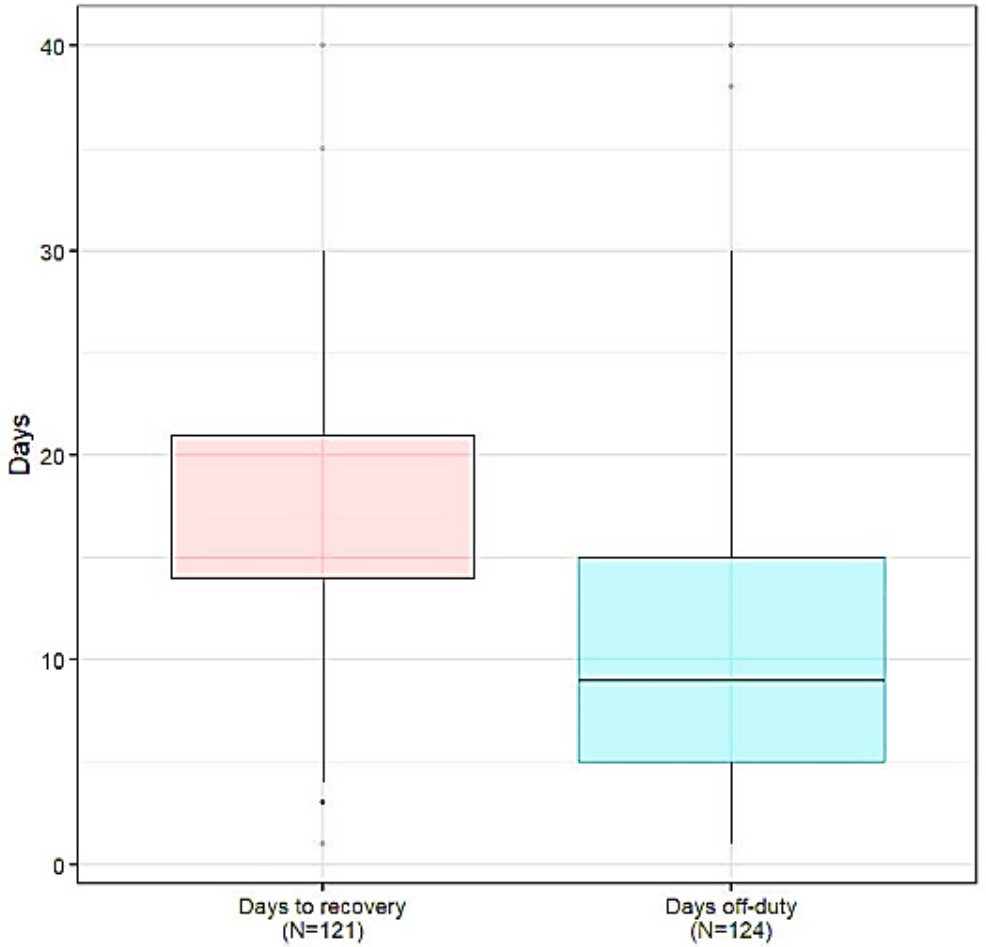
Epidemiology, Immunology & Clinical Characteristics of COVID-19 (EPICC) IDCRP-085

Performance Improvement (PI): Dr. Brian Agan

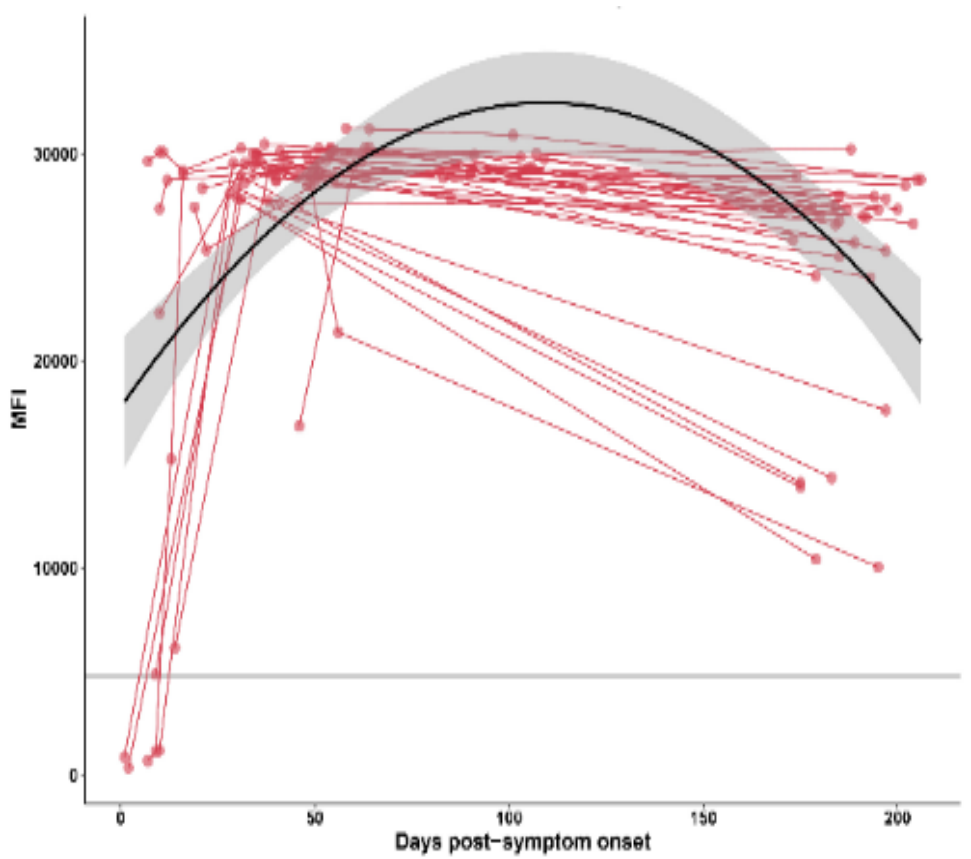
EPICC

- Functional impact of COVID-19 in active-duty service members
  - 25% reported requiring > 15 days off duty
- Vaccine breakthrough infections (VBI)
  - Post vaccine infections are being observed in young healthy ADSM
  - Severe disease not seen with VBI in EPICC cohort, but some cases describe moderate to severe symptoms, activity limitations
  - Live virus shedding noted
- Variants of concern are circulating in the MHS
  - B.1.429 detected in several MTFs with severe outcomes



EPICC

- Immunological and biomarker correlates of severity
  - ❑ Interferon autoantibodies and innate immune deficiency noted in some EPICC subjects with severe outcomes
  - ❑ Distinct early T cell activation signatures of severe COVID-19
- Patterns and correlates of long-term immunity
  - ❑ Persistence of binding IgG to 12 months, but waning of neutralizing antibodies; age and severity correlate
- Thrombotic complications of SARS-CoV-2 in the MHS include DVT, PE, coronary syndromes and stroke



EPICC: assessing post-acute sequelae of COVID-19

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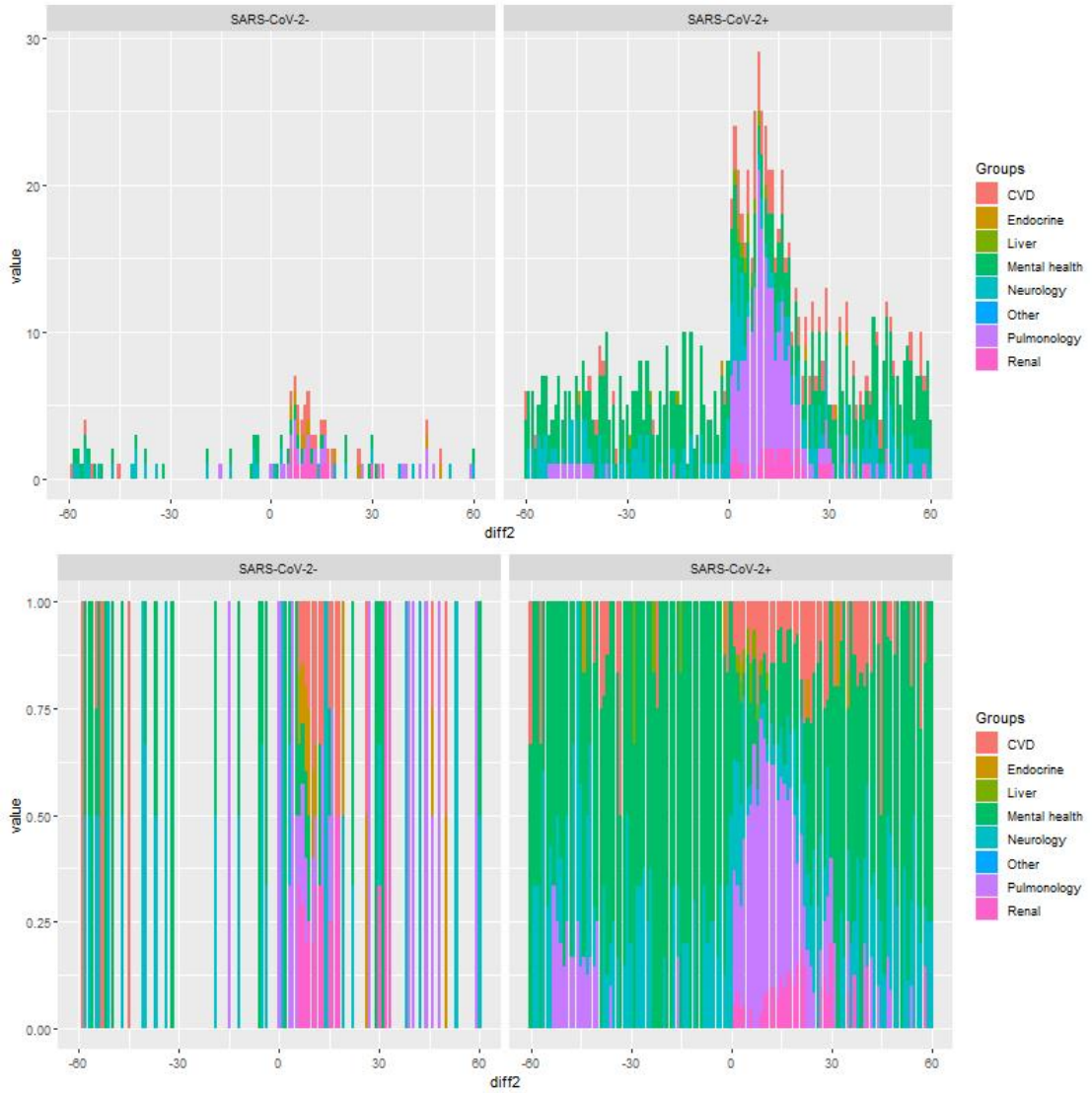
Active duty SARS-2+, long-term symptoms

Sx / Days PSO	<30 (N=33)	30-59 (N=65)	60-119 (N=75)	120-179 (N=87)	180+ (N=89)	Total (N=349)
Long-term cough						
None	25 (75.8%)	58 (89.2%)	68 (90.7%)	81 (93.1%)	81 (91.0%)	313 (89.7%)
Mild-moderate	**8 (24.2%)**	**7 (10.8%)**	**5 (6.7%)**	**6 (6.9%)**	**8 (9.0%)**	**34 (9.7%)**
Severe	**0 (0.0%)**	**0 (0.0%)**	**2 (2.7%)**	**0 (0.0%)**	**0 (0.0%)**	**2 (0.6%)**
Long-term wheezing						
None	32 (97.0%)	62 (95.4%)	70 (93.3%)	83 (95.4%)	85 (95.5%)	332 (95.1%)
Mild-moderate	**1 (3.0%)**	**3 (4.6%)**	**4 (5.3%)**	**4 (4.6%)**	**3 (3.4%)**	**15 (4.3%)**
Severe	**0 (0.0%)**	**0 (0.0%)**	**1 (1.3%)**	**0 (0.0%)**	**1 (1.1%)**	**2 (0.6%)**
Long-term difficulty breathing						
None	29 (87.9%)	57 (87.7%)	69 (92.0%)	80 (92.0%)	79 (88.8%)	314 (90.0%)
Mild-moderate	**4 (12.1%)**	**8 (12.3%)**	**4 (5.3%)**	**6 (6.9%)**	**9 (10.1%)**	**31 (8.9%)**
Severe	**0 (0.0%)**	**0 (0.0%)**	**2 (2.7%)**	**1 (1.1%)**	**1 (1.1%)**	**4 (1.1%)**
Long-term exercise intolerance						
None	28 (84.8%)	59 (90.8%)	66 (88.0%)	79 (90.8%)	81 (91.0%)	313 (89.7%)
Mild-moderate	**4 (12.1%)**	**6 (9.2%)**	**5 (6.7%)**	**5 (5.7%)**	**8 (9.0%)**	**28 (8.0%)**
Severe	**1 (3.0%)**	**0 (0.0%)**	**4 (5.3%)**	**3 (3.4%)**	**0 (0.0%)**	**8 (2.3%)**

New diagnostic codes, pre- and post-COVID onset



Incident MDR signal by diagnostic group, pre- and post- COVID onset
Left total EPICC cohort, SARS-2(-) left panel, SARS-2(+) right panel

Next steps: detailed analyses of specific diagnoses, longer-term follow-up:
(1) Via EPICC modules – Pulmonary, Cardiac, Neuro-cognitive

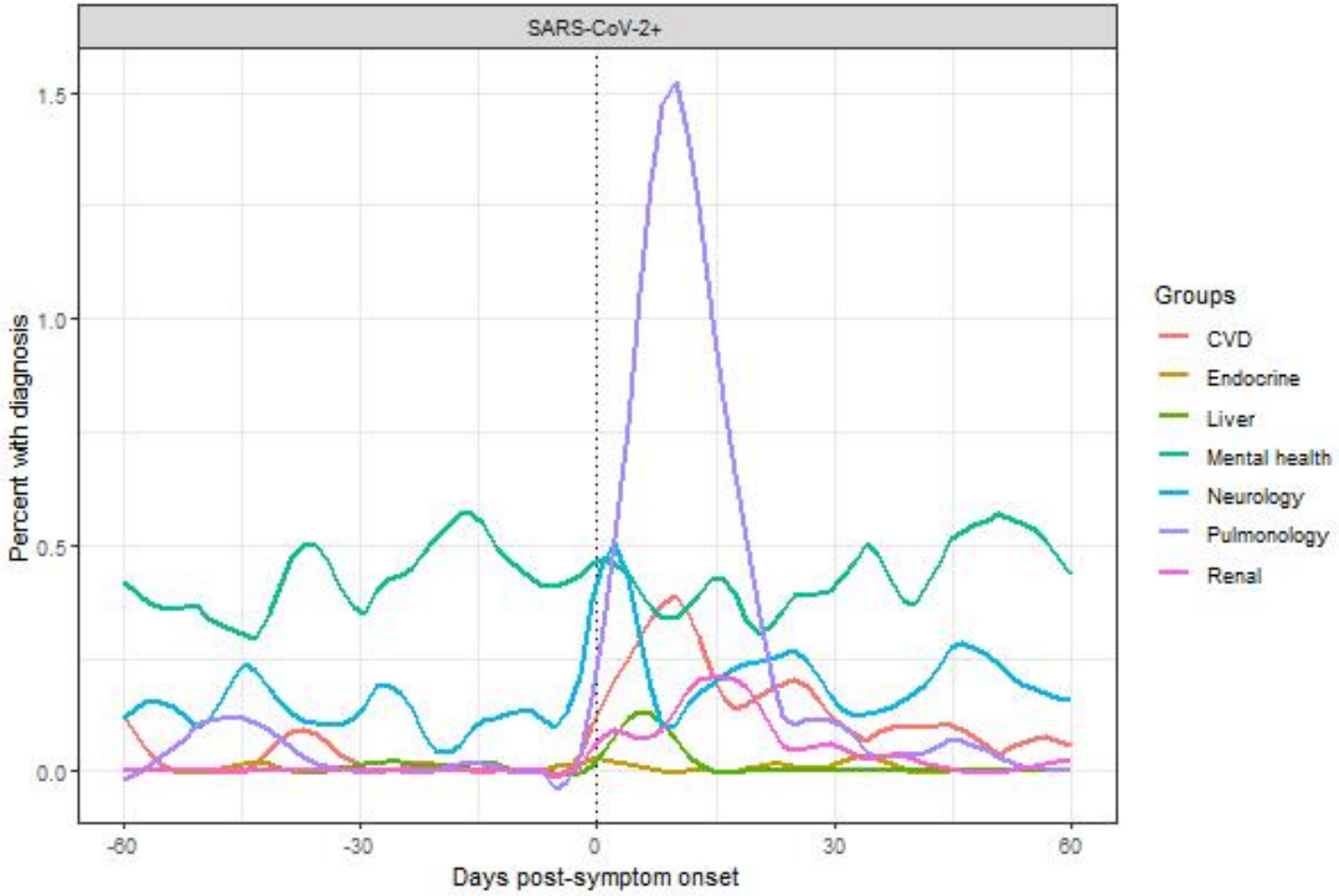
(2) In conjunction with JTS, via Military Covid-19 Registry Analysis Protocol (M-RAP)

New diagnostic codes, pre- and post-COVID onset

Incident MDR signal by diagnostic group, pre- and post- COVID onset
Right: Active duty, SARS-2+ only

Next steps: detailed analyses of specific diagnoses, longer-term follow-up:
(1) Via EPICC modules – Pulmonary, Cardiac, Neuro-cognitive

(2) In conjunction with JTS, via Military COVID-19 Registry Analysis Protocol (M-RAP)



Prospective Assessment of SARS-CoV-2 Seroconversion

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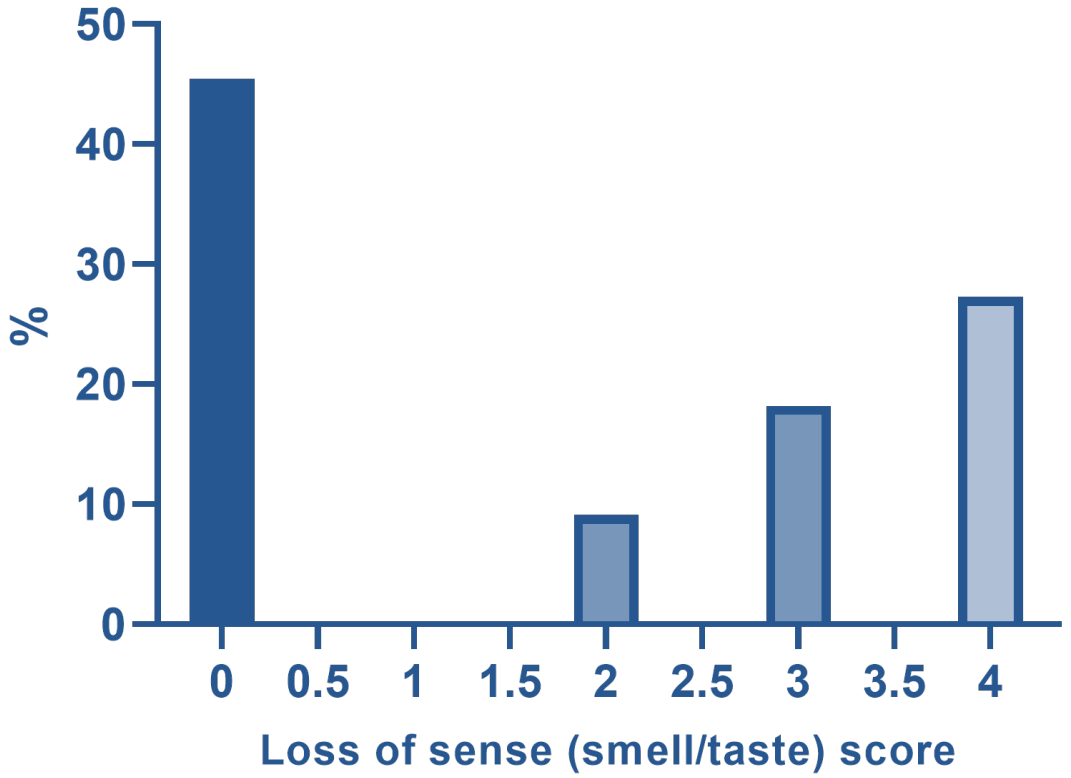
IDCRP-126 // P:I Prof. Ed Mitre

Prospective assessment of symptoms demonstrates that completely asymptomatic SARS-CoV-2 infection is rare in a cohort of healthcare workers.

- Loss of sense/taste is the symptom domain that most differentiates SARS-CoV-2 from other acute illnesses



Prospective Assessment of SARS-CoV-2 Seroconversion

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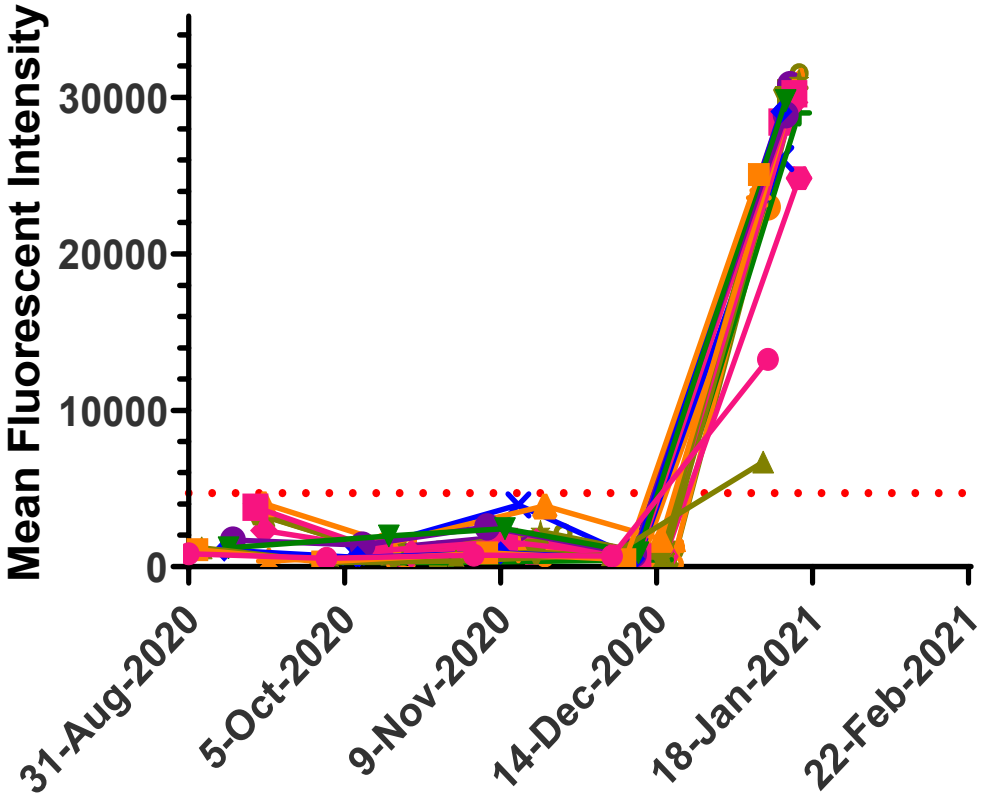
SARS-CoV-2 IgG levels on the first subjects to receive two BNT162b2 vaccinations show robust vaccine responses, but variability noted.

