

Transcript

Beth Linas

Hello, I'm Beth Linas from the RECOVER Administrative Coordinating Center, and the moderator of today's webinar. Welcome to the RECOVER Research Review, our R3 seminar. The goal of this webinar series is to catalyze a shared understanding of the research within the RECOVER consortium. The topic of today's seminar is cardiopulmonary function in PASC. It's important to note that this seminar series is focused on scientific research, and is not intended to provide any clinical guidance. I want to start by thanking everyone who submitted questions. Please submit any questions that arise today using the Q&A feature in Zoom. After the presentation, we'll answer as many questions about today's topic and presentations as possible. Some questions may also be answered within the Q&A. An FAQ document for the seminar will be posted with the recording of the seminar on recovercovid.org. That'll include the answers for questions relevant to the seminar that were submitted in advance, or today.

Questions about other scientific topics will be addressed in future webinars, and answers to broader questions about RECOVER, will be available in the FAQs at recovercovid.org. Today's speakers will discuss what is known about cardiac function in PASC, the gaps in our knowledge and how RECOVER will contribute to filling these knowledge gaps. Today, we'll hear from Dr. Alope Finn, a Physician Scientist, Medical Director, and Chief Scientific Officer for CVPath Institute at the University of Maryland, and a PI for the cover autopsy study. Dr. Finn oversees device development research, and runs a molecular lab with the focus on molecular understanding of vascular wall injury and healing, genetics of sudden cardiac death, molecular basis of coronary artery disease, and pathogenesis of COVID-19 induced cardiac injury.

Dr. Su, the Director of Cardiomyopathy and Cardiac Heart Function Program at Children's Hospital, Los Angeles, whose research interest include biomarkers of heart failure and myocarditis, mechanical circulatory support, heart transplantation, and cardio genomics. And Dr. Matt Oster, a Pediatric Cardiologist at Children's Healthcare of Atlanta, and Associate Professor of Pediatrics and Epidemiology at the Emory School of Medicine and School of Public Health. He also serves as a medical officer at the CDC's National Center on Birth Defects and Developmental Disabilities, and is currently working on CDC's COVID response. His research interests include newborn screening for congenital heart disease, long-term outcomes for patients with congenital heart disease, and cardiac effects COVID-19 and COVID-19 vaccination.

We will also be joined by two discussants, Dr. Anuradha, the Director of Heart Failure Research and Transplant Fellowship at the Icahn School of Medicine at Mount Sinai. Her clinical interests encompass all aspects of management of heart failure, including the selection and care of patients with mechanical circulatory support devices and heart transplantation, as well as preoperative management of high risk cardiac surgical cases. And lastly, Dr. Erika Berman Rosenzweig, Director of Pulmonary Hypertension Center at Columbia University Medical

Center, New York Presbyterian Hospital. Dr. Rosenzweig is also the Director of the Pediatric Pulmonary Hypertension Network of North AmErika. Her research focuses on the study of novel treatments for pulmonary arterial hypertension with a strong interest in novel mechanical support for pulmonary hypertension and right ventricular failure, and the genomics and deep omics signatures of pulmonary hypertension. So thank you, and I will hand it over to Dr. Finn.

Dr. Alope Finn

Great. Thank you so much for that introduction. Can we go to my first slide here? I'm going to be talking about the pathogenesis and mechanism of cardiac injury including myocarditis in COVID-19. And thanks so much to the NIH and everyone else here for allowing me to give this talk. Next slide. Those are my disclosures, no relevant disclosures to this discussion. Next slide. I'm going to take you back a little bit to a time you may or may not want to remember, February 23rd, 2020 when we started to realize the number of cases of COVID-19 in Italy were really exploding, and at this point had really not come to the United States. We weren't really aware of the incredible dangers that we were going to face, but the cases in Italy were really increasing exponentially, especially in the Lombardi region north of the country, that was hardest hit. And remember, they were underwent a lockdown, and then cases spiked across Europe and Latin AmErika. And then of course, on February 28th, we had our first AmErikan COVID-19 death in Seattle. Next slide.

We were in touch with people in Italy at the beginning of the pandemic. We have a lot of international contacts in our research, and we had been in touch with clinicians in Italy, and they had been telling us about cases they had received. And I'm going to review one of these, just to give you a taste or an idea of the kind of things and questions we began to ask after seeing these cases. I feel like personal cases are always the best to bring problems home to people. This was a case of a 43-year old female that presented in Bergamo, at the time of the exponential rise in COVID in 2020 in February. She had been assisting her husband who had, had hospitalized with COVID-19 interstitial pneumonia. She had complaint of abrupt onset chest pain. A 12-lead EKG had been performed two hours after symptom onset, and documented extreme cardiac injury called ST-elevation MI, in the inferior lateral leads. And she was transferred to Bergamo for urgent coronary angiography, and PCI suspecting she had had a heart attack. Next slide.

She was awake as she was hypotensive. Quite sick lady, young lady. Quite sick, high heart rate, breathing was okay. Her echocardiography was done there at the bedside with ejection fraction of 25% with global hypokinesia, and her labs were for the most part okay, except for her troponin I. Her measure of cardiac injury was extremely high at 11,000. Next slide. So this was the EKG. Those of you are familiar with reading EKGs can see that it clearly shows cardiac injury. Next slide. Here's the angiography. Of course, this lady was rushed to angiography, and the corner angiography actually revealed, I don't know if you could play the second one, but it basically shows normal coronary arteries in this young lady that was suspected of having a large heart attack. Next slide.

Questions were really mounting amongst caregivers for this young lady. The nasopharyngeal swab was positive for COVID-19, and she was on antiretroviral therapy. Despite hemodynamic support, she was hypotensive with the poor cardiac indirects, and the repeated EKG showed diffuse ST-segment elevation with severe left ventricular dysfunction. Next slide.

So, there was desperation on the part of the caregivers. She was given actually high dose methylprednisolone and immunoglobulin, suspecting she had myocarditis induced by COVID-19. Nonetheless, she really became sicker and sicker and deteriorated, and eventually died on the 46th hour after admission. Next slide.

So this case speaks to the issue of cardiac injury in subjects with COVID-19, and what exactly is its cause. Now, there have been multiple studies done since this case that have showed that subjects with elevated cardiac troponins, are not uncommon during COVID-19 infection, accounting for about 36% of patients in some studies. And that if you have elevated cardiac troponin levels consistent with cardiac injury, your mortality rate is significantly increased, and it really is dependent on the level of cardiac troponin elevation. So it's important to understand that cardiac injury is not uncommon, and that its causes need to be understood in order for us to deal with this during COVID-19. Next slide. And this just shows a level of cardiac injury. The level of troponin release in the blood correlates with not only hospitalization, but also a less discharge and higher mortality as your troponin levels go up. Next slide.

And this slide also shows that basically, in Italy, under all patients underwent coronary angiography, those with cardiac injury, and out of 28 patients, 17, 60% had culprit lesion requiring revascularization in this study of STEMIs, but 11 patients, that is almost 40%, did not have obstructive coronary disease, but had evidence of cardiac injury on the EKG. So really raising questions about what is going on with COVID-19, how is it injuring the heart? And you can see on the right hand slide, this graph shows that people with COVID-19 have elevated risk of multiple complications after ST-elevation MI, versus those without COVID-19. Next slide.