- Preliminary analyses suggest that baseline antibody responses to seasonal coronaviruses does not boost nor impede early SARS-CoV-2 vaccine-induced antibody responses
- Post-vaccination symptoms do not correlate with short term humoral immune response



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COVID-19 Registry Update

Col Stacy A Shackelford, Director, Joint Trauma System,
Defense Health Agency Combat Support

COVID-19 Positive Hospitalized Patients

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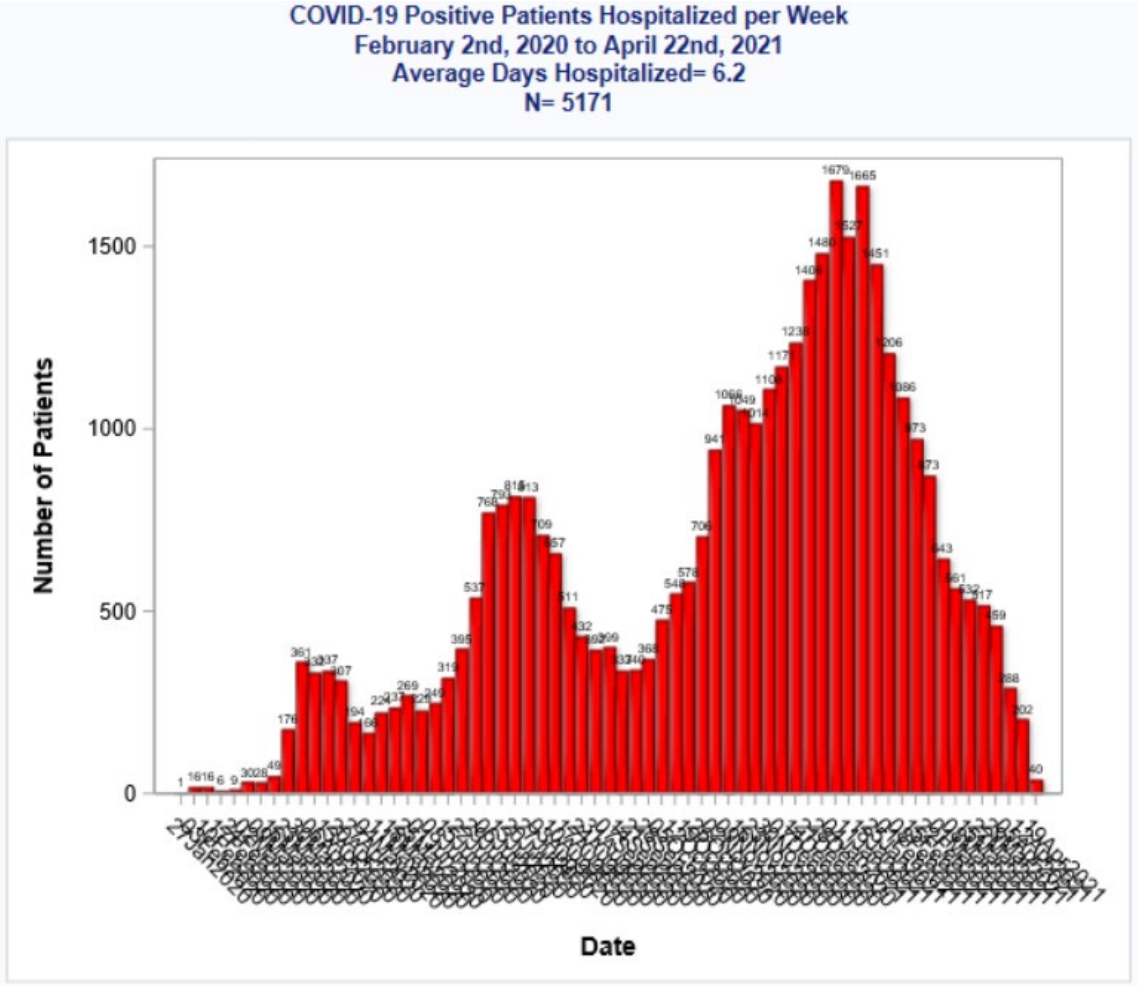

Trends in total hospital days and ICU days

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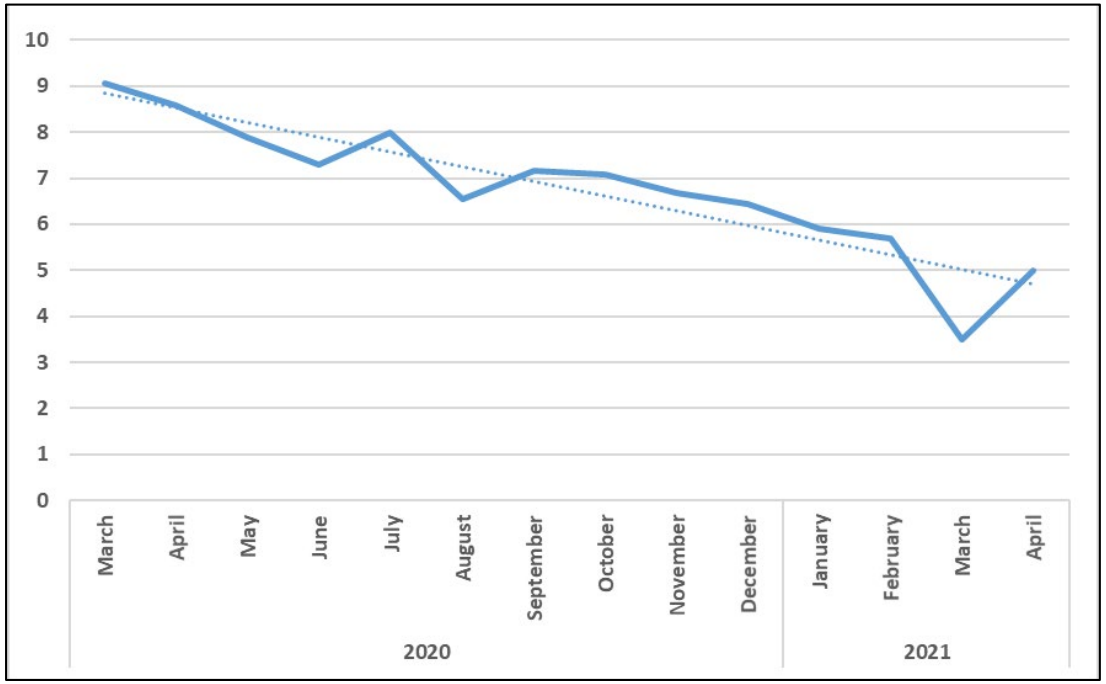
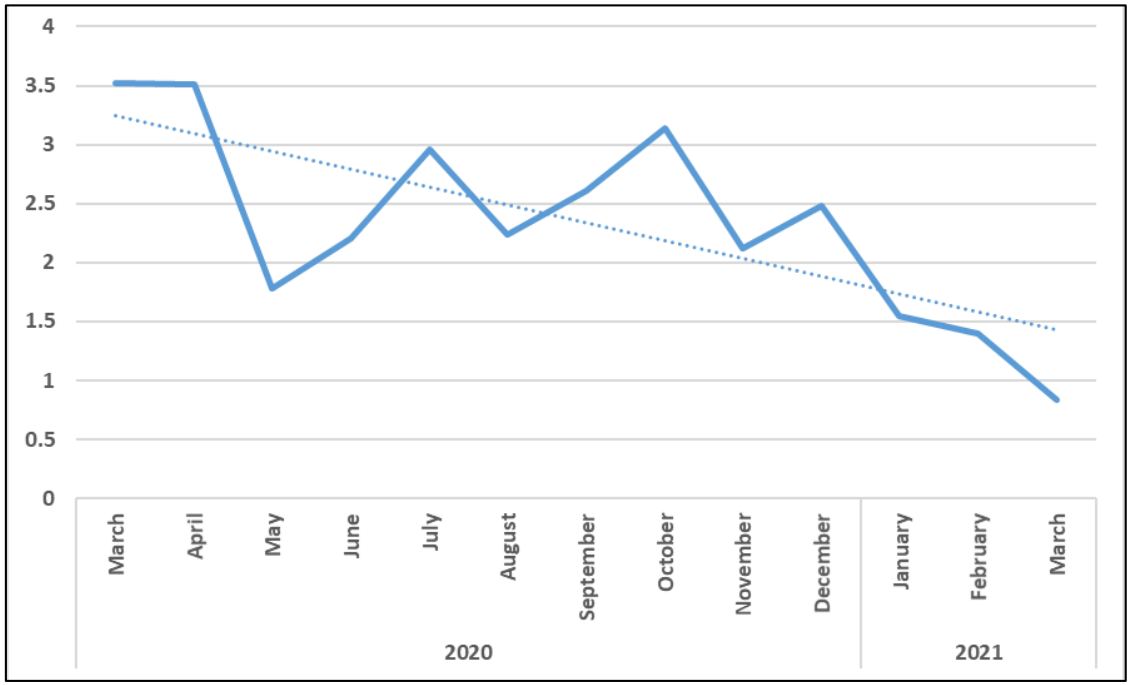
Total hospital days



ICU days

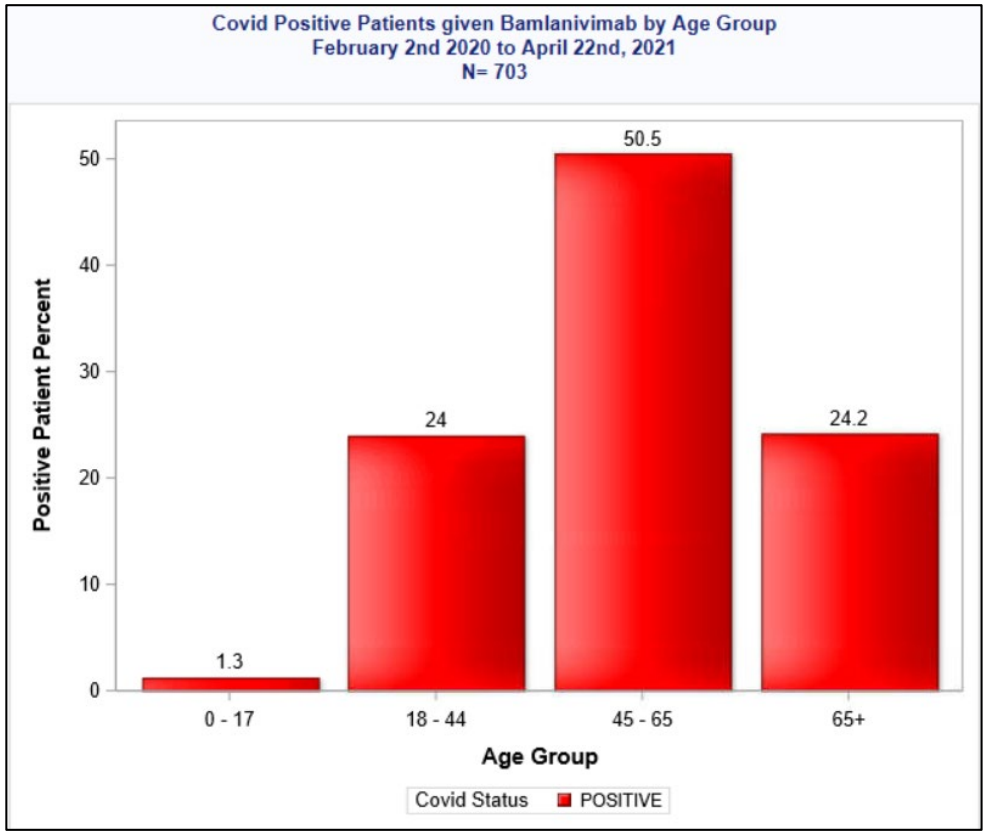


N=2,612 inpatients in registrar-abstracted population with detailed chart review, 2 Feb 2020-22 Apr 2021

Monoclonal Antibody Usage

- 703 COVID-19 positive patients have received monoclonal antibody treatment as of 22 Apr 2021
- 62 patients are Active Duty
- Ages of patients range from 14-89
- Average days after COVID-19 diagnosis to monoclonal antibody (McAb) usage is 2.7 days
- 42 of 703 (6%) of McAb recipients were admitted to a hospital

Average days after COVID-19 diagnosis to monoclonal antibody usage of hospitalized patients is 3.5 days, compared to 2.6 days for patients who were never admitted to the hospital



Percent of Inpatients Receiving CCP

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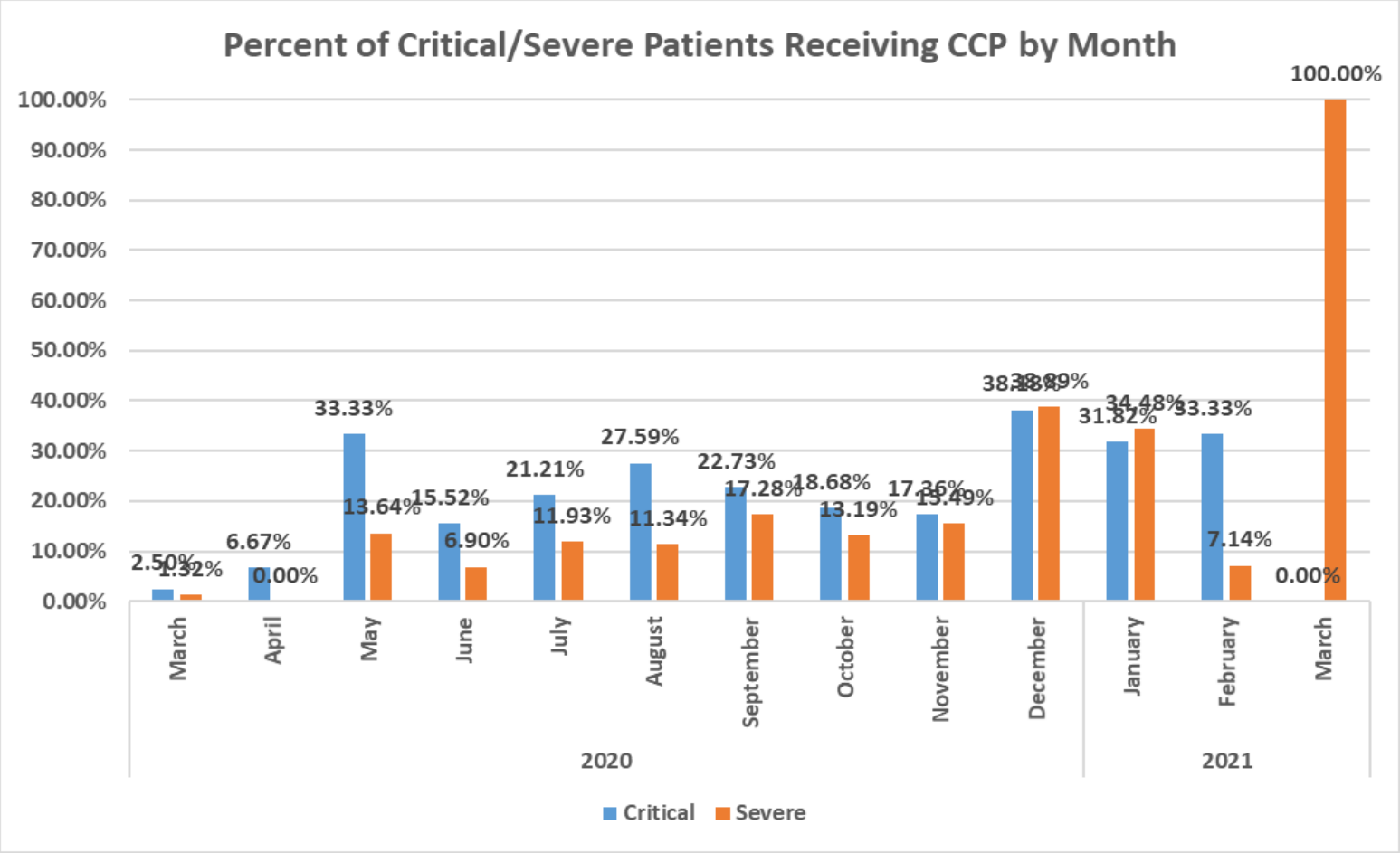
Percent of inpatients receiving CCP by month and severity



Percent of Inpatients Receiving Remdesivir

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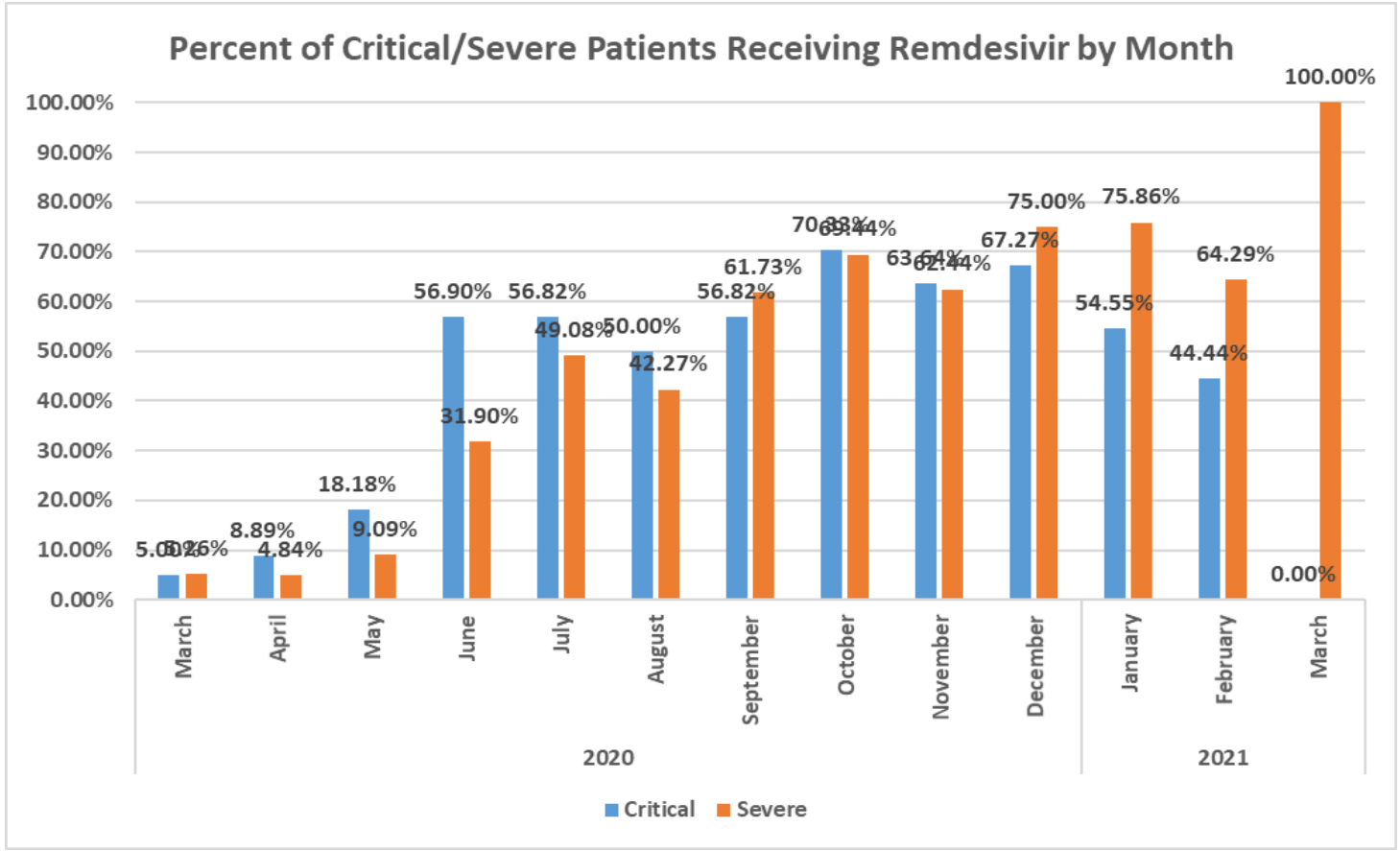
Percent of inpatients receiving Remdesivir by month and severity



Percent of Inpatients Receiving Glucocorticoids

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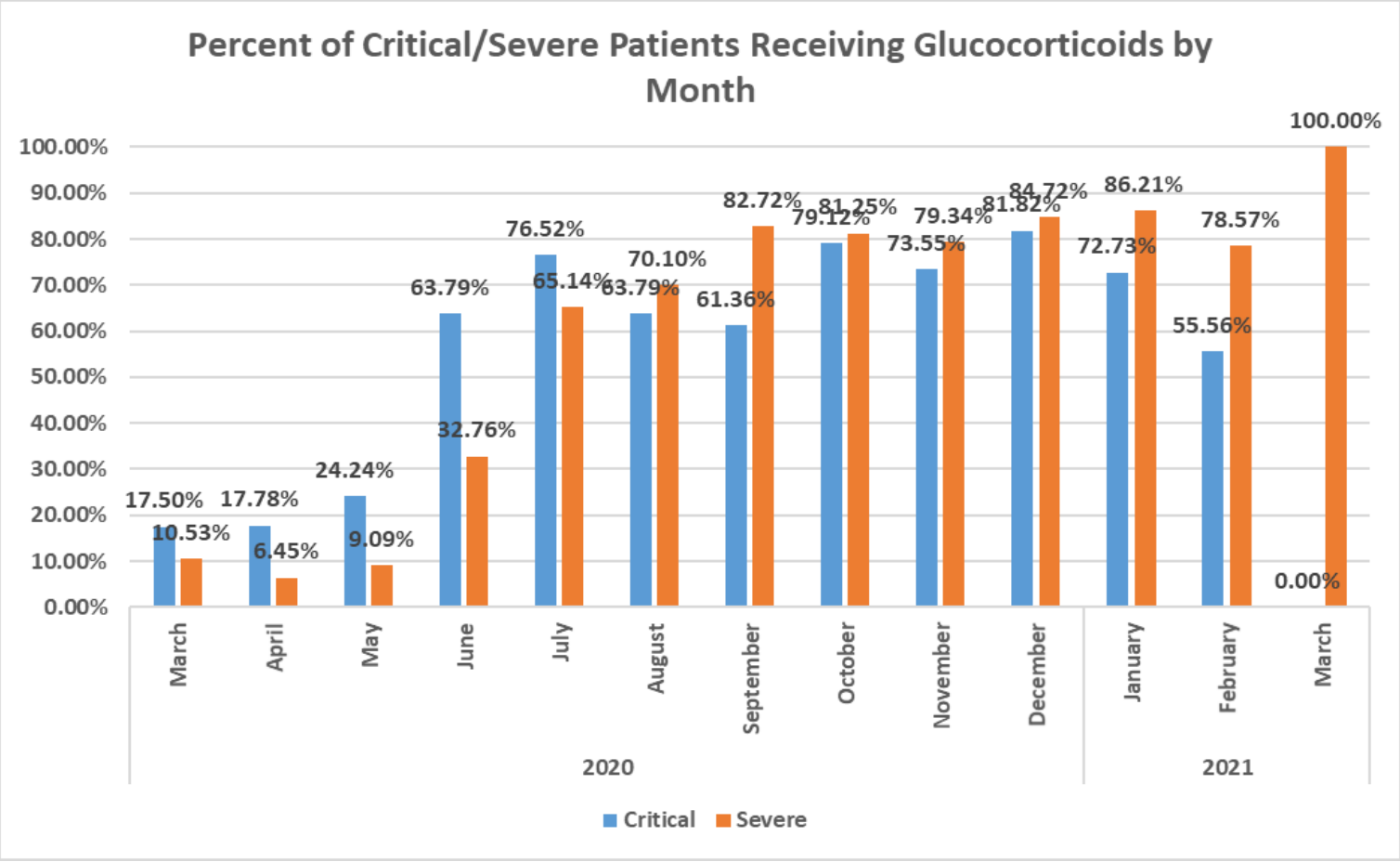
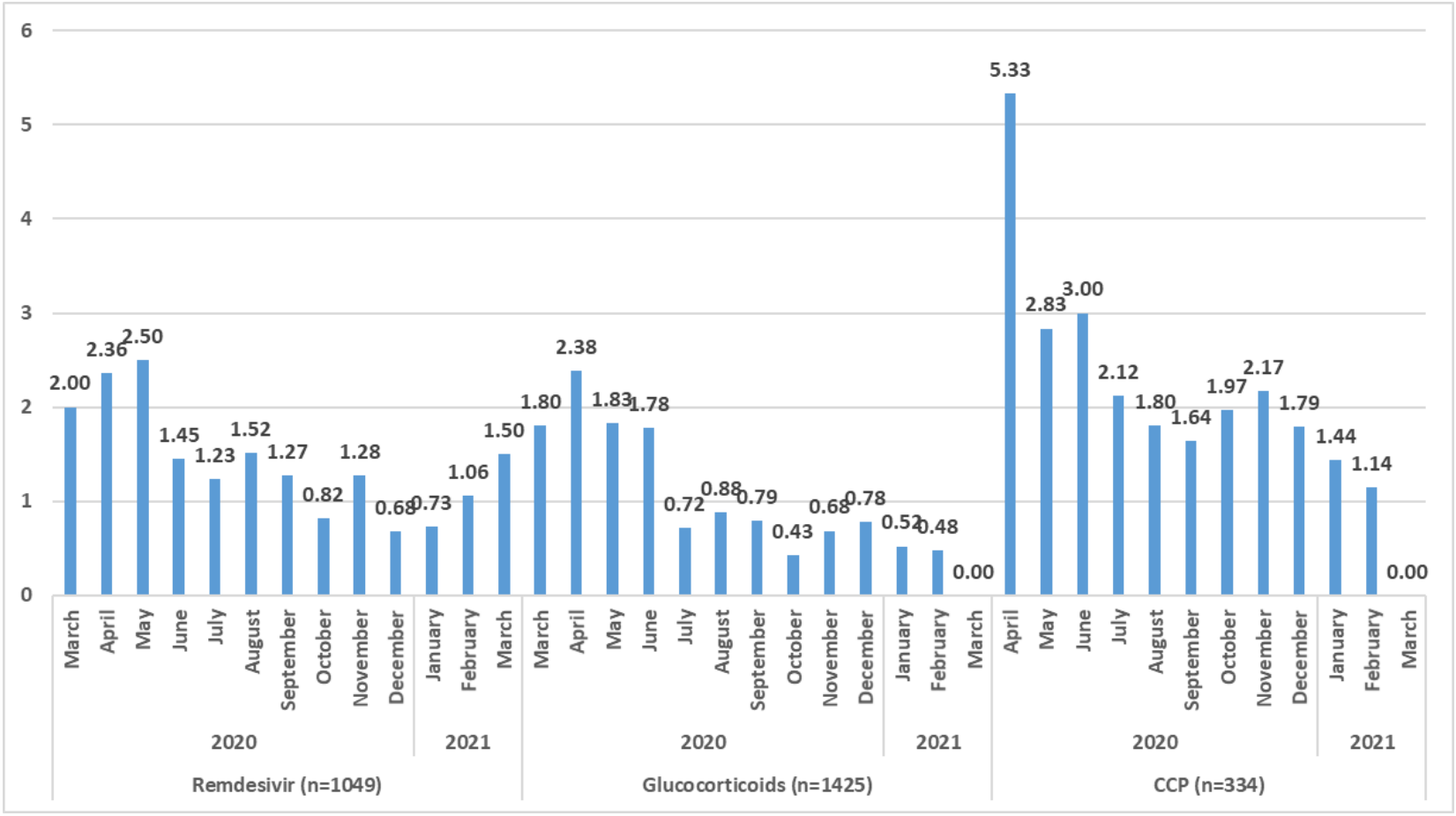
Percent of inpatients receiving Glucocorticoids by month and severity



Days to Treatment Delivery, Post Hospital Admission



N=6,296 patients in registrar-abstracted population with detailed chart review, 2 Feb 2020 - 19 Apr 2021

Performance Improvement Documentation Metrics

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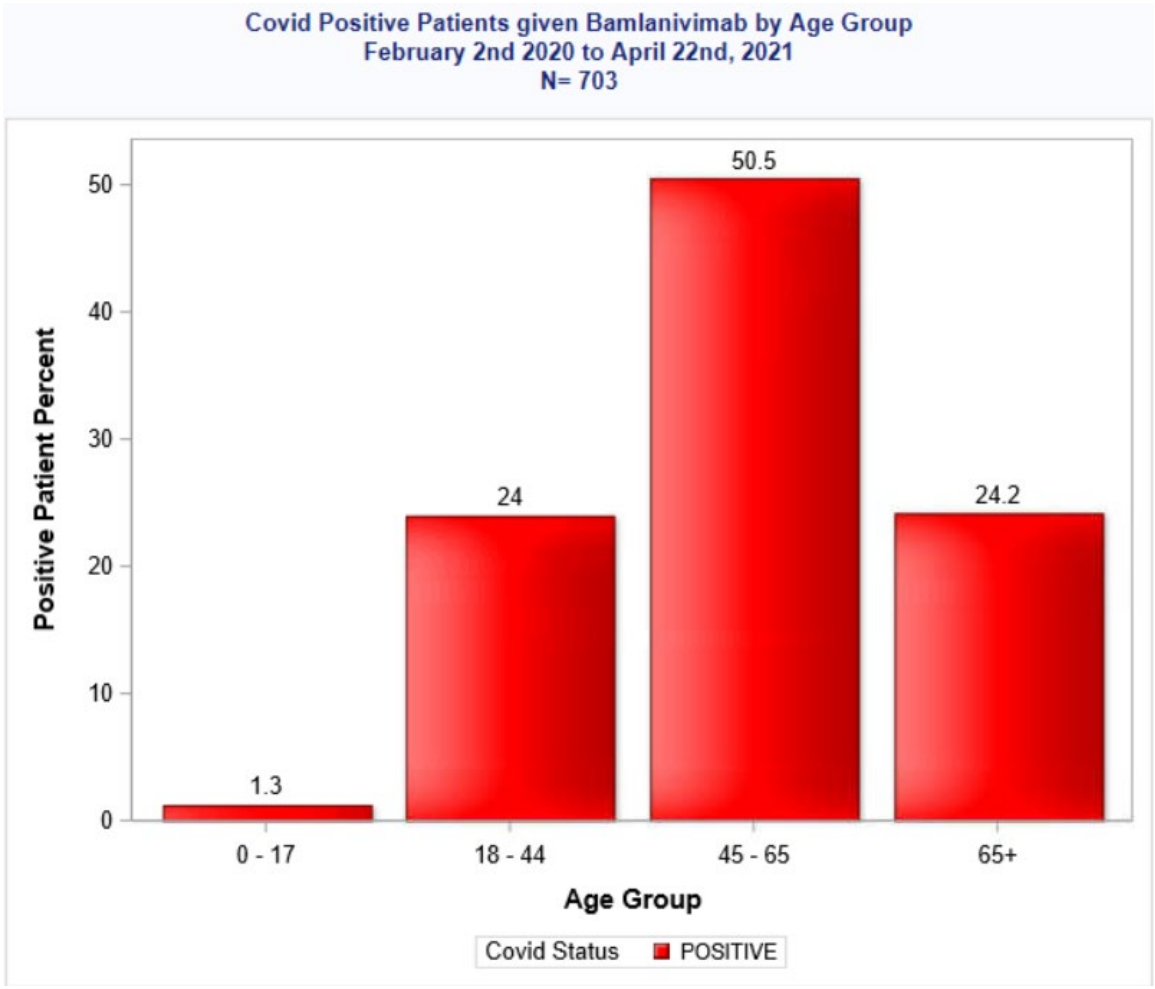
Data Point	% Complete (n=6,296)
Presenting Symptoms	6010 (95.46%)
PMH Documentation	5605 (89.02%)
Smoking History	5159 (81.94%)
Complete Test Dates	6102 (96.92%)
Intubated Patients	**(n=289)**
Level 1 PPE Use	2 (0.69%)
Level 2 PPE Use	14 (4.84%)
Level 3 PPE Use	4 (1.38%)

N=6,296 patients in registrar-abstracted population with detailed chart review, 2 Feb 2020 - 19 Apr 2021

Bamlanivimab/Regeneron Usage

- 703 COVID-19 positive patients have been given Bamlanivimab/ Monoclonal Antibodies as of 22 Apr 2021
- 62 patients are Active Duty
- Ages of patients range from 14-89



Monoclonal Antibodies

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- Average days after COVID-19 diagnosis to monoclonal antibody (McAb) usage is 2.7 days
- Of the 703 McAb recipients, 42 were admitted a hospital
  - Average days after COVID-19 diagnosis to monoclonal antibody usage of these patients is 3.5 days, compared to 2.6 days for patients who were never admitted to the hospital.
    - 26 of the 42, received McAb after hospital admittance
    - The other 16, received McAb before admittance and were admitted, on average, 2.6 days later.

Percent of asymptomatic patients

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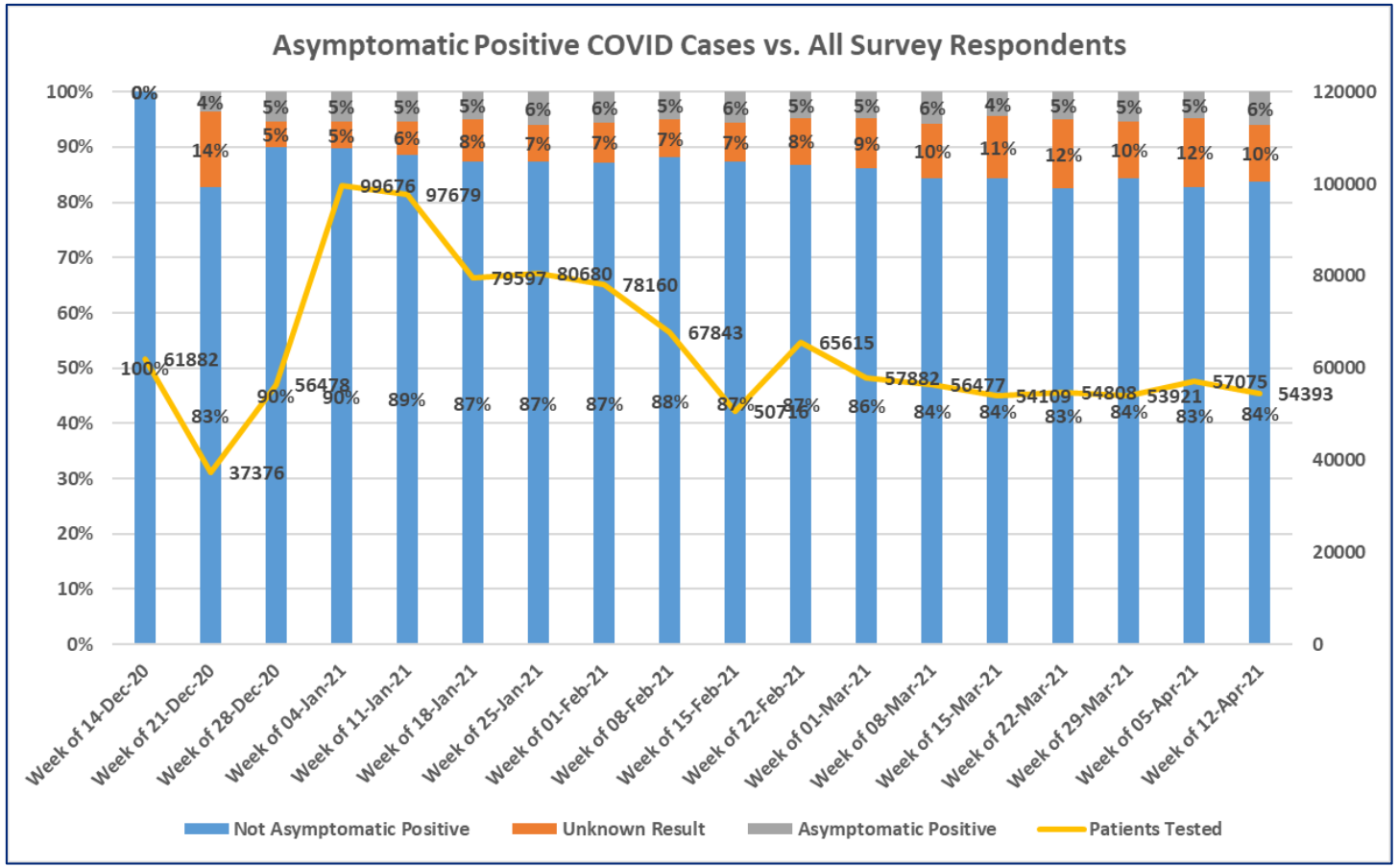
Percent of asymptomatic patients out of all questionnaire respondents by week



Https://testing.mystatus.mil/

N=109,299 responses, 88,785 individuals with COVID-19 test who replied to survey,
21 Dec 2020-22 through Apr 2021

Percent of asymptomatic patients

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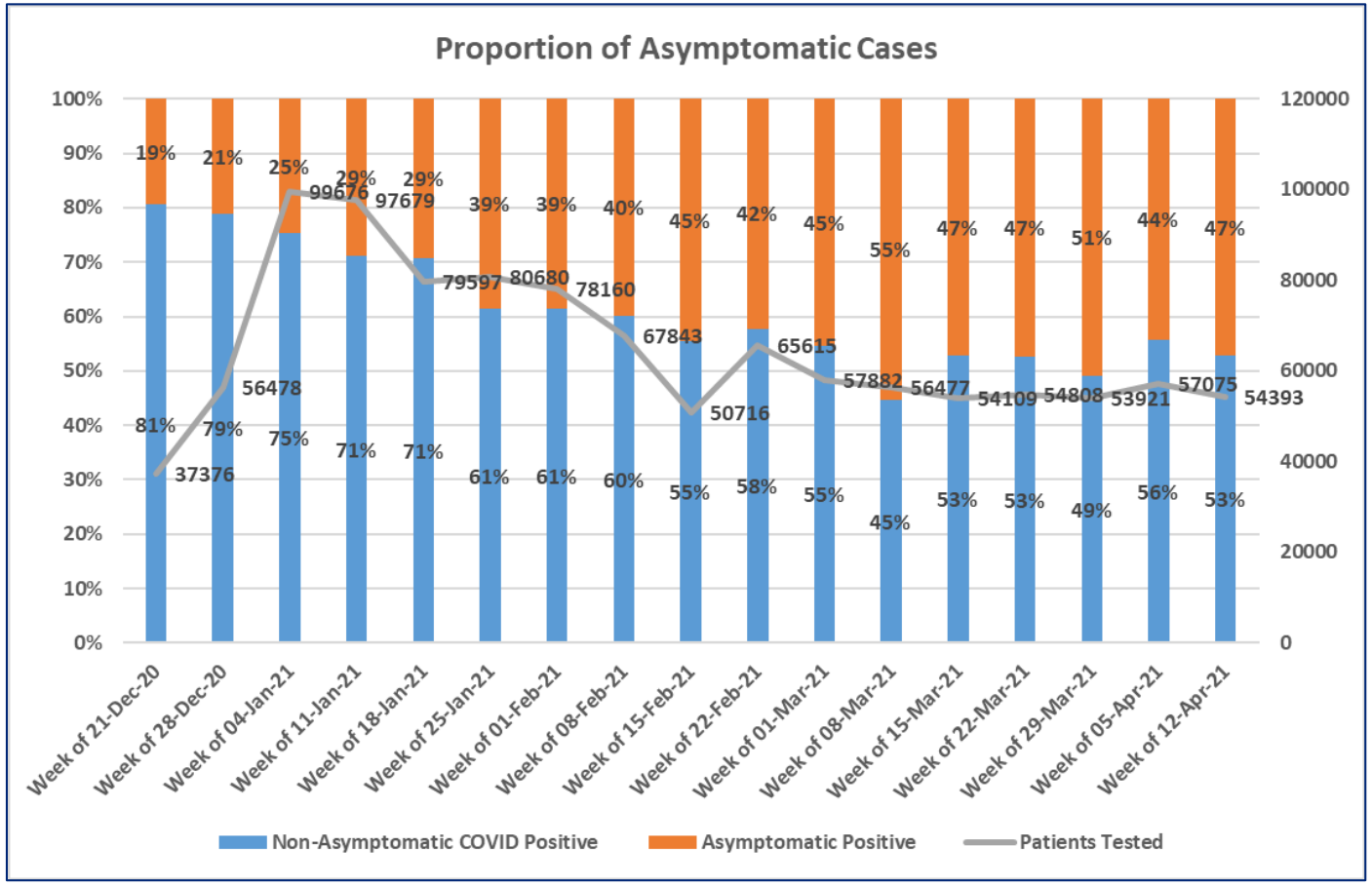
Percent of asymptomatic patients out of all COVID-19 positive respondents by week



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N=109,299 responses, 88,785 individuals with COVID-19 test who replied to survey,
21 Dec 2020-22 through Apr 2021