This has been studied many times, and it just goes to review with you the number of studies that have been done on cardiac injury of COVID-19. Many have shown associated with increased risk of in-hospital mortality. Next slide. And this raised a lot of questions at the time. Another paper was done in 2020 in July, which was a study of people who had recovered from COVID-19, and of those people, they studied the heart with cardiac MRI, and they had reported here that 78% had normal cardiac MRI findings, and that really raised concerns about COVID-19 and its longterm effects on the heart. Next slide.

And really, the news media got wind of this, and it came up with all kinds of things, such as COVID-19 can wreck your heart if you had any symptoms. A lot of rumor and innuendo was out there, and really correcting to make factual statements was extremely important in our mind. Next slide. And the mechanisms of cardiac injury in COVID-19 were proposed to be many. One such thing would be an oxygen supply demand imbalance causing a Type 2 MI that is demand MI. Some people suspect there was direct viral invasion of the heart, causing myocarditis. Other people suspected there could be microvascular thrombosis, other people suspected it was

inflammation, other people suspected it was related to increased risk of artery disease and thrombosis. Really, it was unknown at the time what was the cause of these cases. Next slide.

We had learned from previous data, using SARS. Now, coronaviruses are families of enveloped positive-sense, single-stranded, highly diverse RNA viruses. There're basically three documented, highly pathogenic and lethal human coronaviruses. SARS-CoV, which is the predecessor to SARS-CoV-2, COVID-19, Middle East Respiratory Syndrome and SARS-CoV-2, obviously. And SARS-CoV-2 shares most of its homology with SARS-CoV. And this was data from SARS-CoV earlier in the literature that was published in 2009, showing that of these autopsy cases of people that had died of SARS-CoV, about seven out of 20 had evidence of SARS-CoV in their heart. Now the heart wasn't that well studied at the time. There weren't that many cases, because it was mitigated quickly by intense public health measures, but it was evidence that SARS-CoV could be found in the heart. And that made us raise questions about whether SARS-CoV-2 could be as well. Next slide.

We conducted a initial study to see whether the receptors for SARS-CoV-2, ACE2 and TMPRSS2, could be founded in the heart. I won't go through all the details of this slide, but just to summarize, yes, these receptors were found in the heart and the potential of direct infection was possible. Next slide. And to talk about myocarditis, myocarditis itself is an inflammation of the heart caused by viral pathogenesis for the most part, and it consists of three distinct phases. The first phase is destruction of cardiomyocytes through occurrence of virus-mediated lysis, direct lysis. Second phase is viral infection, involving trigger of immune cells. And third phase could be a dilated cardiomyopathy. Now in the clinic, myocarditis is mainly diagnosed by clinical presentation, and really associated with just clinical rather than pathologic evidence. Next slide.

If you have, for instance, cardiac enzyme elevation, exclusion of coronary artery disease, history of viral predone, we really diagnosed that in the clinic as myocarditis. However, there are specific evidence or there's specific data that correspond to histological evidence from biopsies and autopsy hearts of myocarditis, and that was defined by the Dallas criteria. I won't go over the details for you, but more recently, immunochemical criteria have been defined for myocarditis, and these should be met to make the definition of myocarditis. And it's really the pattern of inflammatory infiltrate in the presence of myocardial degeneration that defines myocarditis. Next slide.

We went through and asked everyone, Hey, what are the exact details and evidence that SARS-CoV-2 could cause myocarditis? So at the time this was done in 2020, we went through all the literature that summarized autopsy and biopsy cases of subjects having SARS-CoV-2 that were conducted, and in how many of those cases was actual myocarditis, that is the histologic definition found. And this just goes through all the studies reviewed. Next slide. Here there's more studies. Next slide. The punchline was that myocarditis that is direct viral invasion of the heart, was found in very, very few of the subject study. 4.5% of the subject study had direct pathologic evidence of myocarditis. Next slide.

At the same time, we had struck a research agreement with the people in Italy, in Lombardi region at this hospital, to start doing a systematic examination of subjects dying of COVID-19, to try to discover what the pathogenesis of cardiac injury was in COVID-19. Now at the time, these patients were dying quite readily, as I told you before. And those hearts were then preserved by the autopsy pathologists and sent to our Institute for examination. Next slide. And you can see here of this as the first 16 subjects sent their hearts. You can see, I just want to summarize for you that in essence, we didn't find a single case in these 16 hearts of myocarditis. Next slide.

What we did find was that people dying of COVID-19 infection could have non-specific inflammation in their heart associated with that infection. In this particular study, we compared control hearts, that is hearts of people dying of things like traumatic deaths, to people dying of COVID-19 without evidence of cardiac, in specific cardiac injury. And we look at the number of inflammatory cells in the myocardium, and you can see for the most part, we saw less T-cells, but more CD68 positive macrophages in those hearts, although we did not see evidence of myocarditis as illustrated on the illustration on the right hand side. Next slide. We then conducted a more systematic study in these 40 hearts that had been sent for us. All the patients had been diagnosed with SARS-CoV, either by nasal swab or post-mortem reverse transcription polymer chain reaction. And we did demographic medical history, clinical precision, did a whole pathologic exam on the heart. Next slide.

And we defined cardiac injury in two different ways. We said that either we could define it as a acute myocardial infarction, that is an area of myocyte necrosis greater than or are equal to one centimeter squared, or as focal myocyte necrosis, that is a small area of cardiac injury, greater than 20 myocytes with an area of necrosis that was very small, greater than or are equal to 0.05 millimeter squared, but less than one centimeter square. So we divided cardiac injury into these two sub-segment past thing. Myocardial infarction as well as focal myocyte necrosis. Next slide. And this is just an example. Myocardial infarction obviously is a large area of myocardial injury and death of myocytes. You can see that on the upper slide there with the intercept wall of this particular subject, having an infarction. Focal myocyte necrosis is much smaller, areas of small infarcts. Next slide.

And these were the patients, and these were the demographics. I don't want to deal with all the issues right here with this, but I can just tell you that overall, I want you to notice that myocyte necrosis was found in 14 of the 40 hearts. So it was not uncommon about the same percentage I showed you before for cardiac injury. Next slide. Now, this is an interesting slide. Here I can tell you how many people had acute myocardial infarction of those 14, versus how many had focal myocyte necrosis. So you can see the majority of subjects with COVID-19 had focal myocyte necrosis, not acute myocardial infarction. And you can see that the thrombus was characterized for the most part as micro thrombi. That is small thrombi and arterials lodged in distal vessels, small vessels, rather than large epicardial coronary arteries. Epicardial coronary artery infarction was found in the minority of cases with myocyte necrosis, 14.2%, versus microthrombi.