Proportion, Count and Locations of Patients

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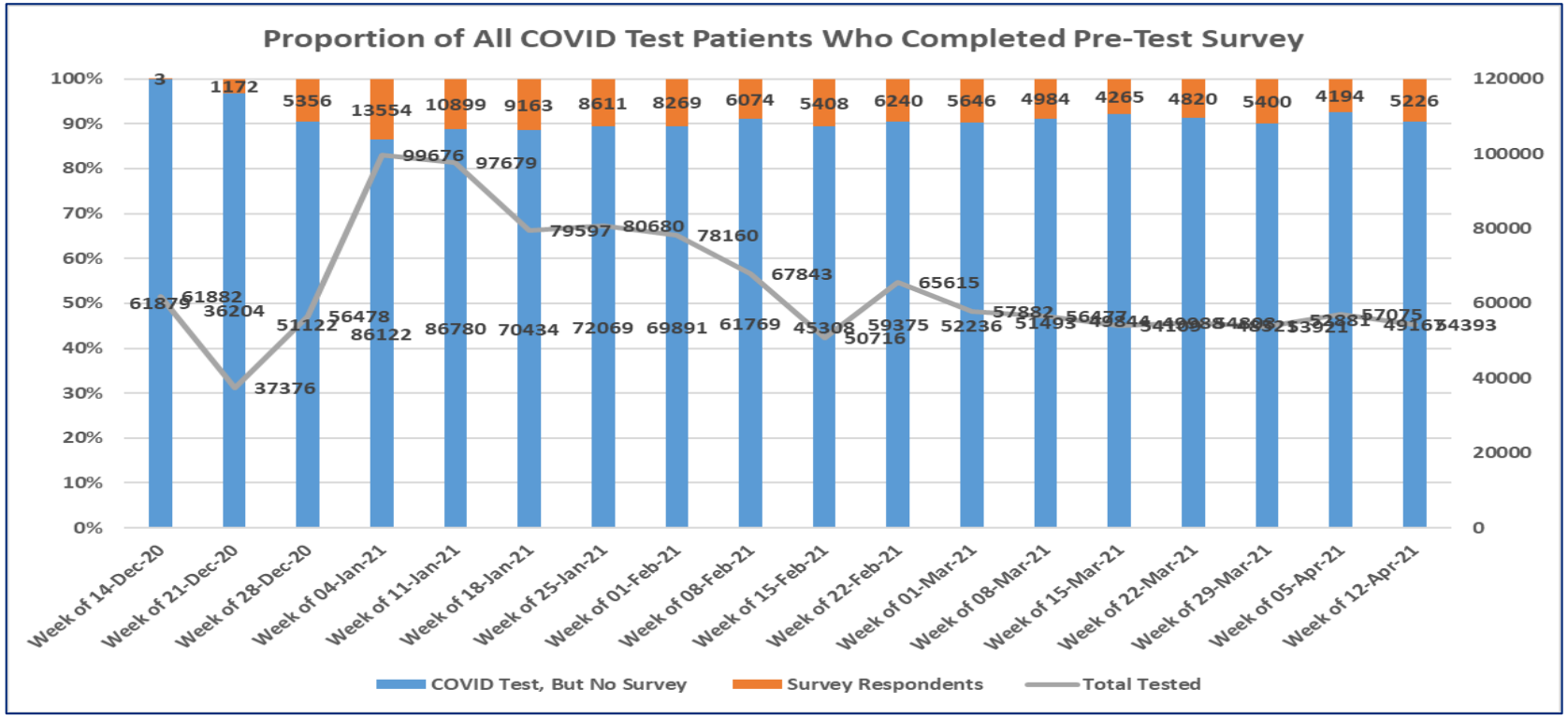
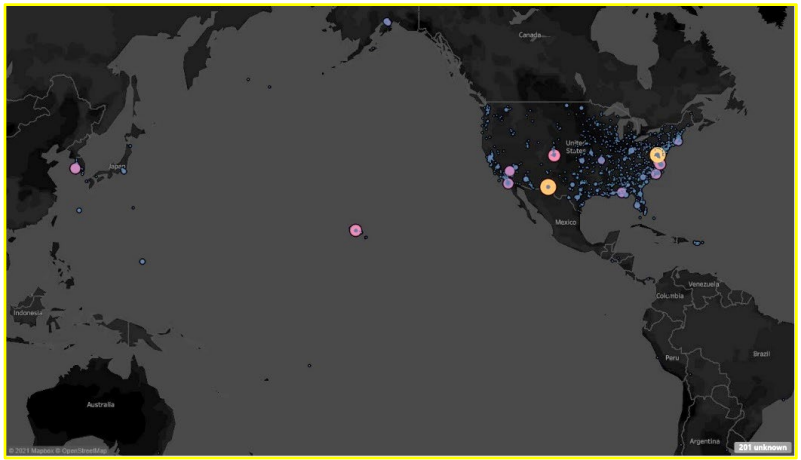
Proportion, count and locations of patients filling out the pre-test questionnaire





N=109,299 responses, 88,785 individuals with COVID-19 test who replied to survey, 21 Dec 2020-22 through Apr 2021

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Post-COVID-19 Health Analysis

Defense Health Agency
J5 and COVID-19 Registry
16 Apr 2021

Diagnosis categories elevated post COVID-19

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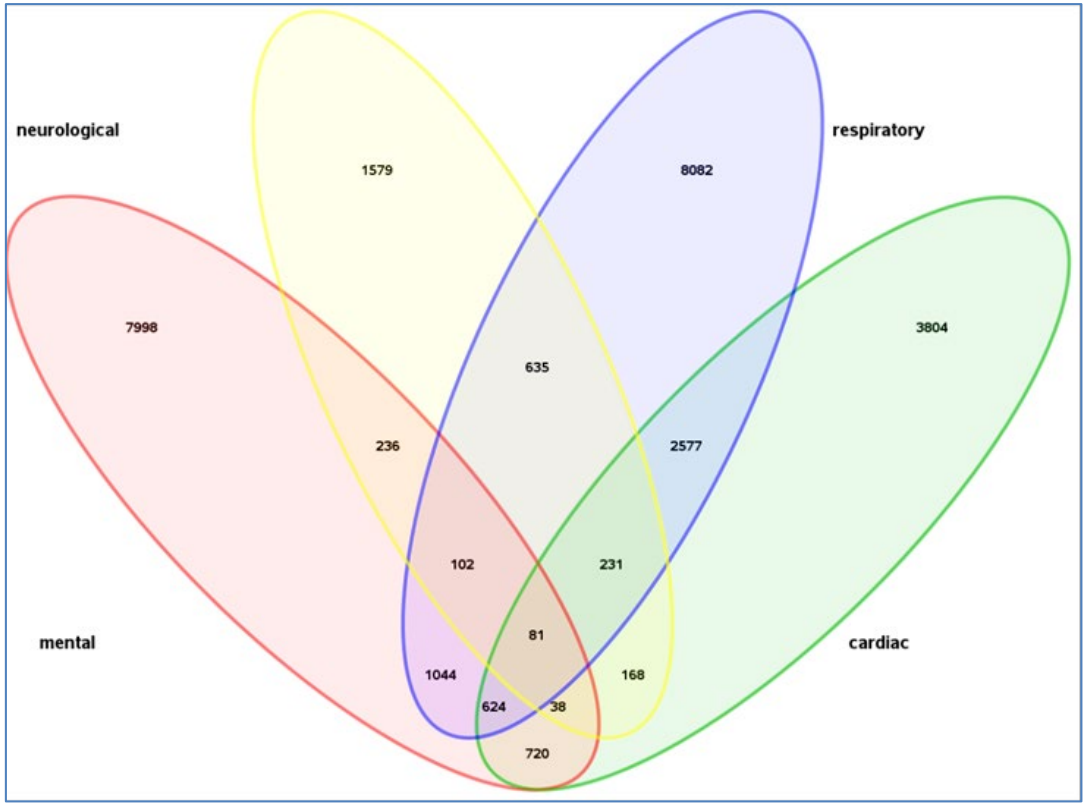
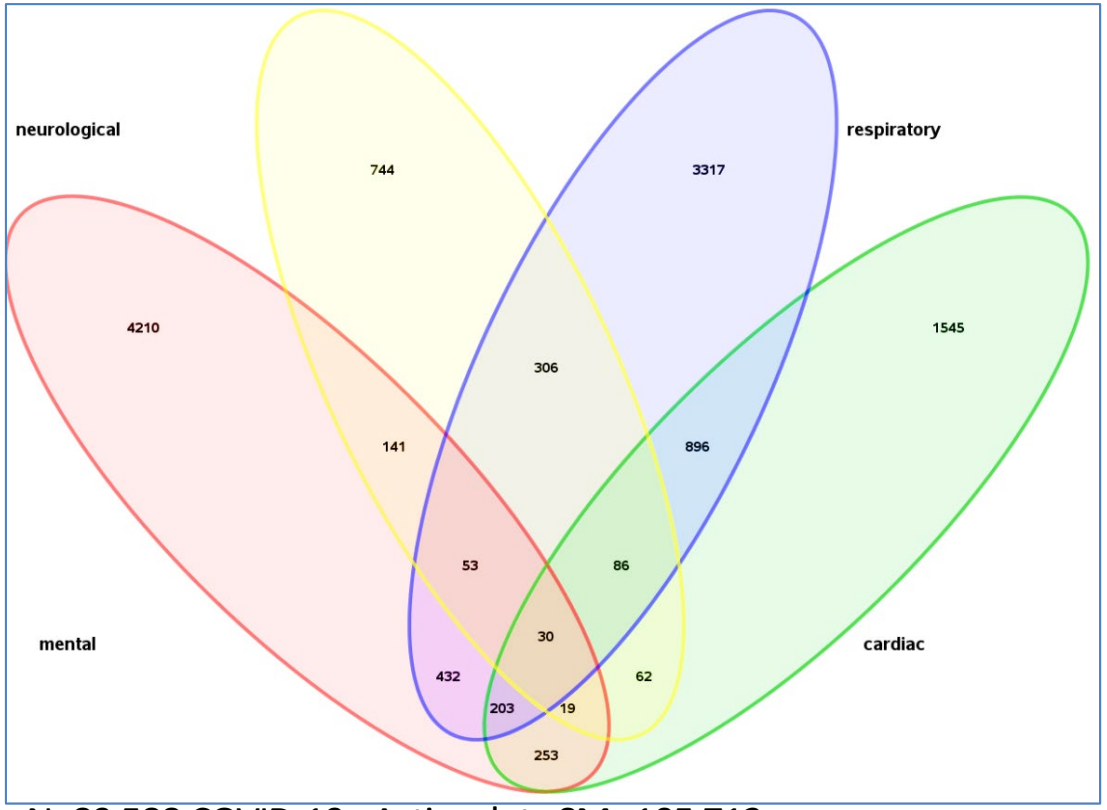
Analysis shows combinations of diagnoses post-COVID. The largest group of combined diagnosis categories is cardiac + respiratory, 2 Feb 2020 -2 Apr 2021



N=185,806 COVID-19+ beneficiaries 1,573,389 controls during pandemic



N=89,588 COVID-19+ Active duty SMs 105,712 controls during pandemic

Increased post COVID-19 post COVID-19 compared to controls, 1st 30 days & 2nd 30 days post diagnosis

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Summary: Patients continue to present with the diagnoses shown during the second month after COVID-19 diagnosis. Most diagnoses are less common during the second month.

ALL BENEFICIARIES: RESPIRATORY	0-30 DAYS		31-60 DAYS	
	Odds Ratio	Chi Sq	Odds Ratio	Chi Sq
Cough	13.27	<.0001	3.60	<.0001
Shortness of Breath	15.61	<.0001	8.23	<.0001
Pulmonary Embolism	10.93	<.0001	4.54	<.0001
Asthma	2.86	<.0001	2.09	<.0001
ACTIVE DUTY: RESPIRATORY				
Cough	3.94	<.0001	1.16	0.0118
Shortness of Breath	6.70	<.0001	4.71	<.0001
Pulmonary Embolism	4.07	<.0001	1.96	0.0405
Asthma	1.11	0.35	0.98	0.8252
ALL BENEFICIARIES: NEUROLOGIC				
Headache	5.89	<.0001	3.31	<.0001
Taste Loss	72.92	<.0001	13.04	<.0001
Seizure	2.31	<.0001	1.64	<.0001
Vertigo	2.97	<.0001	3.34	<.0001
ACTIVE DUTY: NEUROLOGIC				
Headache	1.28	0.0003	0.89	0.114
Taste Loss	27.38	<.0001	5.27	<.0001
Seizure	1.43	0.113	1.30	0.2482
Vertigo	0.77	0.397	0.83	0.5617

ALL BENEFICIARIES: CARDIAC	0-30 DAYS		31-60 DAYS	
	Odds Ratio	Chi Sq	Odds Ratio	Chi Sq
Chest Pain	11.78	<.0001	6.51	<.0001
Palpitations	2.38	<.0001	4.25	<.0001
Atrial Fibrillation	2.46	<.0001	1.55	<.0001
Syncope	4.09	<.0001	2.50	<.0001
Tachycardia	8.93	<.0001	3.38	<.0001
Heart Failure	2.17	<.0001	1.35	0.0011
Bradycardia	3.39	<.0001	1.41	0.0026
ACTIVE DUTY: CARDIAC				
Chest Pain	4.02	<.0001	2.66	<.0001
Palpitations	1.45	0.0007	2.00	<.0001
Atrial Fibrillation	1.10	0.761	0.75	0.3143
Syncope	1.76	<.0001	1.39	0.0207
Tachycardia	3.81	<.0001	1.55	0.0029
Heart Failure	1.39	0..3283	1.71	0.0839
Bradycardia	2.23	<.0001	1.15	0.5428
ALL BENEFICIARIES: MENTAL HEALTH				
Anxiety	3.22	<.0001	3.05	<.0001
Insomnia	3.44	<.0001	3.97	<.0001
PTSD	2.94	<.0001	3.21	<.0001
Major Depression	1.62	<.0001	1.38	<.0001
ACTIVE DUTY: MENTAL HEALTH				
Anxiety	1.43	<.0001	1.48	<.0001
Insomnia	1.12	0.059	1.46	<.0001
PTSD	1.18	0.026	1.31	0.0001
Major Depression	1.16	0.006	1.22	0.0002

N= 185,806 beneficiaries, N=89,588 Active Duty SMs, 2 Feb 2020 – 2 Apr 2021

Results highlighted in **blue** where significantly elevated compared to control group, based on $p < .05$. Odds ratio is the ratio of COVID: non-COVID, therefore odds ratio > 1 is more common in COVID-19 patients. Chi-squared measures the statistical significance of the difference between groups.

Disease-free Survival for New Health Diagnoses over Time after COVID-19, Influenza & Controls

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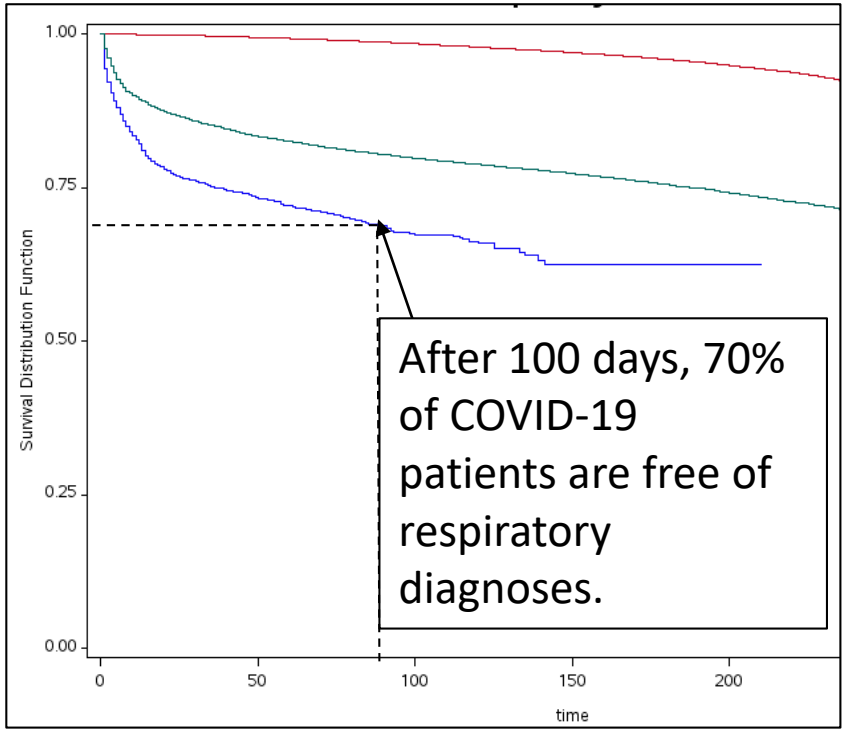
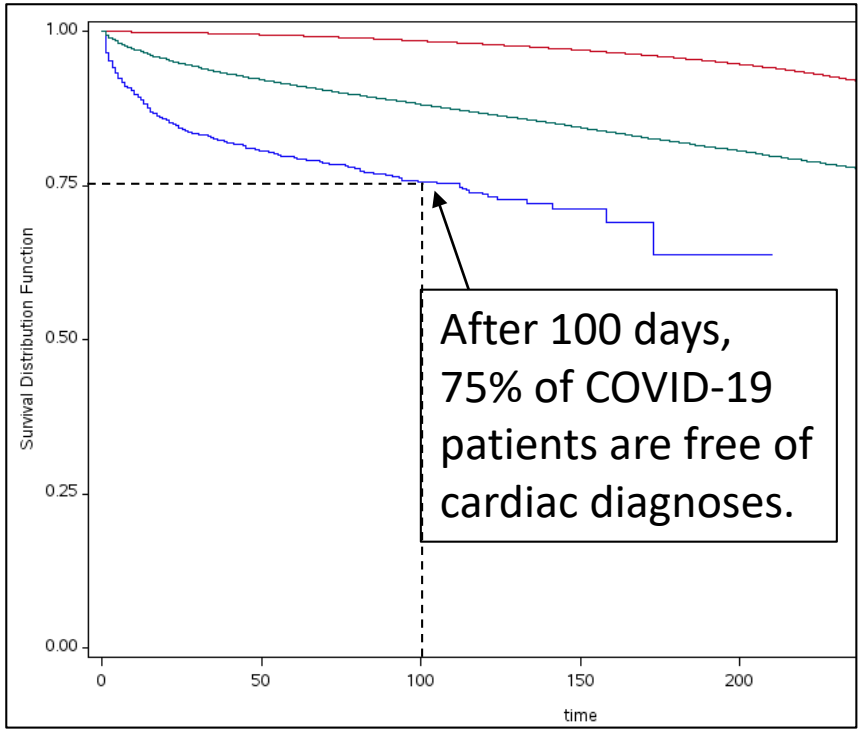
Summary: This analysis compares "disease free survival" for post-COVID diagnoses compared to control group during pandemic and control group with influenza the year prior to pandemic. The disease free survival is lower for COVID-19 in four diagnosis categories.

All respiratory diagnoses



All cardiac diagnoses



Red line= Control
Green line = Influenza
Blue line = COVID

DoD Direct Care Patients: Index date: 2 Dec 2019-21 through Sep 2020, COVID-19 n=55,201, Influenza n=44,315, Control n=4,753,500, Update 11 Jan 2021

Disease-free Survival for New Health Diagnoses over Time after COVID-19, Influenza & Controls

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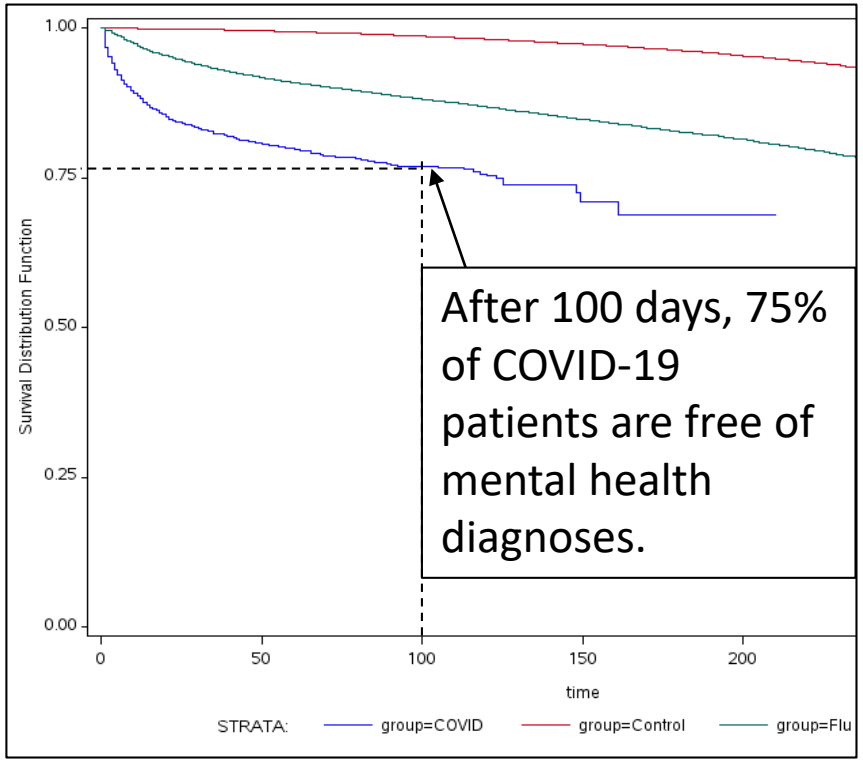
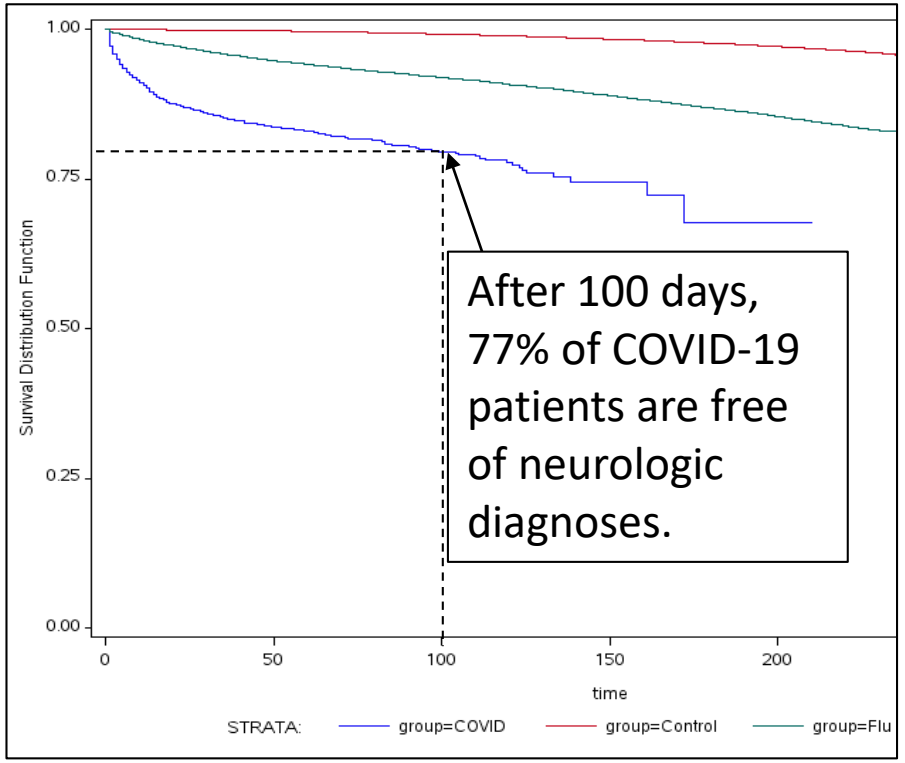
Summary: This analysis compares "disease free survival" for post-COVID diagnoses compared to control group during pandemic and control group with influenza the year prior to pandemic. *The disease free survival is lower for COVID-19 in 4 diagnosis categories.*

All mental health diagnoses



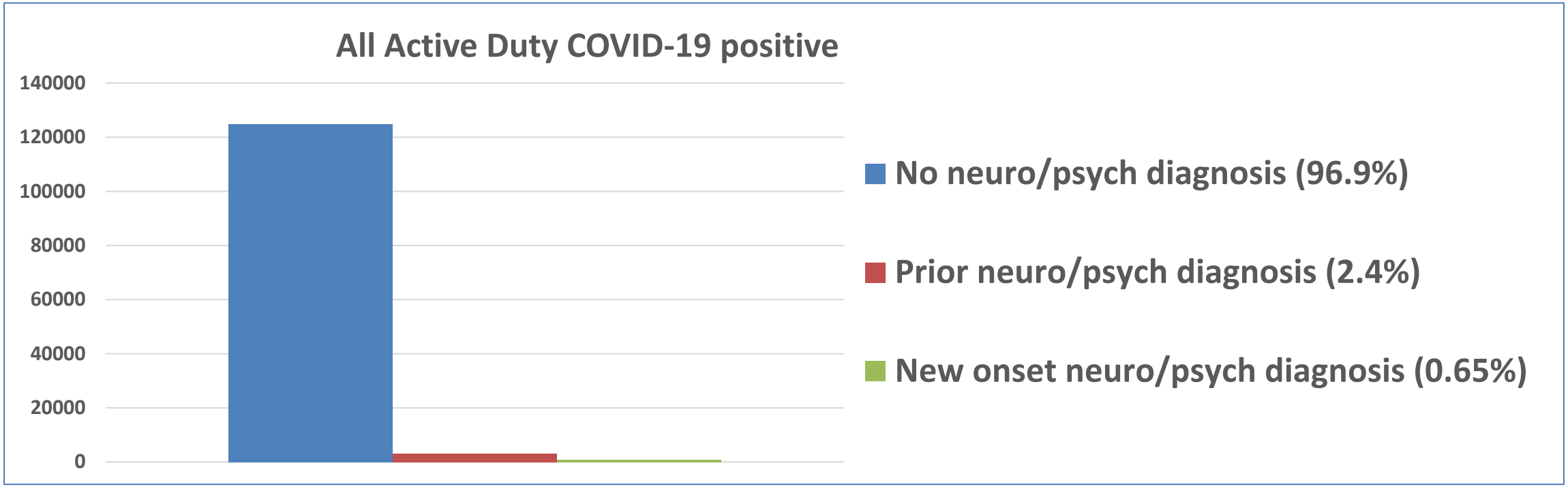
All neurologic diagnoses



Red line= Control
Green line = Influenza
Blue line = COVID

DoD Direct Care Patients: Index date: 2 Dec 2019-21 through Sep 2020, COVID-19 n=55,201, Influenza n=44,315, Control n=4,753,500, Updated 11 Jan 2021

Active Duty Neurologic and Psychiatric Diagnoses within 6 Months post COVID-19 Diagnosis



Out of all Active Duty COVID-19 positive (N=128,742), there are 3,927 (3.05%) who were treated for neuro/psych diagnosis within 6 months of COVID-19 diagnosis. Of these, N=837 (0.65%) did not have a prior neuro/psych diagnosis.

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Pulmonary Disorders Post-COVID-19

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Conflict of Interest

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- The view(s) expressed herein are those of the author(s) and do not reflect the official policy or position of Brooke Army Medical Center, the U.S. Army Medical Department, the U.S. Army Office of the Surgeon General, the Department of the Army, the Department of Defense or the U.S. Government.
- Paid speaker for:
  - ❑ Janssen Pharmaceuticals
  - ❑ Vyaire Medical

Acute Pulmonary

- Dyspnea, decreased exercise capacity, and hypoxia are persistent signs and symptoms
- Reduced DLCO, restrictive pulmonary physiology, and ground-glass opacities and fibrotic changes on imaging have been noted.
- Assessment of progression or recovery of pulmonary disease and function may include home pulse oximetry, 6MWTs, PFTs, HRCT and CTPA as clinically appropriate.

Nalbandian, Nature Med, 2021

COVID-19 Post-MV

- 52 patients (55%) who survived
- 48 patients with 3 month f/u
- Median 6-MWT = 482 meters
- PFTs
  - Decreased TLC in 26 (54%)
  - Decreased DLCO in 36 (75%)
- Chest imaging
  - Ground glass opacities in 89%
  - Fibrosis, bronchiectasis in 67%

Van Gassel, Am J Respir Crit Care Med, 2021

Chronic Symptoms

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- 201 individuals (mean age 44 ±11.0 yrs), 70% female, 87% white; 18% hospitalized
- Pre-existing conditions - Obesity: 20%, hypertension: 6%; diabetes: 2%; heart disease: 4%
- Fatigue (98%), muscle aches (88%), breathlessness (87%), and headaches (83%) most frequently reported symptoms.
- Ongoing cardiorespiratory (92%) and gastrointestinal (73%) symptoms were common; 42% with ten or more symptoms.
- Mild organ impairment in heart (32%), lungs (33%), kidneys (12%), liver (10%), pancreas (17%), and spleen (6%).
- Single (66%) and multi-organ (25%) impairment was observed, and was significantly associated with risk of prior COVID-19 hospitalization

Dennis, MedRvix, 2020

CPET

- 110 consecutive subjects
- 3 month f/u with echo, PFT, and CPET
- Median PFT normal
- Max VO2 (% pred) – 90.9%
  - 38% below 85% pred
- Limitations to exercise
  - Respiratory (21.1%)
  - Cardiac (23.7%)
  - Mixed (7.92)
  - Muscular impairment (47.4%)

Clavario, MedRxiv, 2020

Athlete Evaluation

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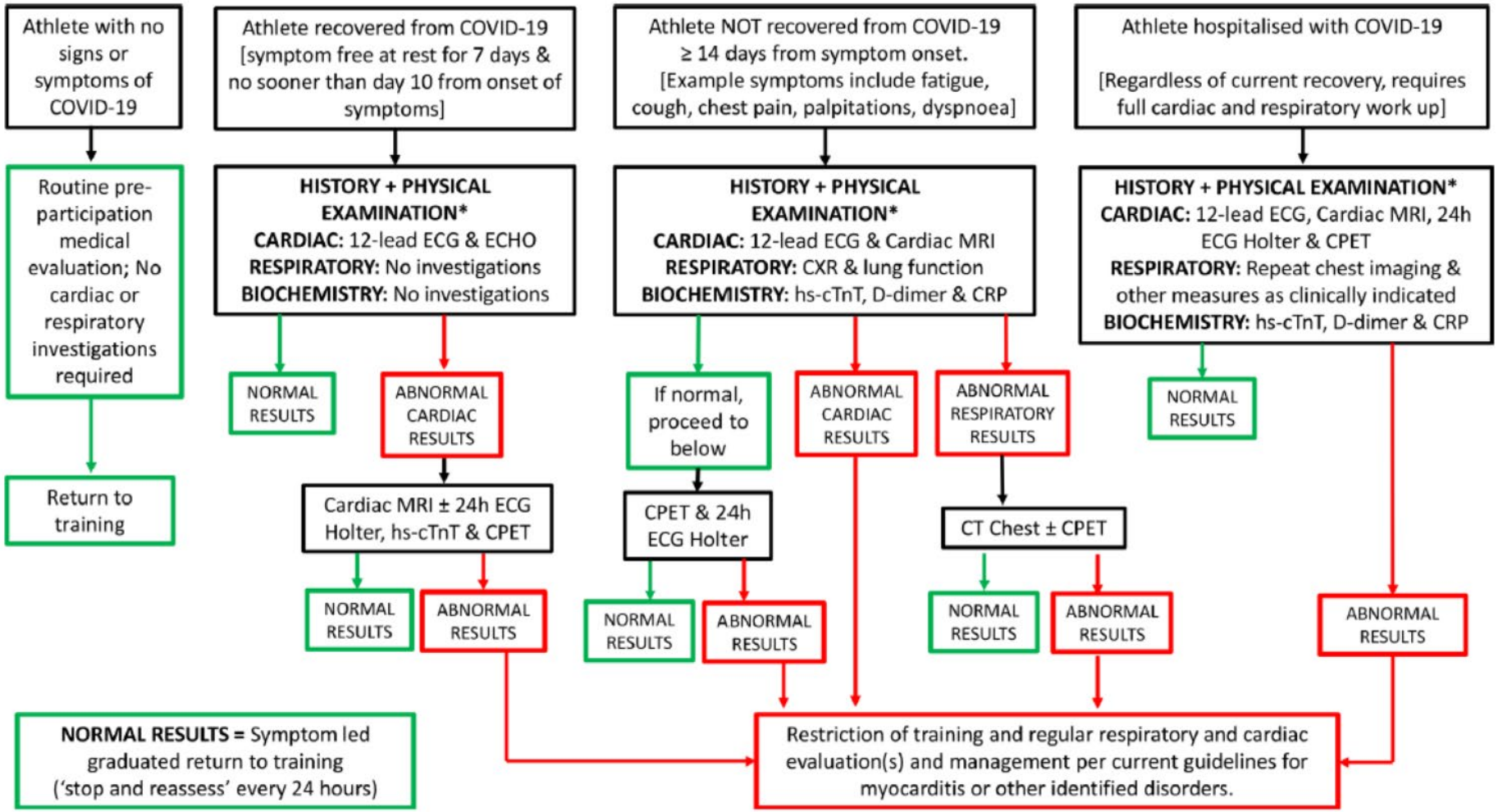

Wilson, Brit J Sports Med, 2020

COVID-19 Severity

- Mild disease is characterized by no evidence of pneumonia on chest radiograph and peripheral capillary oxygenation > 94%.
- Moderate disease is characterized by evidence of pneumonia with imaging, and SpO2 < 94%.
- Severe disease is characterized by resting SpO2 <94%, requiring oxygen supplementation.

EPICC ChiPS

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- **Specific Aim 1**: Define the presence and degree of cardiac and pulmonary function abnormalities in DoD beneficiaries with prior COVID-19 infection
- **Specific Aim 2**: Establish the extent of pulmonary and cardiac imaging abnormalities in DoD beneficiaries with prior COVID-19

Study Enrollment

- **Group 1**: Minimally symptomatic or asymptomatic cohort with mild symptoms of fever, chills, cough or shortness of breath less 3-5 days in duration.
- **Group 2**: Symptomatic cohort with at least 5 days of fever, chills, cough or shortness of breath not requiring supplemental oxygen or clinical need for hospitalization.
- **Group 3**: Any hospitalized patients with requirements for supplemental oxygen or ventilator support.

EPICC ChiPS

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- Minimum of 3 months post-COVID
- Symptomatic vs. asymptomatic
- Standardized testing regimen
  - Full PFTs
  - High Resolution CT
  - EKG
  - Echocardiography
  - 6-minute walk test
- Patients enrolled at larger EPICC sites (NMCSD, MAMC, WRNMMC, BAMC)

AD COVID

- **Specific Aim 1**: Define the presence and degree of cardiac and pulmonary function abnormalities in ADSM with prior COVID-19 infection.
- **Specific Aim 2**: Establish the extent of pulmonary imaging abnormalities in active duty service members with prior COVID-19.
- **Specific Aim 3**: Determine the extent of exercise limitation in active duty service members with prior COVID-19.
- **Specific Aim 4**: Evaluate presence of virologic, metabolic, or respiratory abnormalities which may limit overall fitness and medical readiness.

AD COVID Exclusion

- Age greater than 65
- History of significant cardiopulmonary disease prior to COVID-19
- Treatment for inflammatory disorders, malignancy, or neurological disorders
- Inability to exercise on treadmill
- Significant renal or hepatic dysfunction
- Pregnancy or breastfeeding
- Dyspnea at rest or continued requirement for oxygen
- Inability to perform any study procedures due to continued moderate to severe symptoms.

AD COVID Laboratory

- Metabolic data from EPICC
- SARS-COV-2 antibody testing
- Standard CBC to evaluate for anemia and eosinophilia.
- CRP, ESR, and quantitative immunoglobulin panel.
- Serum allergy panel to evaluate for allergies.
- BAL cytology and flow cytometry

AD COVID Testing

- Full PFTs with BD
- Impulse oscillometry
- Methacholine challenge testing (or EVH)
- High resolution CT chest
- Echocardiography
- EKG
- Cardiopulmonary exercise testing
- Bronchoscopy with BAL

Locations

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- Study approved at BAMC
- Pending sites:
  - WRNMMC
  - NMCSD
  - NMCP
- Air Force Restoral funding support

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- Nalbandian A. Post-acute COVID-19 syndrome. Nature Medicine; 2021
- Van Gassel RJJ. High prevalence of pulmonary sequelae at 3 months after hospital discharge in mechanically ventilated survivors of COVID-19. Am J Respir Crit Care Med 2021; 203:371-374.
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- Wilson MG. Cardiorespiratory considerations for return-to-play in elite athletes after COVID-19 infection: a practical guide for sport and exercise medicine physicians. Brit J Sports Med 2020; 54:1157-1161.
- Clavario P. Assessment of functional capacity with CPET in non-severe COVID-19 patients at 3 months follow up. MedRxiv 2020.

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Short Term & Long-Term Cardiovascular Impact of COVID-19

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Uniformed Services University of the Health Sciences

Proposed Mechanisms For Cardiac Injury

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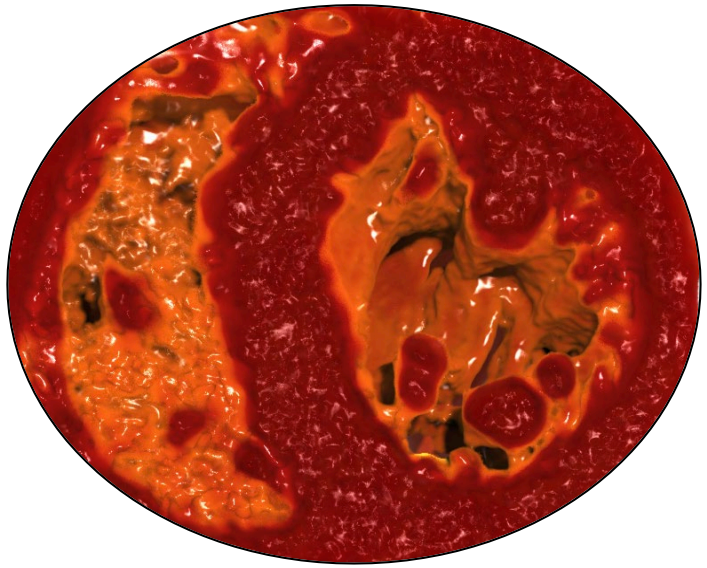
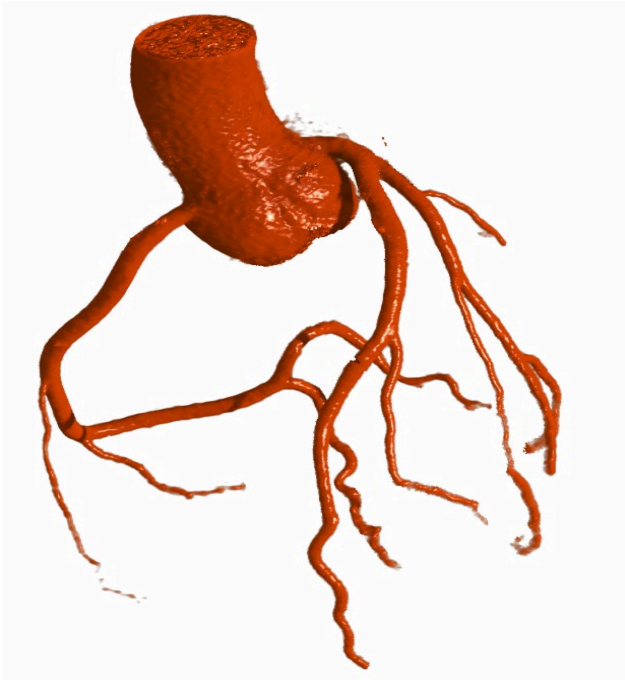
Directly infect cardiomyocytes or pericytes



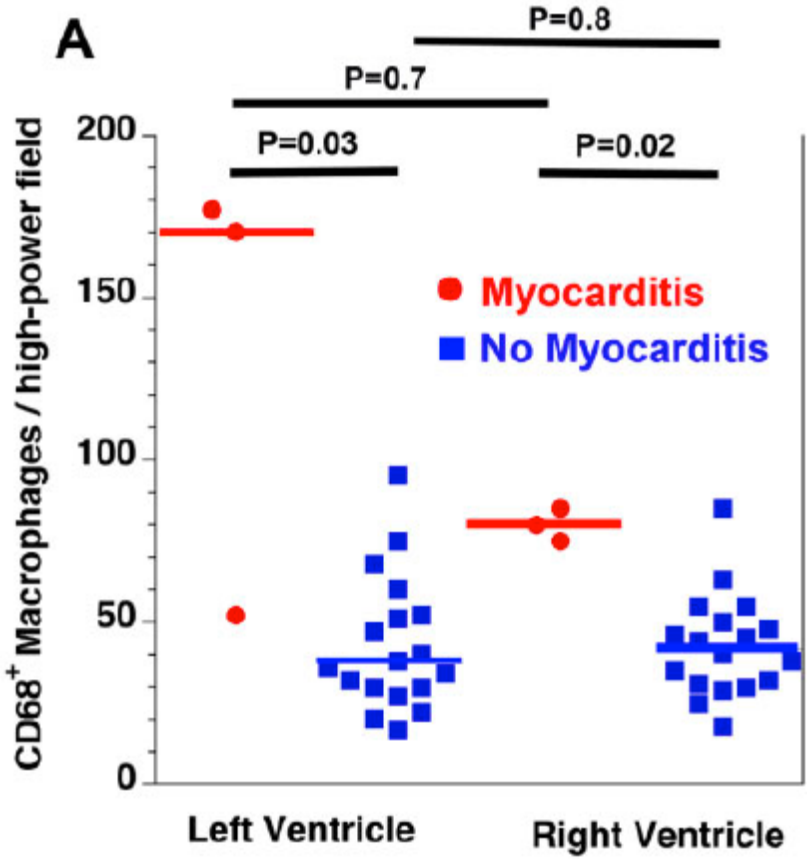
Indirectly damage cardiomyocytes through vascular thrombosis or endothelial cell injury

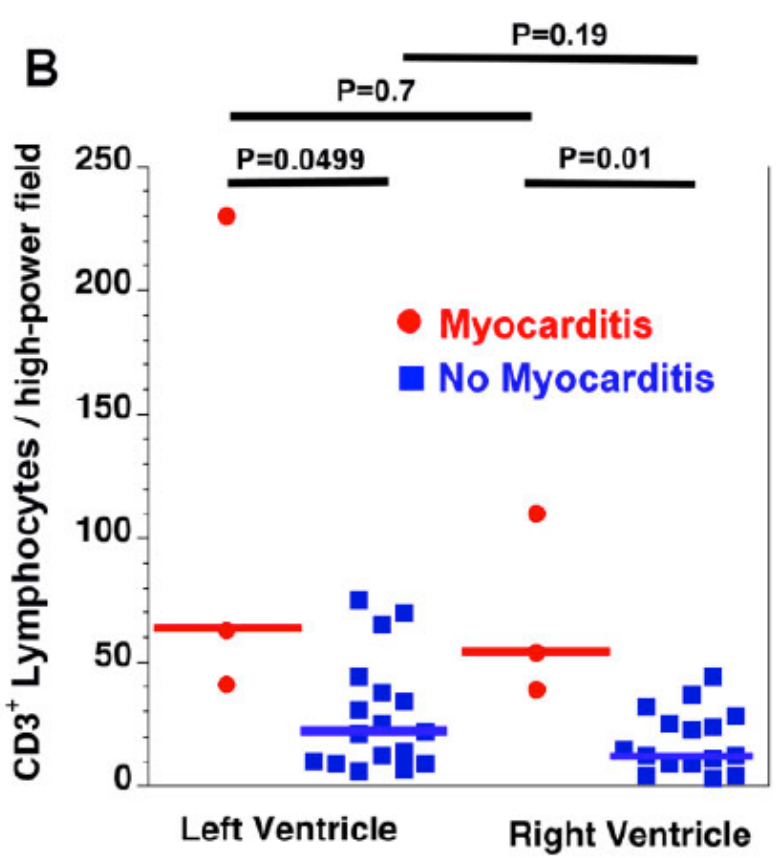


J Mol Cell Cardiol. 2020;147:12-17. doi:10.1016/j.yjmcc.2020.08.002
JAMA Cardiol. Published online December 29, 2020. doi:10.1001/jamacardio.2020.7308
Eur Heart J. 2020;41(39):3827-3835 doi:10.1093/eurheartj/ehaa664

Pathologic Findings in COVID-19

- Viral RNA in Myocardium in up to 61.5% of cases
- Viral load not associated with influx of inflammatory cells
- Degree of myocarditis did not explain elevated troponin levels