And I want to point out to you, some of these cases of course, had existing coronary arteries, but not a lot. And myocarditis was found in none of these cases. Next slide. Here are the cases. I won't go through the details, but you can see, what I want you to notice in the right, is the majority of these cases with cardiac injury had microthrombi. Next slide. And you can see, when we look at cases with focal myocyte necrosis, the majority of those cases had microthrombi, whereas subjects without myocyte necrosis, there were hardly any microthrombi found. Next slide. Now there was evidence in the literature about having direct viral infection of endothelial cells. We looked for direct viral infection of endothelial cells, as well as a positive, positive relationship between microthrombi and COVID-19 injury. Next slide.

And you can see here that we found that... Did you skip a slide? Can you go back one? No, next slide. That's fine. You can see here that I'm showing you microthrombi, small thrombi, large and smaller in the arrows there. We looked at evidence of myocardial infection of the heart with SARS-CoV-2, using in situ hybridization and TM. We could not find any. And we found that overall, there were much more positive SARS-CoV-2 PCR in the lung than in the heart. You can see that a total of 85% of cases were positive for lung SARS-CoV-2 virus found there by PCR, versus only 20% of cases having positive in the heart. And there was no relationship between myocardial necrosis, and having the presence of SARS-CoV-2 found in your heart. In fact, more cases had SARS-CoV-2 of no necrosis that had necrosis evidence of SARS-CoV-2 in the heart. Next slide.

And I want to go back to this lady that I presented in the initial case report that I showed you from Italy. You can see here that we looked at her heart to examine what had happened to this woman, and what had caused her to have such a tragic fatal outcome. And what we really found was, we found extensive microthrombi throughout her heart that were the cause of her demise, causing cardiogenic shock and death. And this was consistent with an acute inflammatory infiltrate in the heart, as well as myocyte necrosis, which was extensive throughout the heart. Microthrombi could also be found in other organs, such as the kidney and the spleen, showing you that COVID-19 pathogenesis microthrombi, are an important thing that needs to be looked at. Next slide.

Now I want to switch topics a little bit to longer term follow-up, because we're interested in the RECOVER study and long-term follow-up. Acute cardiovascular outcomes of COVID-19, as I just told you, are well described, but the post acute cardiovascular manifestations of COVID-19 have not been comprehensively analyzed. And this is a study from the VA which was very interesting, published in Nature of Medicine 2022, which was analysis of VA subjects with COVID-19 and two sets of contemporary controls, to estimate the risks of year of burdens of incident cardiovascular outcomes. And beyond the first 30 days, individuals with COVID-19 were at increased risk, excess increased risk of cardiovascular disease. And you can see the type of disease we're talking about, dysrhythmia, ischemic heart disease, other cardiac disorders, thrombotic disorders. So these risks increase over time, even if you recover from COVID-19, and these were not just hospitalized patients, these were non-hospitalized patients as well.

Tell you just to end, that the RECOVER autopsy cohort will study long-term COVID autopsies to try to understand what is the pathogenesis of cardiovascular outcomes after COVID-19 in patients who have lingering symptoms, and don't have lingering symptoms. Is there any long-term sequelae at having COVID-19? So in summary, I'll just summarize my findings, which are essentially that subjects with COVID-19 are at high risk for cardiovascular events, and those cardiovascular events correlate with mortality. And our own investigation, what we found was, myocarditis was an infrequent cause of cardiovascular mortality. It was really microthrombi and thrombotic events that were much more common in hospitalized patients with COVID-19. And we did not find evidence for direct viral invasion of endothelial cells or any other cells in the heart as causative in its pathogenesis. I think the RECOVER autopsy court will give us more evidence for what the long-term sequelae and evidence is in the heart for a long-term COVID-19 induced cardiac injury. So with that, I'd like to thank you for attention.

Dr. Jennifer Su

Thank you, Dr. Finn. It's really nice to hear about the adult experience with myocarditis and also reassuring that it mirrors the pediatric experience. And so, for the audience, I'm Dr. Jennifer Su, I'm the Director of Cardiomyopathies and Heart Function at Children's Hospital of Los Angeles. I'll be sharing with you the clinical spectrum of COVID myocarditis in kids. Next slide. I have no relevant disclosures or conflicts of interest. Next slide.

So I'll start again by an example case. This is a girl that we first met early on during the pandemic. She was a 15-year old, previously healthy girl who was hospitalized early in 2020 with atrial flutter and acute decompensated heart failure, requiring support with extracorporeal membrane oxygenation, otherwise known as ECMO. Her cardiac MRI findings met criteria for acute myocarditis with the Lake Louise Criteria, although endomyocardial biopsy didn't show any evidence of inflammation or active infection. Next slide. We extensively evaluated her for infectious causes, and she was negative for all traditional causes of myocarditis. Her SARS-CoV-2 PCR was also negative, but interestingly, her anti-SARS-CoV-2 IgG antibody titer was weakly positive upon presentation. And then we found a fourfold increase in her IgG level a month later. Next slide.

Next slide, please. Here is her presenting echocardiogram. So this is what we call an apical four-chamber. It shows the four chambers of the heart, as you can see, the interesting things about this echocardiogram is that her heart rate is incredibly elevated for her age. Again, she was in atrial flutter at some point. And in addition to that, while her left ventricle on the bottom right corner here is dilated, it's not extensively dilated. So it would actually indicate for us that this is a rather acute event, not something that's been going on for too long. And of course, the final thing is that her heart is just not pumping, usually you see much better squeeze than that. Next slide, please.

So we cardioverted her, and upon DC cardioversion, she regained sinus rhythm. She was supported for two weeks with ECMO and finally decannulated two weeks later. She's also successfully waned off of inotropic support by about three weeks. And so, based on the timeline of our patient's clinical course, our team at the time

speculated that her recent COVID infection was somehow responsible for the isolated symptoms of arrhythmia and cardiac dysfunction. And so, I would like to see what you guys think, but before that, I'll provide you with some more information. Next slide, please.

Just to review what Dr. Finn had said about COVID in the heart, in adults, about 19 to 28% of patients diagnosed with COVID-19 exhibit evidence of myocardial injury. In kids, however, COVID-related myocardial injury is much less common. And most published reports of COVID-related cardiac injury in kids, are mostly in the setting of MIS-C or mRNA vaccine associated myocarditis. Next slide.

Here are a few of the more common reasons for COVID-19 affecting the pediatric heart. So first off there's cardiogenic shock, which is perhaps the most extreme manifestation of cardiac disease, which is a severe systemic inflammation causing complete cardiovascular collapse. These patients, if not caught early, can have a very high risk for mortality. Myocarditis, which we're focusing on today, can range from mild to a fulminant myocarditis. It can be a result of an active infection from the virus causing damage to the heart, or a post-viral immune mediated response, and there is definite overlap between the two. Cor pulmonale refers to right heart failure due to acute pulmonary hypertension, which can be precipitated in the setting of COVID-19 by a pulmonary embolism or acute respiratory distress syndrome. And multisystem inflammatory syndrome in children, otherwise known as MIS-C, is a rare, but perhaps the most well known cardiac complication in kids after COVID-19. Its features include rash, fever, gastrointestinal symptoms, shock and myocarditis. And this is, again, after a recent COVID infection.

And cardiac arrhythmias. So QT prolongation, atrial arrhythmias, ventricular arrhythmias, cardiac arrest, AV node block, sinus arrest, they've all been reported in association with COVID, and perhaps sometimes as a result of myocarditis. Next slide, please. In pediatric myocarditis and actually in myocarditis in general, there's many different descriptions, and it can be really easy to get caught up in the details or because of these different ideologies be confused. So there are descriptions based on clinical presentation and timing. And for these, the examples would be fulminant myocarditis, acute, subacute or chronic. There are descriptions based on etiology, such as viral, immune-mediated, allergic myocarditis. And finally there's descriptions based on pathology, so lymphocytic myocarditis, sarcoidotic myocarditis, giant cell. These descriptions are not mutually exclusive, and so for example, a child with COVID-19 myocarditis can also be described to have fulminant myocarditis.

Next slide, please. So in diagnosing myocarditis, endomyocardial biopsy with histologic confirmation, is still considered the gold standard. However, this is based on the Dallas Criteria and an update 30 years later, Dallas Criteria was first started in 1986, so that's 40 years ago. And since then, more recently, academic pediatrics has been moving toward making the diagnosis with cardiac MRI. So cardiac MRI in the last decade has really been helpful in diagnosing myocarditis with the Lake Louise Criteria. With clinical correlation, it can be more than 80% accurate in diagnosis. And then there's clinical symptoms with abnormal cardiac studies in absence of another identifiable cause. This is probably the most common way of diagnosing myocarditis. The other cardiac studies that don't quite meet criteria for confirmed myocarditis, include a troponin leak, which happens very rarely in kids

outside of a coronary anomaly, abnormal EKG consistent with myocarditis. So a new onset AV nodal block, ST elevation, which also is pretty rare in kids, cardiac dysfunction by echocardiogram in absence of another reason, or abnormal cardiac MRI, not meeting Lake Louise Criteria. Next slide, please.

So in pediatric COVID-related myocarditis, there are probably two main mechanisms of myocarditis as Dr. Finn had alluded to earlier. There's active myocarditis in which the SARS-CoV-2 virus directly infects myocardial cells, causing damage and inflammation. Evidence of viral presence can be detected by blood and myocardium by biopsy. And then there's the postviral myocarditis in which immune mediated lymphocytic myocarditis that is triggered by common viruses, such as the coronavirus. This has been known to be more common in influenza viruses and coronaviruses. And so, we would find an absence of viral genome in the blood and myocardium, and the diagnosis would be mainly based off of clinical history and cardiac MRI or biopsy results. Next slide, please.

In our experience, and in what is the very sparse literature reports of COVID-related myocarditis in pediatrics, clinical presentation tends to be fulminant or acute, and this is also because subacute and chronic forms of COVID-related myocarditis are most likely under-reported. First of all, there's reporting bias, because the fulminant and acute presentations really do take precedence when we try to report our experiences and warn other institutions. And also, it's just frankly, quite hard to prove causation in subacute and chronic myocarditis, where you don't really have evidence and it's speculative. Next slide.

So, how frequently do we see COVID myocarditis in kids? In a healthy child, the risk of myocarditis in general, is incredibly low. It's one to four in a 100,000 children. In a healthy child with COVID, the risk of developing myocarditis is still quite low, now it's 133 in a 100,000 children. So the risk for myocarditis is about 30 times more in kids with COVID, than in the healthy child. And another important fact is, between 2020 and 2021 COVID-related myocarditis accounted for 40% of all diagnosed myocarditis cases in children. Next slide. Here's a publication by MMWR, showing the risk ratio of myocarditis comparing patients with and without COVID. This was a population study in children and adults, looking at the differences in sex as well as age group. And you can see here that kids here defined under 16 years old, have about the same relative risk ratio as the elderly, which is a greater than 32 times risk ratio, compared to healthy kids and the cohort. Next slide, please.

And so, first of all, I wanted to reemphasize in case I wasn't clear, that the risk of developing myocarditis is so low, that oftentimes when we report percentages, we're talking about hundreds of a percentage, which it just is really hard to get the point across. So instead, in looking at per 100,000 kids, we can see here that the baseline risk for myocarditis in a healthy child, is low. Again, wonderful. The risk of COVID-related myocarditis is 133 per 100,000. And the mRNA vaccines that we have heard so much in the news about, yes, it's higher than baseline risk, but still, just a very tiny fraction of what the myocarditis burden is with COVID. And here in the blue, is the mRNA vaccine-related myocarditis in adolescent males, which is the population as you know, with the highest risk of developing the side effect. Next slide, please.

So for those of you who aren't quite familiar with the pediatric landscape, Children's Hospital Los Angeles, is the largest volume children's hospital in the Western region in the United States. And I'll be sharing with you the CHLA experience with COVID-related cardiac admissions during the pandemic. So, between January 2020 and this month, we looked at our myocarditis admissions to the hospital. For COVID-related myocarditis, we've only actually admitted seven patients. Half of them, 43% were in the ICU, and 43 were on the floor. In comparison, we admitted 194 patients with MIS-C, with 36% of them being in the ICU. As for other myocarditises, we have seen a bump in those as well, 21 patients with myocarditis in general, not related to COVID, and they seem to not require ICU admission as much. Although the numbers are incredibly low, we can't really make firm conclusions.

And for post-vaccine myocarditis, post-COVID vaccine myocarditis, we have admitted a few, nine of them. Two of them were in the ICU, and those are actually the very first patients with post-vaccine myocarditis in which we were observing them as cautiously as possible. So retrospectively, they probably didn't warrant ICU care. Next slide, please. Signs and symptoms of myocarditis in children. In the dark blue is just general trends in symptomatology of myocarditis in children, published in *Circulation* 2021 by Yuk Law, and in light blue is our experience with COVID-related myocarditis at CHLA. So these are just the seven patients, again, not much to make definitive conclusions from. Here we see that the symptomatology is similar, except that there does seem to be an increase in cardiac-related symptoms, with chest pain being much higher in COVID-related myocarditis than just general myocarditis. And we do see gallop and poor perfusion signs of more hemodynamic compromise, being more prominent in our COVID-related myocarditis patients. Next slide, please.

And looking a little more into the demographics, they were all at adolescents, ranges 14 to 19 years old. They were predominantly male, and these two demographic factors actually are very much in alignment with the regular epidemiology of myocarditis in general, tends to happen in adolescents, tends to happen more in male. And then, only 1% of them had a preexisting condition, meaning six of them were actually completely healthy before having COVID-related myocarditis. Interestingly, a 100% of them were unvaccinated, either because the vaccine hadn't come out for a pediatric population yet. There were a few stragglers who didn't get vaccinated and were admitted recently. Only one of them were biopsy or MRI confirmed myocarditis.

The diagnosis was made up with troponin leak with all of them, but also with a PCR positivity or immunoglobulin positivity in most of them. And in terms of outcome, three of them, 43% required ICU care, two of them required ECMO. None of them died. Next slide, please. So back to our original case. Our 15-year old patient from before, was in the hospital for two months. Ultimately she required inpatient rehabilitation before discharge home safely. And this was between June and August 2020. Her heart function had normalized by discharge in August. She had no recurrent arrhythmias and her persistent morbidities upon our last visit, which was only a few weeks ago, shows that she has a vocal cord paresis from her prolonged intubation. And she also has keloids on her chest and abdomen. Very importantly, she has understandably, significant PTSD and depression from this last two years of experience.