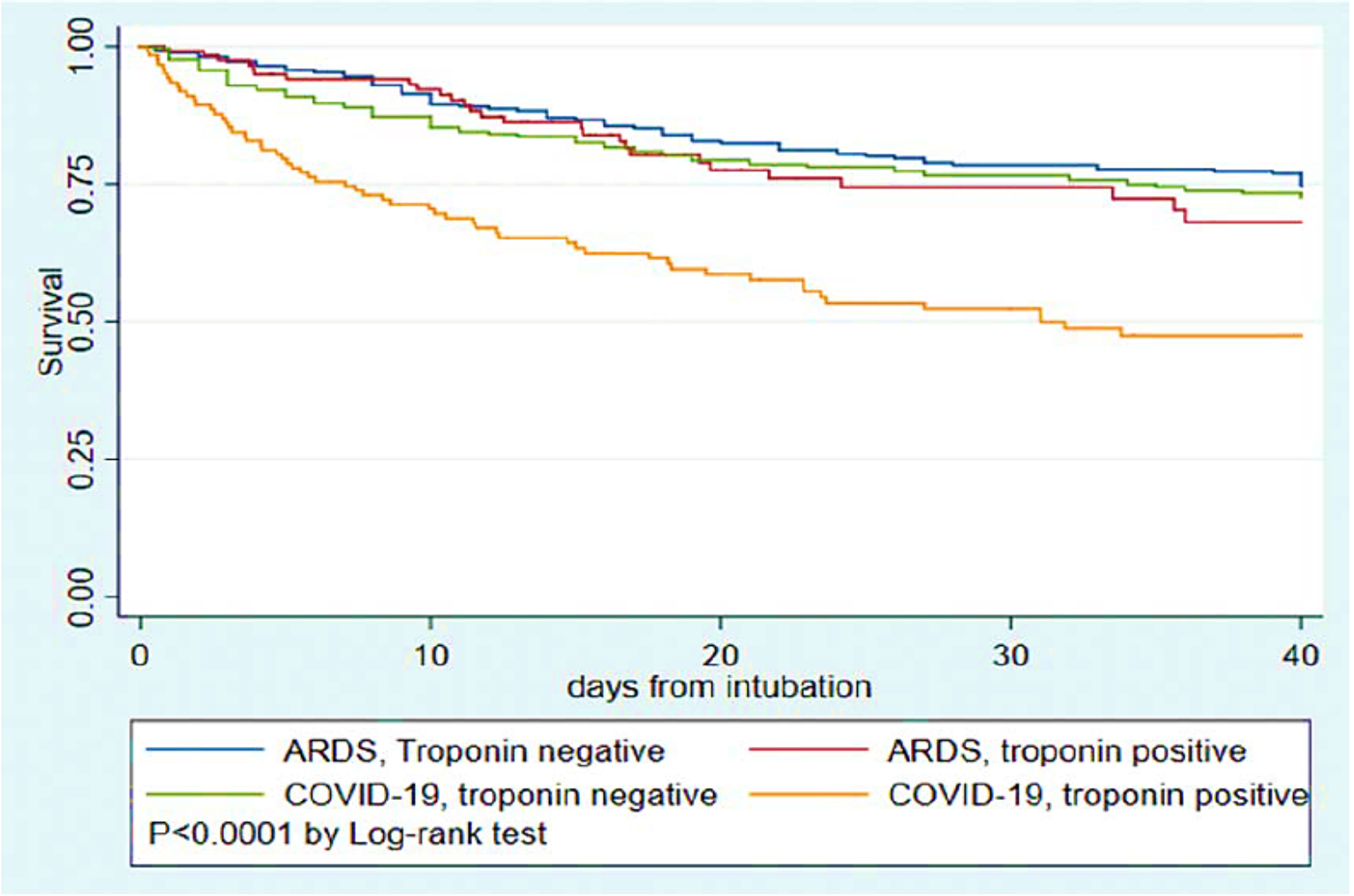




- *JAMA Cardiol*. 2020;5(11):1281-1285. doi:10.1001/jamacardio.2020.3551
- *Eur Heart J*. 2020;41(39):3827-3835 doi:10.1093/eurheartj/ehaa664

Myocardial Injury in COVID-19

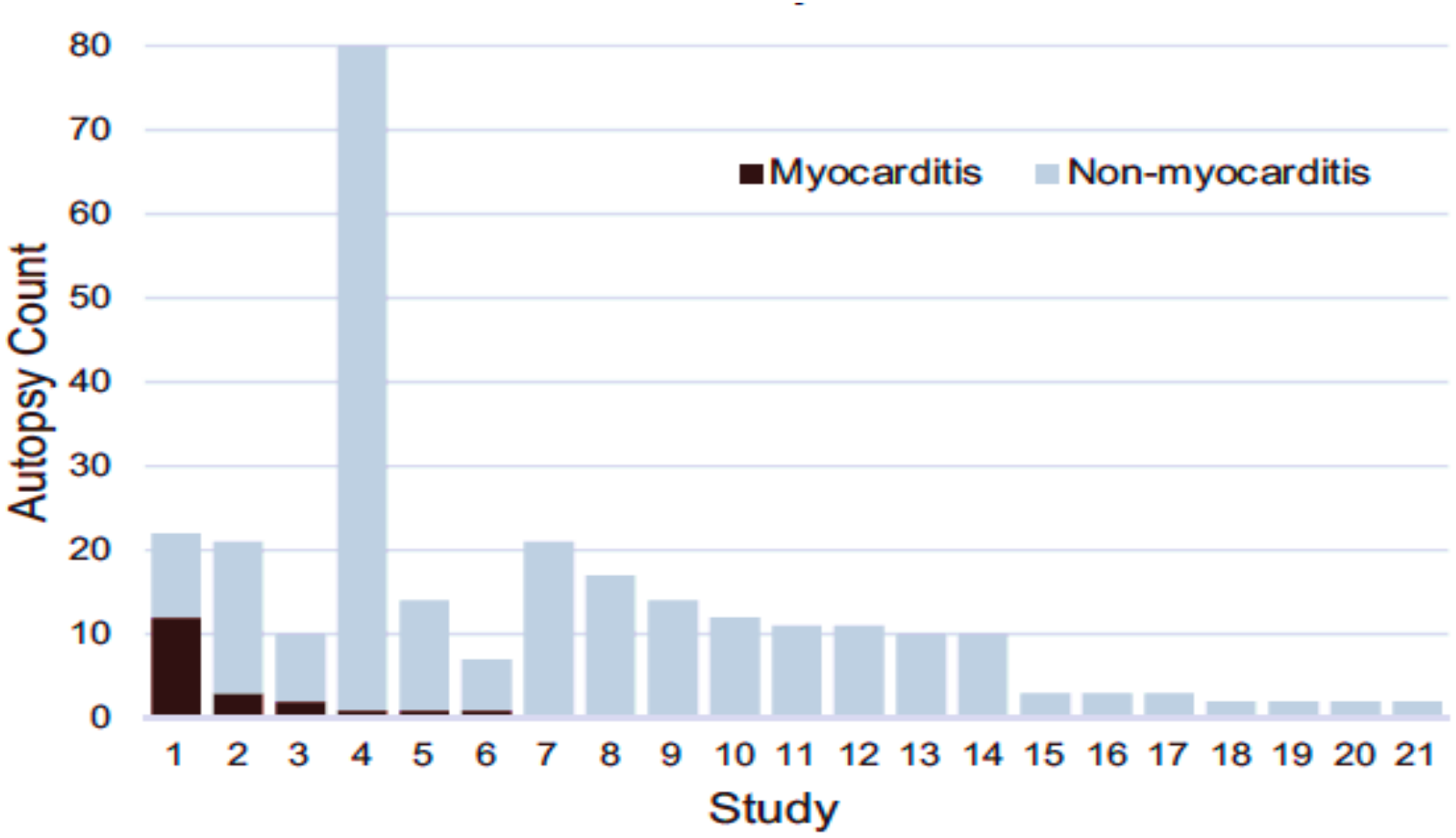
- Myocardial injury is less common in COVID-19 ARDS than in non-COVID ARDS.
- ***Patients with COVID-19 with myocardial injury have the highest mortality observed.***



Circulation. 2021;143(6):553-565.
doi:10.1161/CIRCULATIONAHA.120.050543

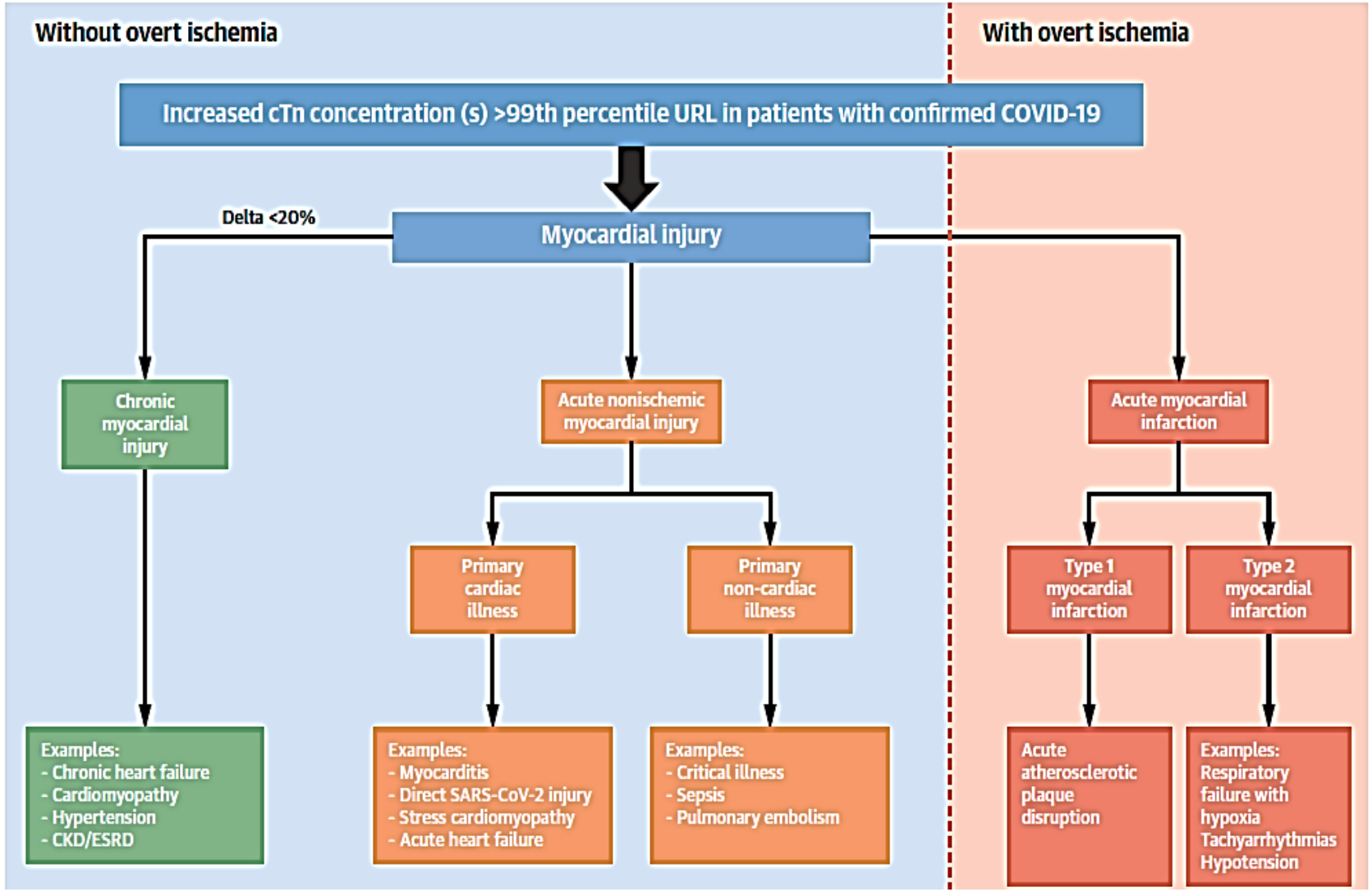
Pathologic Findings in COVID-19

- Initial review suggests myocarditis present in ***7.2% of cases***
- Closer examination suggests a true prevalence in ***1.4% of cases***



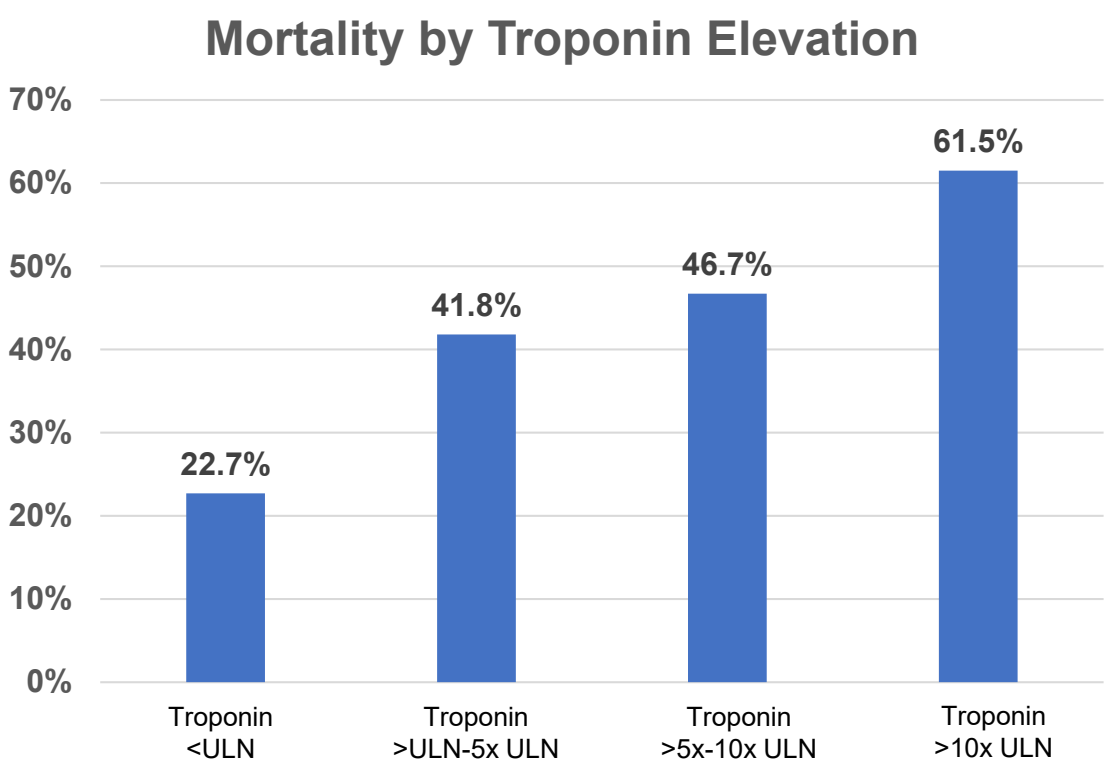
Cardiovasc Pathol. 2021;50:107300. doi:10.1016/j.carpath.2020.107300

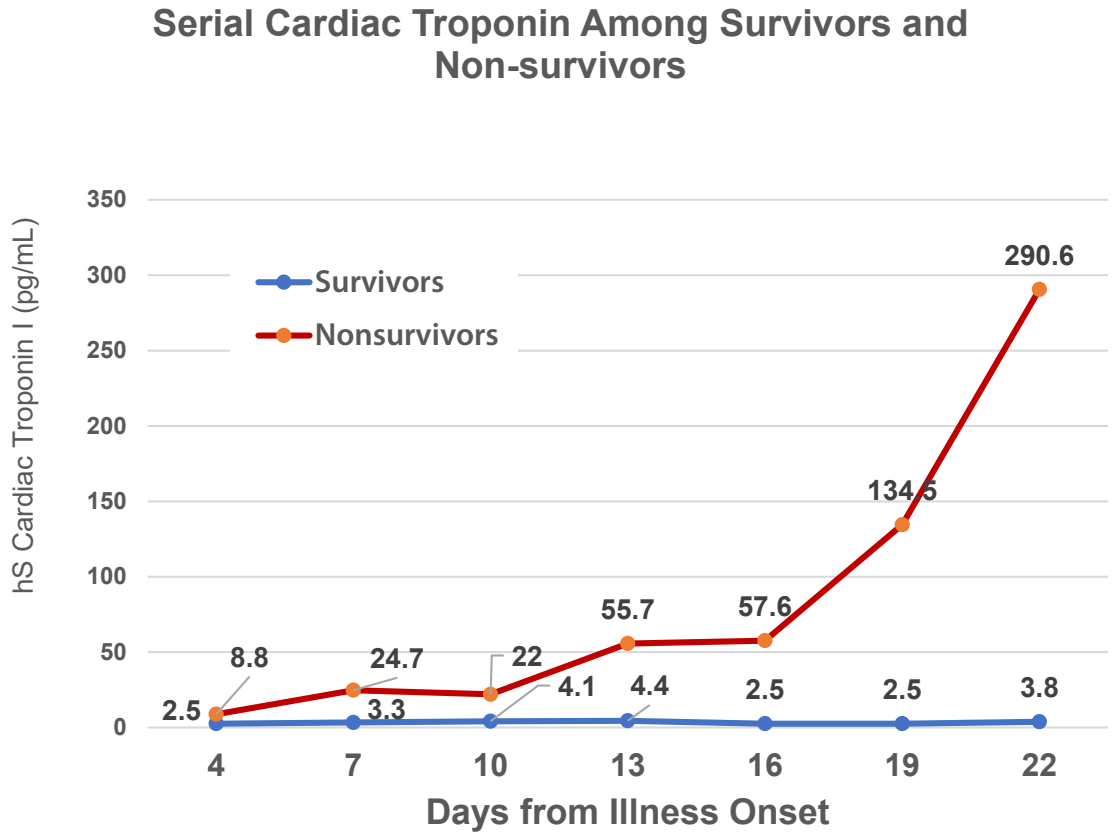
Myocardial Injury in COVID-19



- *J Am Coll Cardiol. 2020;76(10):1244-1258. doi:10.1016/j.jacc.2020.06.068*
- *J Am Coll Cardiol. 2020;76(18):2043-2055. doi:10.1016/j.jacc.2020.08.069*

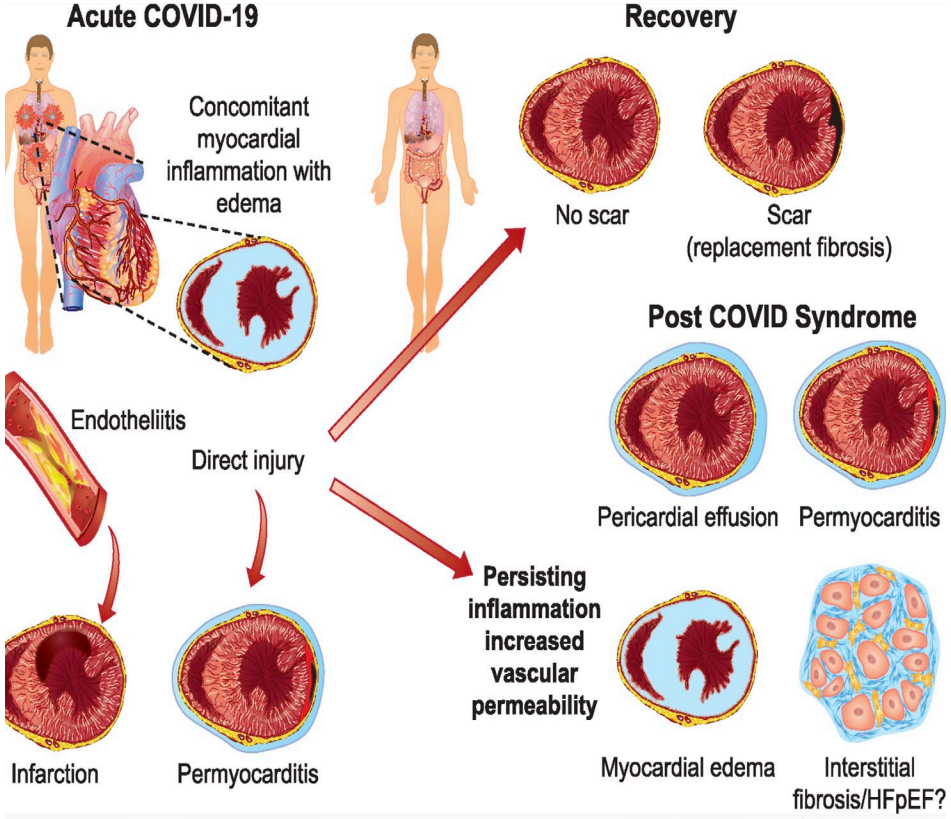
Myocardial Injury in COVID-19

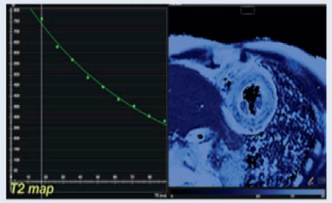
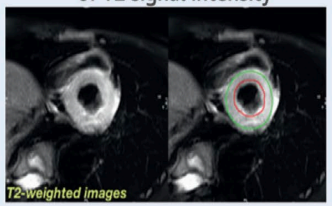
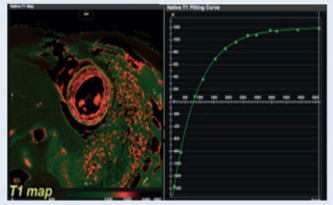
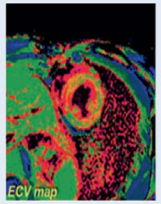
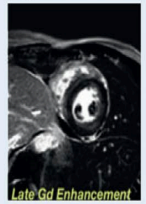
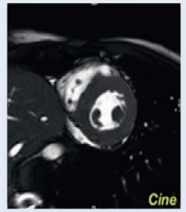
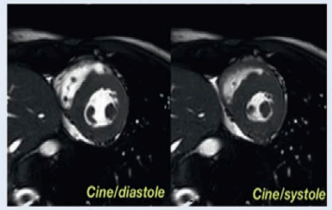




- *J Am Coll Cardiol*. 2020;76(10):1244-1258. doi:10.1016/j.jacc.2020.06.068
- *Circulation*. 2021;143(6):553-565. doi:10.1161/CIRCULATIONAHA.120.050543

Advanced Cardiac Imaging after COVID-19



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

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Cardiac MRI in COVID-19 (Nonathletic Cohorts)