Next slide. So with an additional two year benefit of COVID information now in 2022, her diagnosis still remains uncertain. It's important to know that isolated atrial flutter in adolescence is exceedingly rare, estimated three in one million patients of her age group, and based on her serologic evidence, her preceding COVID infection really was the most likely reason for acute cardiac decline. Next slide.

So in conclusion, COVID myocarditis can be caused directly by viral damage, or due to an immune mediated response to the virus, or both. Myocarditis as part of MIS-C, is much more common than isolated COVID myocarditis, and both are still more common than vaccine-mediated myocarditis. Clinical course and symptoms of COVID myocarditis, excluding MIS-C, are typical of viral myocarditis. And in kids there's much overlap between COVID-related manifestations such as cardiogenic shock, arrhythmias, myocarditis, and MIS-C. So the definitive diagnosis can be challenging.

Initiatives such as RECOVER are essential and seeking answers to the many knowledge gaps that remain. Next slide. And this is just a very adorable picture of a three-year old who got the vaccine last week, and to remind everyone the vaccine is now available to most of us older than six months old. Thank you.

Dr. Matt Oster

Good afternoon. Thank you. My name is Matt Oster, and I'm going to speak to you about some of the intermediate and long-term cardiac outcomes in children and adults with COVID-19. Next slide. I have no conflicts of interest or disclosures to tell you. I did just want to mention that as mentioned in the introduction, I do work part-time at CDC. I just want to make it clear that the findings and conclusions of this presentation are my own. I'm doing this wearing my pediatric cardiologist hat, not my CDC hat. Next slide.

Today I'm going to first start talking about what we know about adults longer term, who've had COVID, then move on a little bit to the children. And some of this, you may have heard a little bit already in earlier presentations, but hearing it again, doesn't hurt. And then I'll touch briefly upon the COVID-19 vaccine associated myocarditis. Well, not technically part of RECOVER. I think it's an important question that keeps coming up in our community. Next slide.

First, let's talk about the adults. Next slide. Myocarditis in adults, as you heard Dr. Finn talk about, there was concerns certainly with acute infection of COVID very early on in the pandemic. And then in the summer of 2020, we started to really get concerned though, about even people who weren't hospitalized and did not have significant, severe disease. In Germany, there was a study of a 100 adults, about a median age of 49, and two thirds of those were not hospitalized, and some of them were even asymptomatic, weren't picked up by screening. And so, they did MRIs, cardiac MRIs in all these individuals a few months after COVID infection. And it raised a lot of alarms, because they noticed that about 78% had some degree of cardiac involvement, with a large number that having some sort of ongoing inflammation. Now this made people really worry about myocarditis following COVID. Next slide.

And so, there are a lot of different potential ways though that COVID can lead to myocardial injury, including respiratory distress syndrome, hypoxemia, hypotension, hyperadrenergic state, pro-inflammatory storm, hypercoagulable state, or direct damage to some of the cells. And then that can lead to different types of myocardial injuries, whether that be myocardial infarctions, pulmonary embolism, myocarditis, takotsubo's, or just even those sorts of arrhythmias and such. Next slide.

And so, as you heard Dr. Finn talk about though, while there's been a lot done in inpatient, we're still learning more about outpatient. And this study that was presented earlier, really, I think is the biggest study to date to really look at the long-term outcomes of people who had, had COVID 19. And this study was really well done. That blue group in the middle is the group that had COVID-19, this is all VA patients. That yellow group was contemporary control. So same timeframe, but not positive for COVID. And then, that salmon colored group was historical control, so from the pre-COVID era what did they find. And so, they were able to look at differences in the COVID group compared to these two groups to really identify the cardiac findings and the excess cases due to COVID. Next slide.

As you can see, there are a number of different cardiac findings that can happen. So cerebrovascular disorders, particularly stroke, increased risk following COVID, dysrhythmias, especially atrial fibrillation or atrial flutters down there as well, so Dr. Su talked about one of her patients, although a number of other types of dysrhythmias. Interestingly, you can have both sinus tachycardia, so increased heart rate after COVID, as well as sinus bradycardia, to talk about in a little bit actually, where the heart rate's a little bit lower than usual.

Inflammatory heart disease. You heard a little bit about myocarditis, which again, does happen after COVID, but especially in kids not as commonly, and this is even in adults, few excess cases, but not a lot. More commonly following COVID, is perikarditis, which is inflammation of the lining around the heart. And again, this is the estimates that are in adults, and these are VA patients with the average age in the upper 60s. Next slide.

Also from the study, looking at ischemic heart disease such as acute coronary disease and myocardial infarction, heart failure, very common with a high excess burden, but then also thrombotic disorders. We know that thrombosis can be important consequence of COVID. Next slide. So with all that in mind, and with what we have learned, I just want to make sure that people are aware of the latest expert consensus decision pathway on cardiovascular sequelae of COVID-19 in adults. So this is really trying to get at the question of, what do we need to worry about from a cardiac standpoint following COVID in adults? Again, this is expert consensus, they tried to use as much data as is available at the time. It takes a long while for these documents to come out, so some of the data is older, but there's still a lot of gaps, at least from an evidence standpoint. So there's definitely a role for RECOVER here. Next slide.

But with this, they identified a number of different ways and different mechanisms that can lead to cardiac dysfunction from SARS-CoV-2 and immune system activation. Many different symptoms that can occur in the cardiovascular realm, in particular tachycardia, palpitations, chest pain, dyspnea on exertion, and exercise

intolerance. And some of these don't really become evident until someone has presumably recovered from COVID and is returning to the regular activities. Next slide.

And so, this is a busy slide, but this is just to make sure that people are aware that there is an algorithm and recommendations in place for what to do for the patient who's had COVID and is starting to show some symptoms of a post-acute sequelae, and when is a cardiac consultation required. I'm not going to go through this, but it is available for free on the web, in the AmErikan College Cardiology. Next slide. But I did want to take a moment to mention the evaluation of the athletic patient with COVID-19. Over the past two years, there have been lots of different iterations of what are the recommendations for people who are returning to exercise, who had, had COVID. What should we be looking for? Whom should we be screening? And there's different recommendations for adults and kids. This guideline was meant to be specific to adults. Next slide.

But I did want to highlight that all of the different roads that lead to testing for, looking for cardiac sequelae, all really now depend on symptoms. This is really a big symptoms based approach. So whether that's cardiopulmonary symptoms during the time of COVID infection, whether someone was hospitalized and had cardiac involvement or hospitalization, whether someone developed some new symptoms just during their recovery from COVID, or whether they develop new cardiopulmonary symptoms only when they started exercising. So the ACC at least is not recommending a full on-screening approach following COVID, they really want people to take a symptom-based approach. Next slide. Okay, so now I'm going to move on towards children, and talking more about from a pediatric perspective. Next slide.

This is a study that most people here either are, or should be familiar with. This is clinical features and burden of post-acute sequelae of SARS-CoV-2 infection in children and adolescents. And this really used an EHR-based cohort, so electronic health record based cohort study from the RECOVER program. And the key finding here was that there was some indication of PASC in about 41.9% of PCR-positive children, versus about 38.2% among PCR-negative children, so a difference of about 3.7%. Showing that, yes, there does seem to be some increase in PASC in children, about 3.7% of those infected versus those not infected. Again, this was just exploratory based on coding, which has its advantages and disadvantages, and the more in-depth RECOVER study will be able to get at these in more detail. Next slide.

But in this study, I just wanted to highlight the cardiac findings in terms of the symptoms, chest pain and cardio respiratory signs and symptoms, which sometimes can be big, were two of the more commonly reported findings. And then in terms of diagnosis, myocarditis was one of the most commonly found there, and that can be as you heard from Dr. Su. Next slide.

I wanted to share what we were doing in Atlanta [inaudible 00:51:43], is what we were doing in Atlanta, our pediatric practice. And as I said, there were no real pediatric guidelines, there were people talking different things. So we came up with this guideline based on what some of the adults were doing, and what some people in the pediatric realm were recommending. Next slide. And so, we basically said, those kids who were hospitalized

with cardiac involvement or are they MIS-C, yes, to a cardiologist. Otherwise, if they had COVID, there is something mild, didn't necessarily need to see us, but their pediatrician, they should do a physical exam and do an EKG. And this was the summer of 2020, when we were starting to come up and learn more about this outcomes in children. A lot of those EKGs were sent to us, because the pediatricians didn't have capability. Next slide.

So we decided to look at what we're refining, what were we seeing? So we looked at our patients from about August of 2020, through the end of October, about a three month period. And after, including only those who didn't have MIS-C or did not have a history congenital heart disease, were 206 patients. Next line.

And so, those 206, 26 had some sort of cardiac symptoms post COVID-19. So those were the kids we were really interested in. Interesting, 180 had none, but we still were looking at them. 34 were sent for a full cardiology clearance and evaluation, about 146 were sent for EKG only. Only 10 of them were then turned into a full clinic visit, based some of their findings. And those findings were primarily some left ventricular hypertrophy, right ventricular particular hypertrophy, or some ectopy and exam. And so we had seven who had a full clinical evaluation. Next slide.

And so, those seven who had the full clinical evaluation, we determined that echocardiograms indicated about half of those, and the other half of was not, based on a full evaluation. And the echos were all normal, but out of the 206, we had 205 with no cardiac pathology identified. And I mentioned sinus bradycardia. We did have about 57 patients, about a quarter of our patients had sinus bradycardia for age, which is a little unusual. So we have seen that. It's just not something we worry about, those kids we're not symptomatic. And a couple that we followed up have completely returned to normal, so we don't really necessarily follow those or worry about those. There was one patient out of 206 though, who did have a significant finding. That was a patient with significant ventricular ectopy that was clearly audible on exam. And so, a good physical exam can find this. That was a patient who had been hospitalized and had some severe associations with their COVID infection. Next slide.

As a result, we then changed our algorithm. Next slide. And now, we really take the approach that, yes, if you have cardiac involvement or an acute illness, or MIS-C, yes, come and see us. And next slide. Next. But otherwise, really it's just signs and symptoms based approach. Not seeing the next slide, go forward yet. There you go. Right. So we're taking a cardiac signs and symptoms. So we are not recommending screening all patients to come and see us before return to play. Next slide.

Move on a little bit to multisystem inflammatory syndrome. You heard about this a little bit earlier, so I'm going to speak really just from the cardiac involvement. In this MMWR in 2020, looking at about the first 600 or so patients reported to CDC, it was reported that about 86% had some evidence of cardiac involvement. As you see there, about a quarter of those having alert myocarditis diagnosed. Next slide. In a similar study from a multicenter trial overcoming COVID, we'll just collecting data from a number of hospitals, so more of a clinical based evaluation. They similarly found cardiovascular involvement in about 80% of cases, with that troponin elevation about 50% of cases, and some decreased ejection fraction in about a third of cases. Next slide.

And in New York state, there was a group that looked at just the hospitals there and looked at myocarditis, but varying by age and noticed that with MIS-C, myocarditis was most common in the teenagers, which goes in line with what we know traditionally about myocarditis. Next slide. But the good news with MIS-C at least, was that from a cardiac standpoint, they tend to resolve rather quickly, kids do turn around. There is about a 1% mortality rate with MIS-C, but those who are able to get prompt treatment, do tend to make a very quick recovery. This shows the LV ejection fraction over time in the top right panel, which shows that the red line is the normal bar that you want to be at. And you see about half the kids at their lowest year, below that. But even by discharge, the orange line, the vast majority were already back to normal. And by six months, all the kids in the study were back to normal.

Similarly for coronary dilation on the bottom panel, there are some that certainly have coronary dilation, especially during the hospitalization, but that does tend to rapidly improve. There are certainly exceptions to any rule that for the vast majority of kids, their cardiac recovery certainly tends to be good, but there's still more to learn about some of their other recovery, especially some of their psychosocial domains during their recovery. Next slide.

Now I'm going to speak briefly on COVID-19 vaccine associated myocarditis. Next slide. So the CDC reported their experience with myocarditis cases after mRNA-based COVID-19 vaccination from December through August of last year. Next slide. And as you'll see here, so this is the males that I'm going to show. I'm not going to show the females, they're slightly elevated, but not to the extent of males, that with the Pfizer vaccine, that's the first two columns of doses there, certainly elevated in the 12 to 24 age group after the first dose, and about 12 to 49 that really peaking in that 16 to 24 group, or 12 to 24 group after the second dose. Similar findings with Moderna. Not given to under 18, but certainly higher doses in the younger adult men. Next slide.

A study was published this past March though, looking at the risk of myocarditis after COVID, versus after mRNA COVID-19 vaccination. And so, when you consider heart complications after COVID-19, and that includes your COVID myocarditis or your MIS-C myocarditis, or other arrhythmias or other heart problems that can happen after COVID-19 or with MIS, that even in the group with the highest risk of having complications after vaccination, which is those boys 12 to seven, and men 18 to 29, even in those groups, the risk of heart complications is much higher after COVID-19 than after COVID-19 vaccination. Next slide.

And I show this slide just to drive on the point though, we've mentioned the word myocarditis quite a bit, but not all myocarditis is the same. And I think people need to recognize that there are different mechanisms going on, and we're not sure about exactly all of them. This was our experience at our hospital, where we looked at, in the green group is the COVID vaccine myocarditis group. The red is the MIS-C myocarditis group and the blue is our classic myocarditis group from a pre-COVID cohort. And we looked at what percent of the patients had decreased cardiac function, where time zero was their time at presentation when they were diagnosed, then going forward.

And you'll see the classic myocarditis group, the blue group, can take a while. And by a couple of weeks, still about a third of the patients still have not regained complete normal function. The MIS-C group I mentioned earlier, they tend to have pretty good and quick resolution of function, whereas a couple of weeks afterwards, almost all those patients had regained a normal function. And in the myocarditis group, two things jump out. First, only two of our nine patients here had decreased function at presentation, and both of them rebound it after just a couple of days to completely normal function. Next slide.