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Author	Patients (N)	Mean Age	Severity of illness	Diagnosis to CMR (mean)	CMR findings
Kotecha et al	148	64	**Hospitalized** all with elevated troponin	68 days	**54% total abnormal** 32% inflammatory pattern 28% ischemic pattern
Raman et al	58	55	**All hospitalized**	69 days	28% increased native T1, 11.5% inflammatory LGE
Puntman et al	100	49	18% asymptomatic 49% mild-moderate symptomatic **33% severe**	71 days	**78% abnormal,** 32% abnormal LGE
Li et al	40	54	60% moderate **40% severe**	158 days	2% LGE ECV increased in COVID-19.
Huang et al	26	38	85% moderate **15% severe**	47 days	54% increased T2, 31% abnormal LGE

- *Eur Heart J. Published online February 18, 2021:ehab075. doi:10.1093/eurheartj/ehab075*
- *EClinicalMedicine. 2021;31:100683. doi:10.1016/j.eclinm.2020.100683*
- *JAMA Cardiol. Published online July 27, 2020. doi:10.1001/jamacardio.2020.3557*
- *Radiology. Published online January 12, 2021:203998. doi:10.1148/radiol.2021203998*
- *JACC Cardiovasc Imaging. Published online May 2020:S1936878X20304034. doi:10.1016/j.jcmg.2020.05.004*

Cardiac MRI in COVID-19 (Athletic Cohorts)

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Author	Patients (N)	Mean Age	Severity of illness	Diagnosis to CMR (mean)	CMR findings	Organization
Rajpal et al	26	20	**73.1% asymptomatic** 26.9% mild symptoms	11-53 days	**15% with MRI criteria for myocarditis** 30.8% LGE without T2 Normal EF	Ohio State University
Brito et al	54	19	**30% asymptomatic** 4% moderate symptoms	27 days	**40% had late pericardial enhancement** 22% with pericardial enhancement also had LGE 1 athlete with reduced LVEF	West Virginia University
Clark et al	59	20	**22% asymptomatic** 78% mildly symptomatic	21 days	**3% had MRI criteria for myocarditis** Focal LGE at RV insertion seen in 22% of COVID-19 and 24% of athletic controls. **No statistical difference in MRI findings when compared to athletic control except ECV in mid septum**	Vanderbilt
Starekova et al	145	20	**16.6% asymptomatic** 49% mild symptoms 27.6% moderate symptoms	15 days	**1.4% of patients had myocarditis by MRI criteria** Nonspecific LGE at RV insertion in 26%	University of Wisconsin

- *JAMA Cardiol. 2021;6(1):116-118. doi:10.1001/jamacardio.2020.4916*
- *JACC Cardiovasc Imaging. 2021;14(3):541-555. doi:10.1016/j.jcmg.2020.10.023*
- *Circulation. 2021;143(6):609-612. doi:10.1161/CIRCULATIONAHA.120.052573*
- *JAMA Cardiol. Published online January 14, 2021. doi:10.1001/jamacardio.2020.7444*

Cardiac MRI in COVID 19 (Athletic Cohorts)

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Author	Patients (N)	Mean Age	Severity of illness	Diagnosis to CMR (mean)	CMR findings	Organization
Martinez et al	789	25	**41.7% asymptomatic or minimal symptoms** 58.3% with symptoms	19 days	**0.6% had CMR findings of inflammation** (3 myocarditis, 2 pericarditis)	MLS, NHL, NFL, NBA, WNBA
Moulson et al	3018	20	**62% asymptomatic or mild symptoms** 13% with cardiovascular symptoms	33 days	**0.7% of athletes had definite, probable or possible** SARS-CoV-2 cardiac involvement.	ORCCA Investigators (42 Universities)

- *JAMA Cardiol. Published online March 4, 2021. doi:10.1001/jamacardio.2021.0565*
- *Circulation. Published online April 17, 2021:CIRCULATIONAHA.121.054824. doi:10.1161/CIRCULATIONAHA.121.054824*

DHA COVID-19 CPG Version 7

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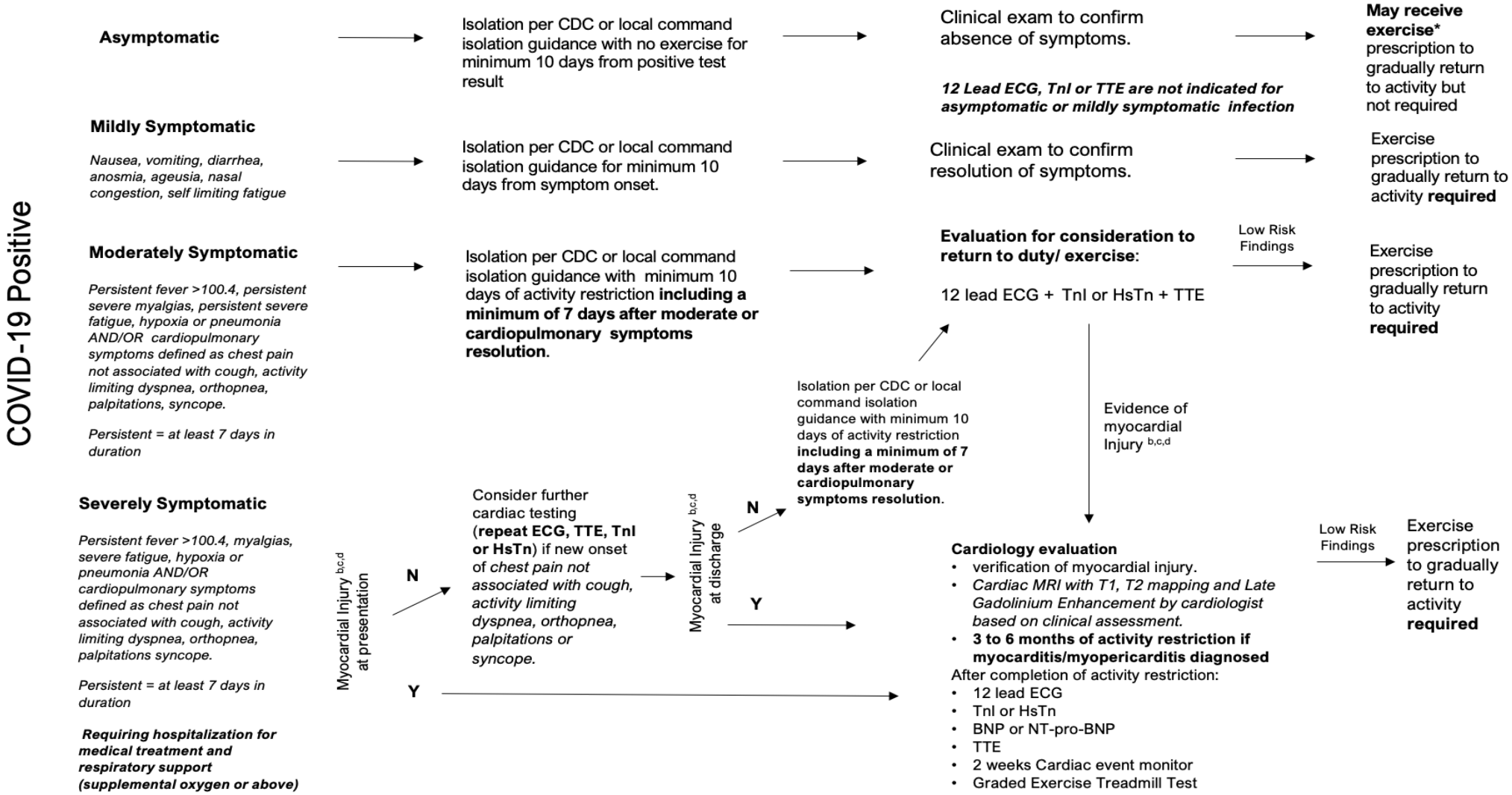

Cardiovascular COVID-related Symptoms

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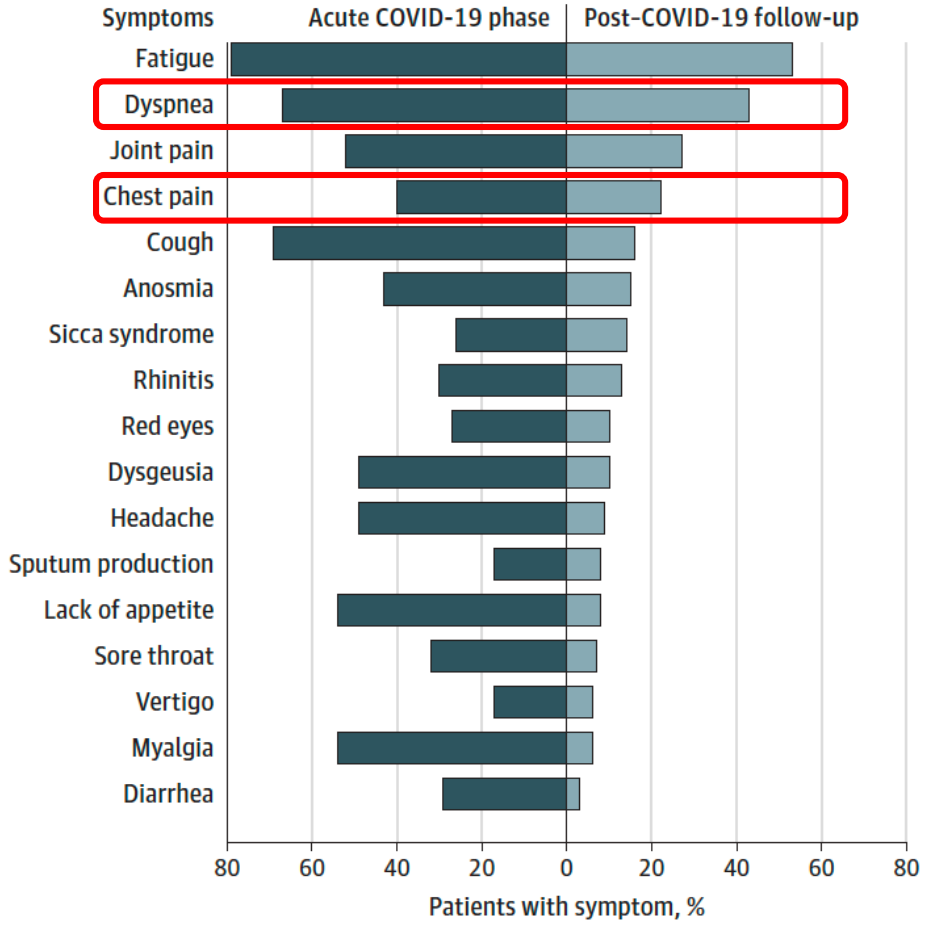
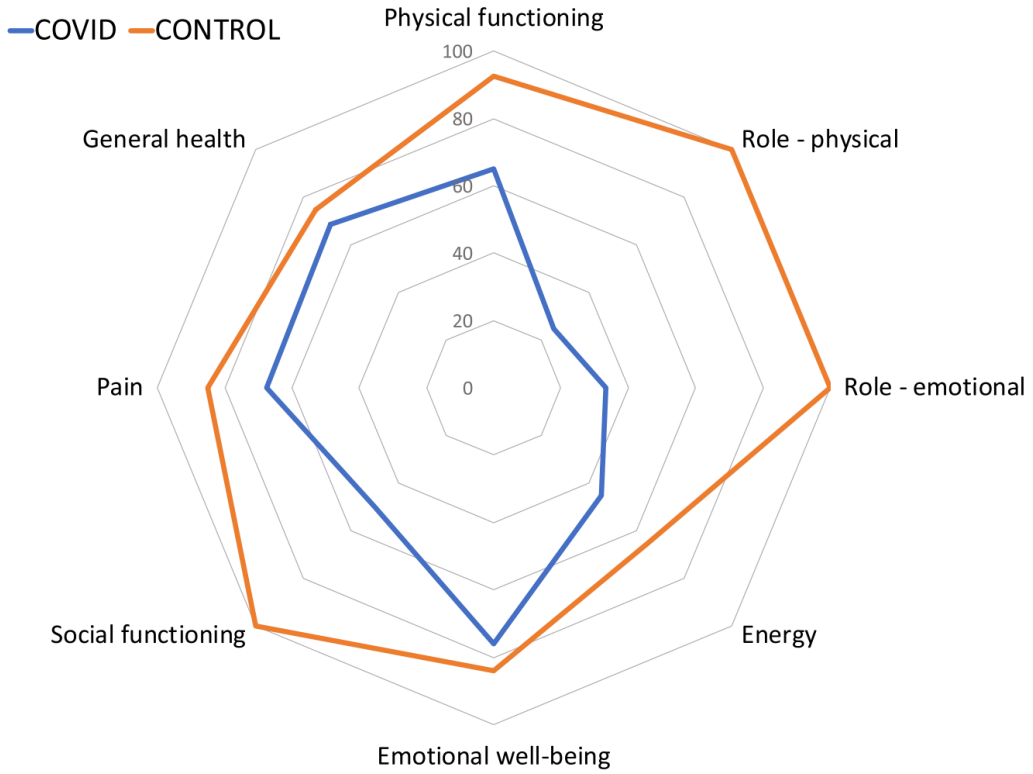
36 Days Post Discharge



60-90 Days Post Discharge

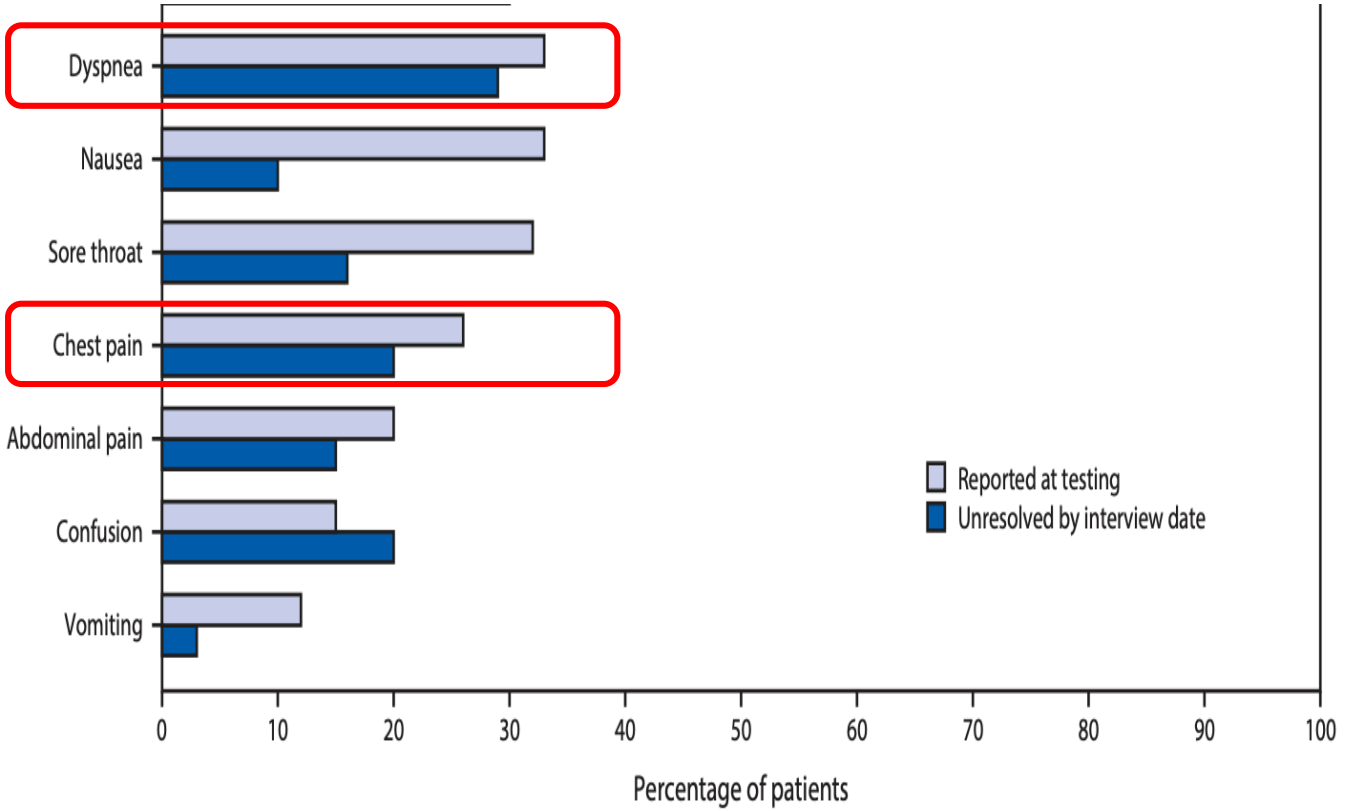


- *JAMA. 2020;324(6):603. doi:10.1001/jama.2020.12603*
- *EClinicalMedicine. 2021;31:100683. doi:10.1016/j.eclinm.2020.100683*

Cardiovascular COVID-related Symptoms

Table. The 10 Most Common Moderate to Severe Long-term Symptoms in Seropositive and Seronegative Participants

Duration of symptom, mo	No. (%) Seropositive (n = 323)	Seronegative (n = 1072)
Dyspnea		
≥2	14 (4.3)	12 (1.1)
≥4	11 (3.4)	10 (0.9)
≥8	6 (1.9)	3 (0.3)
Palpitations		
≥2	8 (2.5)	18 (1.7)
≥4	7 (1.9)	13 (1.2)
≥8	2 (0.6)	7 (0.7)

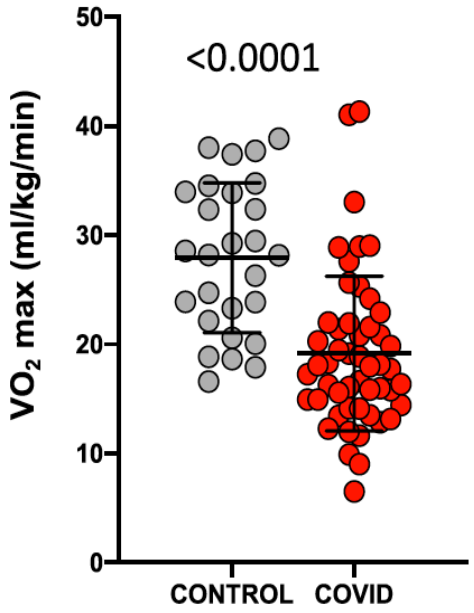


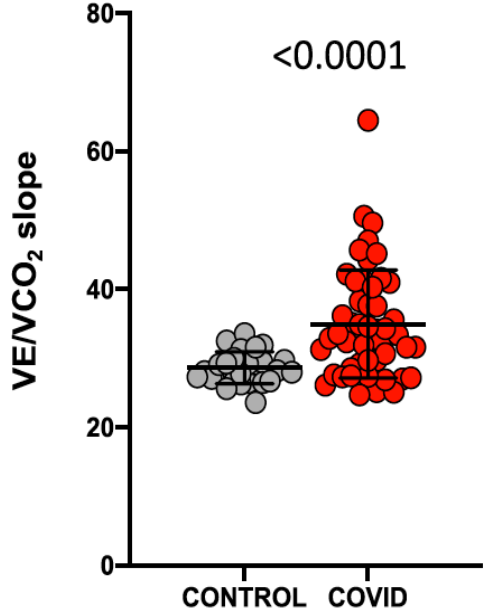
- *JAMA. Published online April 7, 2021. doi:10.1001/jama.2021.5612*
- *Morb Mortal Wkly Rep. 2020;69(30):993-998. doi:10.15585/mmwr.mm6930e1*

Cardiovascular COVID-19 related Symptoms

Spirometry and cardiopulmonary exercise test results from patients and controls.