So what about the long-terms in this group in the vaccine marketized group? CDC presented these slides at a recent meeting of ACIP, and CDC has been contacting patients and cardiologists to find out how have patients been doing, and this is the subjective interpretation by cardiologists, how do they think the patients are doing. And about 63% have said that the patients have fully recovered by about three months, with another 17% saying, "I think they fully recovered, but I'm still doing some other tests to verify all that." And usually that's means, waiting for MRI. So that is certainly better than the classic myocarditis group, but we're still following and still trying to learn more about this whole cohort. Next slide.

And then lastly, some unpublished data from our institution, looking at MRI findings at the three to six month interval after myocarditis. So on the left is the classic myocarditis group. And at about three to six months, about 75% will still have some late gadolinium enhancement, that's some sign or some scarring on that. The significance of what that means is debatable in the cardiology community, but I'm just showing this to compare that the MIS-C group, hardly any of the patients had that at about three to six months. So we're really talking about two different types of diseases, and the vaccine myocarditis group falls somewhere in the middle, where most don't show that, but some do. And many of them did show it early on, but it does tend to resolve pretty quickly or at least get better. Next slide.

So in summary, cardiovascular sequelae is very common, or is common in older adults. Atrial fibrillation and heart failure have the highest excess cases. Cardiovascular sequelae is not that common after children, especially after acute COVID, but with MIS-C, certainly you can have frequent cardiac involvement. For MIS-C, the vast majority recover by 3 to six months, at least from a cardiac standpoint. And the vaccine associate myocarditis has rapid recovery symptoms, but may have some lingering MRI findings. Next slide. Thank you very much, and I think we can move on to our discussions.

Dr. Anu Lala

Great. Thank you so much. My name is Anu Lala, and I'm joining you from New York, and I am a Heart Failure Cardiologist here at Mount Sinai. I'm just going to take the next three to five minutes or so, just outlining the summary points of these three excellent talks, and then hopefully we'll move on with Dr. Rosenzweig with some interesting questions for the panel and some discussion to follow. So first summary points, for adults, what are the take homes? One, cardiac injury as denoted by troponin elevation is common, especially amongst the

hospitalized population of patients with acute COVID-19 in up to a third, if not more of the population, and its presence is associated with higher mortality. The mechanism of cardiac injury is still not entirely clear, but what everyone was really wondering, is whether SARS-CoV-2 direct injury is possible. And indeed it is, but what we have founded, that it's not common.

Dr. Finn presented really nice data from his group and otherwise showing that necrosis was indeed common on autopsy. Abnormal findings on MRI are also common, and this included patients who were both hospitalized and not hospitalized. So more to come, and hopefully RECOVER will shed some light on the significance of these findings. And then finally, one of the themes that's been reiterated that I'm sure this audience is well aware of, is how exceedingly common microthrombi are, and thrombosis in general, particularly on the autopsy findings. Moving on to the children, and the cardiovascular manifestations presenting cases in children are generally of the more extreme or fulminant nature, just by nature of how they're presenting and what prompts the attention. Myocarditis, I think Dr. Su really nicely pointed out, can be related to viral myocarditis itself, so direct viral mediated injury. In this, young adult males, I'm sorry, young adolescent males are most commonly affected or at least more commonly reported.

But importantly here, the risk was pointed out that the risk in a healthy child of myocarditis was one in four per 100,000 versus the risk in COVID-positive children is 133, so a basically 130 fold increase in risk. And if you compare that to the risk of myocarditis with the vaccine, that was on the order of eight to 10, per a 100,000. So while elevated, the media has really sensationalized this risk, and it's important to take these numbers into account within the context of what really is showing more risk, which is those patients who actually contract COVID, pointing out and underscoring the importance of the vaccine.

And then we have the immune mediated or postviral infection, or MIS-C, mediated myocarditis, which is more common than the traditional myocarditis, in which immune dysregulation paradoxically leads to fulminant presentations very commonly. And then lastly, in terms of the long-term or intermediate term outcomes, which were nicely presented in adults, there's I think, the most comprehensive study to date comes from the VA of over five and a half million patients, showing increased risk of cardiovascular disease after COVID-19 infection, even in mild cases. The most common complications were heart failure and atrial fibrillation.

The ACC has released a consensus pathway document on PASC, and importantly, the return to play is determined based on cardiopulmonary symptoms, more than anything else, and there are a number of important algorithms that we invite you to look at. In terms of children, cardiovascular involvement seems to be less commonly reported, post sequelae, and screening ECGs are one way to pursue when patients and when children can return to play, but again, is largely more sign and symptom based. In terms of MIS-C or the multisystem inflammatory disease, 80% did show some cardiovascular involvement, but fortunately, most of the cases have shown that they've been prone to resolve or tend to resolve. Importantly, I thought this point was brought up,

which we should take note of, is that what warrants further study, is the psychosocial domains in terms of their recovery for children and adolescence.

And then finally, myocarditis and post-sequelae of vaccine-related cardiovascular involvement, again, seen amongst young boys and young men. But again, reminding us that the risk of COVID infection associated myocarditis far outweighs the risk of vaccine-related myocarditis, low cardiovascular function, or reduction in cardiovascular function or ejection fraction, if you will, seem to be less common in this scenario. And fortunately, what has been reported, is an 80% full recovery, and then an additional 17% that show that they've probably recovered. So with that, I'll turn over to my colleague, Dr. Rosenzweig, to start us off on some interesting discussions. Thank you to the panelists for some excellent presentations.

Dr. Erika Berman Rosenzweig

Thank you very much, Dr. Lala, and thank you to the presenters. These were truly wonderful and so informative as we embark on the RECOVER trial. And so, we heard a lot about the entire spectrum, really from the pathologic sequelae and features of myocardial injury, to the clinical features, ranging in all ages and degrees of severity from microthrombi to cardiogenic shock. So I just wanted to frame a lot of the work that we'll be doing on RECOVER by asking our panelists, how might we be able to detect some of these long-term sequelae in the protocol? What's being put forth so that we can learn what we don't know, and aside from pathology specimens, which we hope never to have to encounter, Dr. Finn, sorry, but what are we doing clinically to look at this? And anyone can take this question.

Dr. Alope Finn

I guess I could take it, because I'm involved with the clinical aspect as well. I think we are doing some intensive cardiopulmonary testing on these subjects with and without long COVID, to try to figure out whether there are differences in their cardiovascular physiology, and try to distinguish whether these are specifically linked to specific symptoms of PASC. And so, there's a whole testing algorithm in the RECOVER clinical cohort that involves multiple cardiovascular tests like echo's and right heart caths and cardiopulmonary exercise testing. There's a lot of different tests that one could have if they qualify for those. So I think we will get a lot of information out of RECOVER, and we will get some idea of whether the actual occurrence of symptoms of long COVID correlate with actual physiologic abnormalities that can be found either in the heart or the lungs.

Dr. Erika Berman Rosenzweig

Thank you. That's going to be critical, because I think as much as we know, there's so much that we don't know yet. And specifically, there had been a question about the microthrombi, which I thought was, your points

around that were fascinating, and how we would necessarily detect these inpatients long-term.