Spirometry	COVID-19	CONTROL	p-value
FVC, % predicted	108·3 (22·8)	131·4 (21·8)	< 0·0001
< 80%	7/56 (12·5%)	0/28	0·090[ε]
FEV_1, % predicted	101·4 (19·7)	118·7 (22·1)	0·0004
< 80%	6/56 (10·7%)	1/28 (3·6%)	0·42[ε]
FEV_1/FVC	0·77 (0·73 - 0·80)	0·75 (0·70 - 0·78)	0·027[+]
FEF_{25}, % predicted	97·0 (27·6)	110·1 (30·4)	0·020
FEF_{50}, % predicted	81·0 (23·2)	86·9 (24·5)	0·13
FEF_{75}, % predicted	54·5 (42·8 - 70·0)	54·0 (48·5 - 69·5)	0·60[+]
Peak expiratory flow, % predicted	105·7 (27·7)	114·5 (24·7)	0·16
Cardiopulmonary exercise test			
VO_2 peak, % of predicted VO_2 max	80·5 (23·1)	112·7 (27·0)	< 0·0001
< 80%	28/51 (54·9%)	2/27(7·4%)	< 0·0001[ε]
Anaerobic threshold (% of predicted VO_2 max)	40·7 (36·2 - 47·5)	46·8 (43·3 - 51·3)	0·0005[+]
VE/VCO_2 Slope	33·4 (29·2 - 40·3)	28·2 (26·7 - 30·0)	< 0·0001[+]
Oxygen Uptake Efficiency Slope	1·9 (1·6 - 2·4)	2·7 (2·0 - 3·2)	0·001[+]





EClinicalMedicine. 2021;31:100683. doi:10.1016/j.eclinm.2020.100683

COVID-19 & Cardiac Symptoms Among AD Service Members

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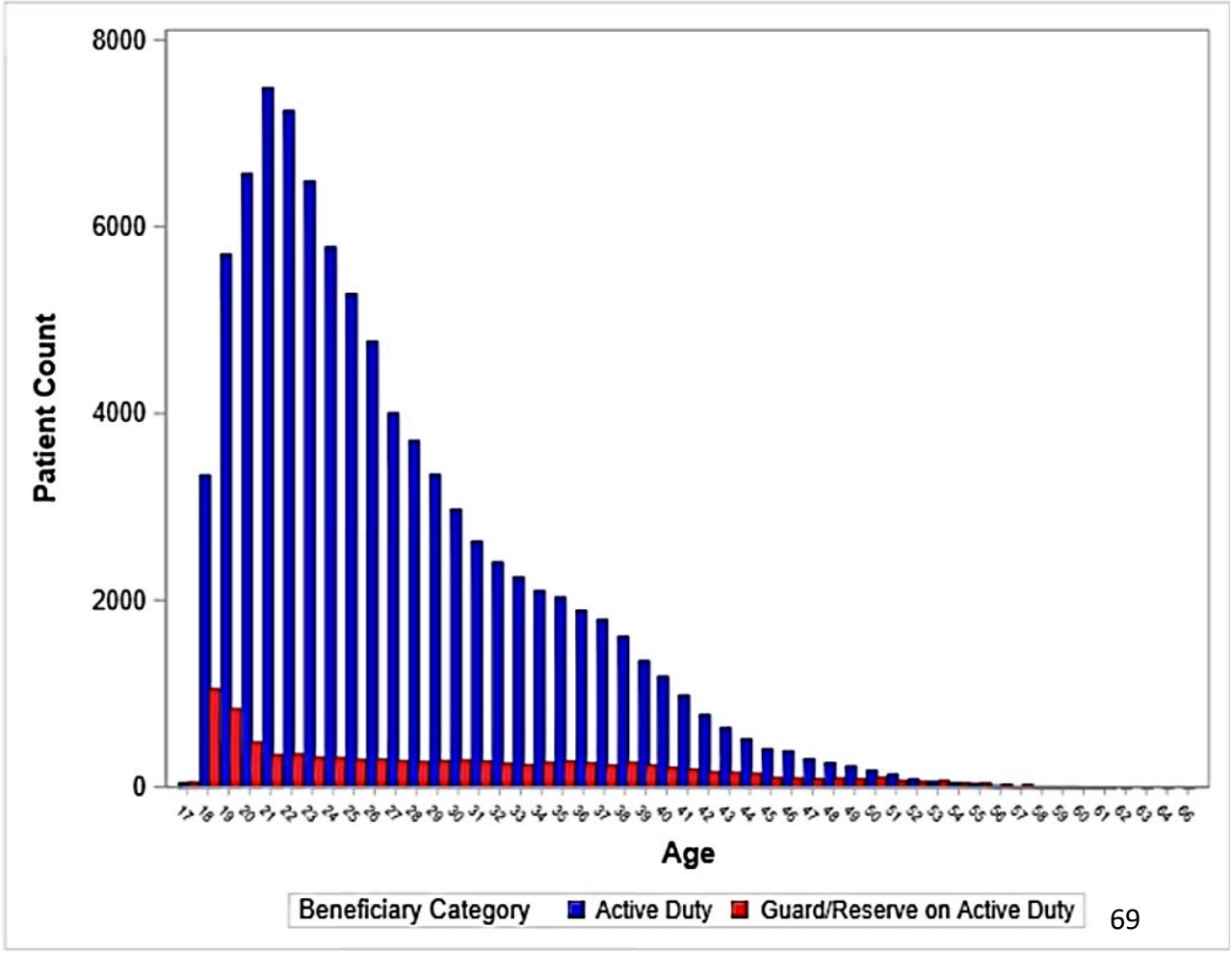
First 30 Days Post Diagnosis

stats - Active Duty beneficiaries: resp		
Effect	OddsRatioEst	ProbChiSq
dx_Cough	4.532	<.0001
dx_ShortOfBreath	5.906	<.0001
dx_PulmEmbolism	3.831	<.0001
dx_Asthma	1.115	0.097

stats - Active Duty beneficiaries: cardiac		
Effect	OddsRatioEst	ProbChiSq
dx_chestPain	4.306	<.0001
dx_palpitations	1.284	<.0001
dx_atrial	1.332	0.1115
dx_syncope	1.733	<.0001
dx_tachycardia	3.337	<.0001
dx_heartFailure	1.069	0.7349
dx_bradycardia	1.877	<.0001

AD Status by Age Feb 2020- Jan 2021, N = 102,006



Clinical Questions To Be Addressed

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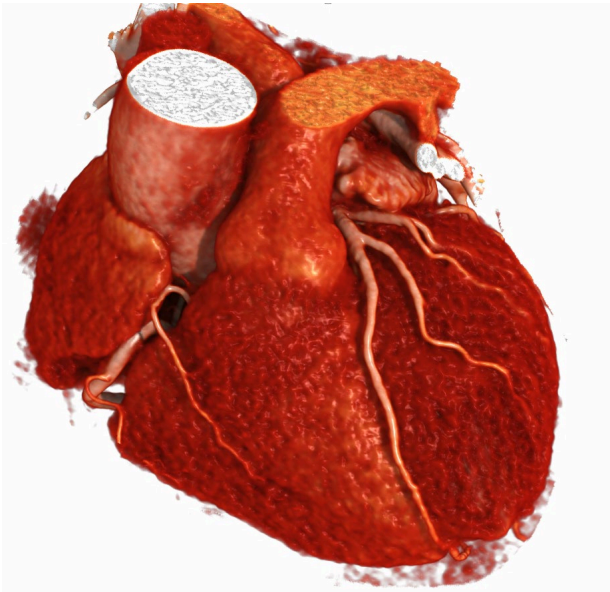
Cardiology Led collaborative efforts between the Cardiovascular Care Community, Military Cardiovascular Outcomes Research (MiCOR) Program, Joint Trauma Service, and EPICC investigators

- What is the incidence/ prevalence of myocardial injury among all AD service members evaluated? (Both hospitalized and non hospitalized)
- What is the incidence / prevalence of myocarditis among AD service members following a COVID-19 diagnosis? How many patients were symptomatic vs asymptomatic?
- What is the incidence / prevalence of arrhythmias, heart failure, pericardial diseases, thromboembolic events among AD service members?
- What is the impact of cardiovascular testing on military patients with COVID-19 in respect to military readiness (looking at return to duty, testing, stratifying by rank/age)?

Summary



- COVID-19 infection has both intermediate and long-term consequences for the cardiovascular system.
- Troponin elevation is likely a consequence of indirect cardiac injury.
- Attention should be paid to athletes with resolved infection with residual cardiopulmonary symptoms.
- Appropriate testing is imperative.

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Neurological and Psychiatric Aspects of Long-haul COVID

Shannon Ford, MD, FAPA, LTC, MC, USA
C-L Psychiatry Fellowship Program Director

As many as 1 in 3 COVID-19 survivors may have a psychiatric or neurological disorder within 6 months of infection.

Taquet et al, The Lancet Psychiatry Vol 8, May 2021
https://doi.org/10.1016/ S2215-0366(21)00084-5

Risk is Not Insignificant

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- Probability of developing a new psychiatric illness within 90 days is 5.8% *(Nalbandian)*
- In the ≥ 65 year old population, 1.6% developed dementia *(Nalbandian)*
- Of the 236,379 records reviewed, incidence of a neurological or psychiatric diagnosis in the following 6 months was 33.62% *(Taquet)*
  - 12.84% with first time diagnosis
  - If hospitalized in the ICU, incidence increased to 46.42%, first time diagnosis 25.79%
  - If diagnosed with encephalopathy incidence increased to 62.34%

Risk Factors for Development

- Gender (female: male – 2.3:1) *(Graham 2021)*
- Age
- Having more than 5 symptoms in the first week of illness (odds ratio 3.53) *(Sudre 2021)*
- History of psychiatric disorders
- Severe acute illness: Encephalopathy, ICU admission, Delirium
- Psychiatric illness did not correlate as closely to severity of illness as the neurological diagnoses did

Reported Neuropsychiatric Symptoms

- Fatigue
- Myalgia
- Chronic malaise
- Low grade fever
- Lymphadenopathy
- Headache
- Hypogeusia/ Hyposmia (1/10 has persistent symptoms after 6mo)
- Blurred vision
- Tinnitus
- Dysautonomia
  - Tachycardia with mild exercise or standing
  - Night sweats
  - Temperature dysregulation
  - Gastroparesis
  - Constipation/ loose stools
  - Peripheral vasoconstriction

Reported Neuropsychiatric Symptoms

- Anxiety
- Depression
- Sleep disturbance (non-restorative)
- PTSD
- Obsessive-Compulsive Symptomology
- Hypomania
- Persistent effects of acute illness:
  - Ischemic or hemorrhagic stroke
  - Hypoxic-anoxic damage
  - Posterior reversible encephalopathy syndrome
  - Acute disseminated myelitis
- Cognitive impairment (brain fog)
  - May fluctuate
  - Difficulty with sustain attention
  - Impaired executive functioning
  - Memory difficulties
  - Global impairment (62% in one small study Miskowiak)

Possible Mechanisms

- Neuronal damage
  Degeneration of functional neuronal and glial cells
- Anoxia
- Immune dysregulation
- Inflammation
- Microvascular thrombosis
- Hypercoagulable state
- Iatrogenic effects of medications
- Psychosocial impacts of infection

- *Sollini et al, March 2021*
- *Guedj et al, Adv Online*

Neuroimaging Findings

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^{18}F-FDG-PET/CT imaging shows brain hypometabolism in the…

- Right Parahippocampal Gyrus
- Right temporal lobe
  - Amygdala
  - Hippocampus
  - Thalamus
  - Bilateral pons/ medulla brainstem
  - Bilateral cerebellum
- Bilateral rectal/ orbital gyrus
  - Olfactory gyrus
- Locations consistent with patient's reported persistent symptoms
- Supports hypothesis of systemic inflammation as contributing factor

Assessment/ Treatment Options?

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- Standard screening tools and therapy modalities are generally appropriate
- Multi-disciplinary rehabilitation effort
- Ensure adequate nutrition in recovery
- Address health anxiety and depressive symptoms associated with hopelessness
- No literature currently suggests that using psychotropic medications to treat comorbidities causes worsening of physical symptoms
- Assess and treat any underlying suicidality
  - Illness is frightening and disabling
  - Medical knowledge about virus and recovery can be contradictory and uncertain
  - Small improvements can be followed by large setbacks (emotional and physical)

Next Steps - Potential Pitfalls

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Medically Unexplained Symptoms ≠Psychogenic illness

- Case report in 2020 discussed that the virus could have ”substantial” impact by exacerbating or suggesting psychiatric illness independent of being infected
  - Fear of developing disease and being diagnosed
- Qualitative study showed that fluctuating symptoms were often exacerbated by uncertain prognosis and stalled recovery

Next Steps - Potential Pitfalls

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- Using out of date protocols *(Vink, 2020)*
  - Cognitive Behavioral Therapy (CBT) is effective in reducing depression, anxiety, and stress in hospitalized patients with COVID-19 when compared to no treatment
  - CBT is no longer considered a standard of care for treating fatigue associated with myalgic encephalomyelitis/ chronic fatigue syndrome despite previous studies' claims; do not anticipate it will be efficacious in this population
  - Alternative: "NICE guideline" (nice.org.uk/guidance/ng188) is a living document
- Failing to pursue this from a multi-disciplinary perspective
  - Access to care issues
  - Lack of clear pathway for treatment without referral guidance

Opportunities for Future Research

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- Unique opportunity to study clinicians and scientists who have both clinical and experiential knowledge
  - Occupational exposure + multisystem complications
- A few active studies:
  - What are the physical examination and brain-imaging characteristics in those with persistent neurological symptoms in post-acute COVID-19?
  - What are the long-term psychiatric sequelae of COVID-19? (At least 3)
  - Impact of COVID-19 on Dementia Risk, Progression and Outcomes in ADRD Populations
  - Neurological and Neurocognitive Sequelae from SARS-CoV-2 Infection and COVID-19 in Aging and Age-Related Neurodegeneration

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Long-haul COVID-19 and the BAMC Acute Care Clinic

Alison Wiesenthal, M.D., BAMC
Uniformed Services University of the Health Sciences,
Chair, Dept. of Rehabilitation, BAMC

Disclosures

- Dr. Wiesenthal has no relevant financial or non-financial relationships to disclose relating to the content of this activity.
- The views expressed in this presentation are those of the author and do not necessarily reflect the official policy or position of the Department of Defense, not the U.S. Government.

Lingering COVID-19 Symptoms

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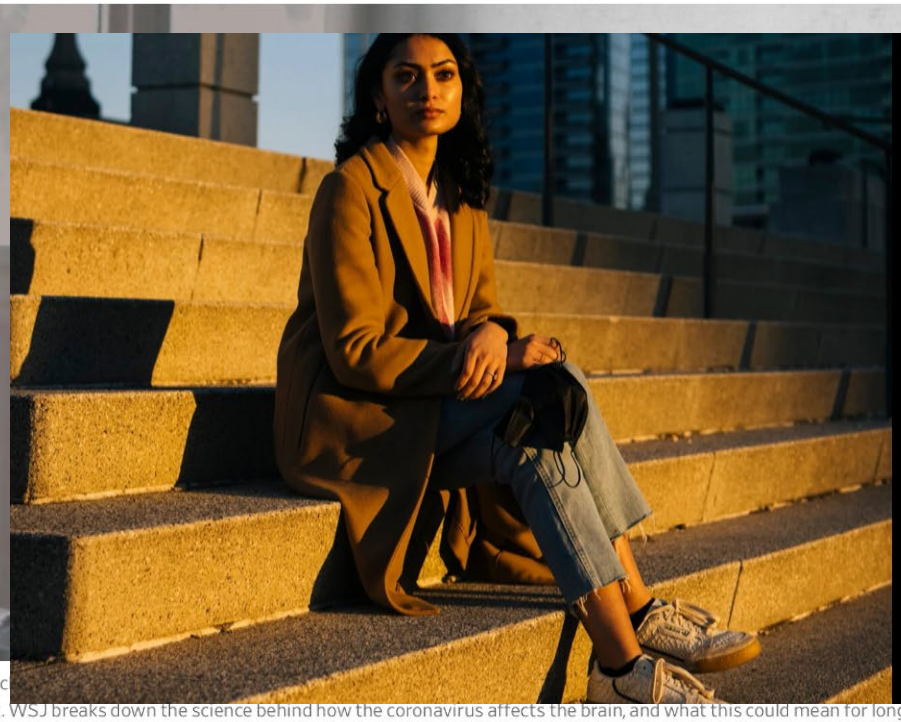
They Got Covid One Year Ago. They're Still Sick.

Scientists are putting new effort into understanding the troubling symptoms of long Covid. These patients are waiting for answers.



New researc
getting sick. WSJ breaks down the science behind how the coronavirus affects the brain, and what this could mean for long-haul patients.
Illustration: Nick Collingwood/WSJ

They Had Mild Covid. Then Their Serious Symptoms Kicked In.

A new study illuminates the complex array of neurological issues experienced by people months after their coronavirus infections.

CNN health Food Fitness Wellness Parenting Vital Signs • LIVE TV Edition

7 in 10 people hospitalized for Covid-19 have not fully recovered five months after discharge, study says

By Meera Senthilingam, CNN

Updated 10:58 AM ET, Wed March 24, 2021

(wsj.com, 2021); (nytimes.com, 2021); (cnn.com, 2021)

Post-Acute COVID-19 Defined

- **Post-acute COVID-19:** Persistent symptoms and/or delayed or long-term complications of SARS-CoV-2 infection beyond 4 weeks from the onset of symptoms
- **Subacute or ongoing COVID-19**: symptoms from 4–12 weeks beyond acute COVID-19
- **Chronic or post-COVID-19 syndrome**: symptoms and abnormalities persisting or present beyond 12 weeks of the onset of acute COVID-19 and not attributable to alternative diagnosis

Post-COVID Care Clinic: A New Frontier

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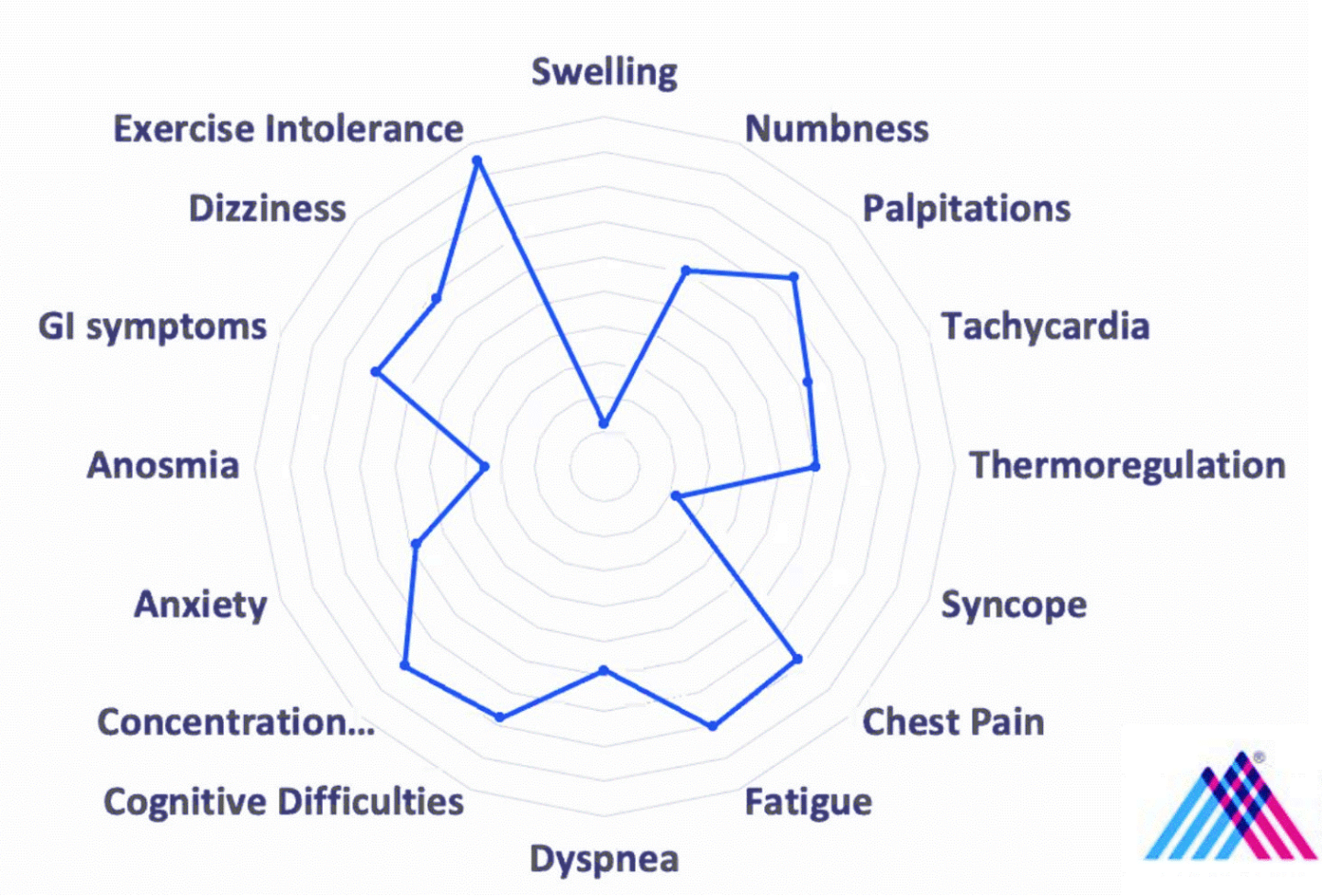
- **Program Goal**: Provide comprehensive interdisciplinary care to patients in the convalescent phase of the COVID-19 disease
- **Methodology Structure**: Interdisciplinary Working Group to support the diverse needs of ‘long-haulers’
- **COVID-19 Patient Program Enrollment**: The program will be activated for each patient with a prior diagnosis of COVID-19 and long-term sequelae causing symptoms or disability

Post-COVID Symptoms



BAMC's Post-Acute COVID-19 Interdisciplinary Care Team: We're all in this together

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Mental Health
- Depression / Anxiety
- PTSD

Speech Pathology
- Aspiration
- Dysphagia & Speech
- Tracheal Stenosis

Cardiovascular
- Cardiomyopathy
- Ischemic Events

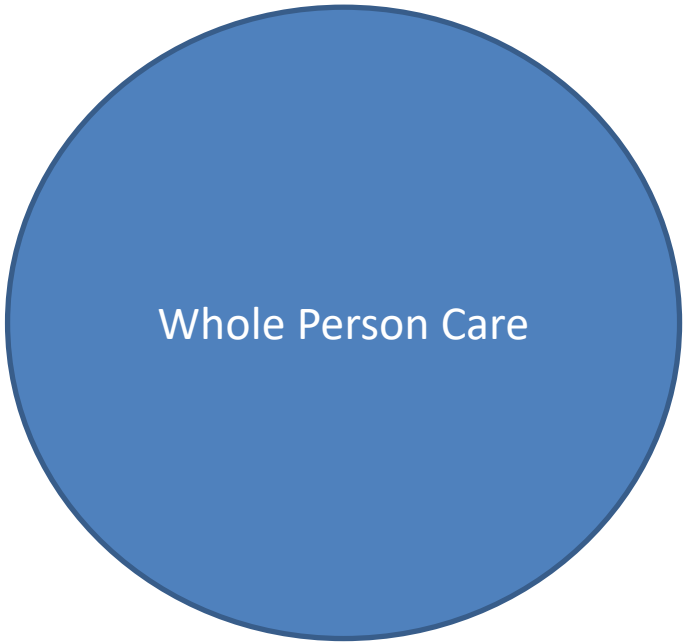
Infectious Disease
- COVID-19 Reinfection
- Disease Resolution

Social Work
- Psychosocial Needs

Whole Health
- Complementary therapies
- Self-care

Audiology
- Tinnitus
- Vestibular Issues

Primary Care
- Symptom Control
- Outpatient Care Coordination
- Goals of Care
- Early Decline / Frailty



Neurology
- Delirium
- Dementia
- Neuropathy
- Myopathy
- Stroke

Pulmonary
- Pulmonary fibrosis
- Interstitial lung disease
- Dyspnea

Immunology
- Immunosuppression
- Inflammation

Rehabilitation
- Weakness/Disability
- Brain Fog
- Arthalgias/paresthesias

Pharmacy
- Anticoagulation Needs

Chaplaincy
- Spiritual Needs

"Medically Ready Force…Ready Medical Force"

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Thanks for all you do…

…JTS, Out.