Dr. Alope Finn

Yeah. I mean, Erika, I think it's a great question. I sometimes wonder, and some of the data Jennifer and Matt presented, I discussed the issue of myocarditis and it being mainly a clinical diagnosis, we rarely do get tissue to diagnose myocarditis as you know, and how many, because we can't detect microthrombi clinically, we really don't have any known modalities or tests that definitively can diagnose microthrombi. How many of these cases that we're reporting as so-called myocarditis or other cardiac injury, are actually microthrombi induced. And I think at this current time, and I'd like to welcome any other comments from Anu or anybody else. I don't think we have a really good way to get that data, and that's a big problem, because it really speaks to the pathogenesis of what the disease clots. As I've mentioned, we didn't find any evidence of myocarditis in any of the cases we have examined so far. So I actually think it's a much rarer entity than what's reported in literature.

Dr. Matt Oster

Yeah. And I'll add to that. We certainly see, I didn't have time to present today, just looking for myocarditis, looking for inflammation. There's a study of athletes, at least in the big 10 that there are kids who had COVID, and upwards of about 2% of them have some sort of inflammation if you did MRIs on all of them. But first of all, what does it mean, because these were asymptomatic people. Second of all, how's it compared to prior infections like the flu or other stuff, because we didn't MRI any of those people just standardly. So it's hard to know exactly what it means just finding stuff, which I think is important.

But then the second, getting to the mechanisms, as I alluded to, as I mentioned, these are different things. The myocarditis after COVID, versus after MIC-C, versus after vaccine, even the myocarditis after COVID vaccines, very different than the myocarditis after a smallpox vaccine. So there are different pathways and we just need to learn a lot more about exactly what they are, because maybe they can help understand a little bit more how these things are happening, and how we can prevent them and treat them better.

Dr. Jennifer Su

I think I want to also highlight that, speaking outside of myocarditis, just in cardiology in general, we oftentimes see that even if an echocardiogram is normal or even if a cardiac MRI is normal, there are subclinical elements that do manifest later on in life. We see this in some of our dilated cardiomyopathy, sometimes in myocarditis and also in anthracycline, or other toxicity related cardiomyopathies, that they may actually have normal heart function in testing during the pediatrics, but we know now that they are at increased risk with

multiple factors during adulthood for developing heart failure later on in life, earlier than their cohorts.

Dr. Erika Berman Rosenzweig

And I suppose that remains to be seen, there's going to be hopefully long-term follow-up, and we can sip that out. I think before we pass it on to some of the Q&A from the audience, I just have one other question, which is, so many of the patients complain of these non-specific dyspnea, and which may or may not be cardiac or pulmonary or something else, and is there any way to determine that? And that was another question from our audience previously, whether it is more likely, or a red flag is raised that this particular patient with dyspnea needs more of a cardiac evaluation.

Dr. Jennifer Su

I think the silence highlights that we just don't know yet. We are still learning, and I think we need to take the symptoms seriously, because just because we don't understand it, doesn't mean it's not physiologically based. And that maybe a year from now, with the RECOVER initiative, we'll find much more information and we'll be able to have a more robust conversation about this.

Dr. Erika Berman Rosenzweig

And then finally, again, I know this is a little bit clinical, but there was interest, a couple of people asked about pErikarditis. We didn't really talk about that, but that it seems to be lingering signs of pErikarditis sometimes in the order of six to nine months. Any idea from even a pathologic mechanism, you know why that is?

Dr. Alope Finn

I mean, I will speak a little bit to that in the sense that we did find that the epicardial lining of the heart does have some evidence of increased inflammation during these acute COVID cases. So I think that's linked to the occurrence of pErikarditis, and I do think that the virus does induce. I did show you data that shows that there is some more evidence of inflammation in the heart, although it may not amount to a cardiac injury. There is inflammation that occurs in the heart more than is seen in control cases. So I do think that occurrence of pErikarditis is probably very real, and how long it takes to settle down, I think, is an issue of how well you can resolve the viral infection. And remember, I never tested in these cases, the PCR positive pErikardial fluid or the paracardial sac. We actually never got that data. So I can't give you good information about viral persistence in the paracardial space.

Dr. Erika Berman Rosenzweig

I mean, it's interesting because of the high prevalence of chest pain is one of the symptoms, in addition to myocardial injury. Just wondering about that, particularly in children.

Dr. Matt Oster

Yeah. I think it's important, as I've been saying, that this is all a spectrum. That some people are going to have absolutely nothing, some are going to get mild stuff, which on testing will find it, but may never rise to a level of clinical importance, and others can have important clinical stuff, and it's never really clear exactly what's going on. So hopefully RECOVER can help delineate some of that and put people in these different areas of the spectrum so we can treat them better.

Dr. Erika Berman Rosenzweig

Thank you. I think now it's time to pass this over to Beth.

Beth Linas

Thank you so much to everyone, I appreciate it. There was a couple questions that were overarching and some other specific questions that were to individual panelists, so I'll start with the overarching question. So far, there's a lot of discussion of myocarditis, excuse me, and direct effects on the heart. Are you finding any evidence of effects on the vascular system without desirable effects on the heart, according to current testing protocols like echo's, for example, that might cause blood flow issues for the heart beat harder, not faster, in long COVID patients?

Dr. Alope Finn

I guess I could comment a little bit. I think that the issue of the autonomic regulation of the heart, as well as the brain in terms of, the brain-heart have a very close relationship, and whether or not the heart rate is often controlled by the balance between the sympathetic and parasympathetic nervous systems, and whether there's some nervous system involvement. COVID-19 can be found in the brain in some situations. And I sometimes wonder whether there is some relationship between autonomic nervous system balance and having COVID-19, and whether there's some, the virus does something to throw off that balance and change heart rate. That's one possible explanation, but that's just speculation, and I'd love to hear what anybody else has to say about it.

Dr. Matt Oster

Yeah. I would echo that. You can have science tachycardia or science bradycardia all over the place. We have talked a lot about myocarditis, but apart from MIS-C, honestly in my clinics, I've seen more kids with new onset pots after COVID, than myocarditis. And that is certainly an autonomic phenomenon, which is not something new, it's been around for a while, but it's new that COVID is now a trigger for it. And so, yes, I do think that COVID can have different vascular long-term effects that we're just on the cusp of starting appreciate better.

Dr. Alope Finn

And I think one of the things that RECOVER will do, and I hate to mention the autopsy, cohort just cause I'm involved with it, but it will get the brains of these subjects that are dying of long COVID. Now these people are not going to be dying of COVID itself, there is that set of the study, but there are whole subjects that have died of other causes that had a history of COVID, and we'll look at the brain as well and see whether there's any abnormalities associated with the brain and having a history of COVID. We'll also try to do a study of viral persistence and see whether there's evidence of viral reservoirs. There's some hypothesis that some tissues serve as reservoirs for the virus, and those are maintained long-term, and whether or not this really exists in these long COVID cases, is hard to know, but that was one thing the autopsy cohort can help answer.

Beth Linas

Thanks. And then this is another question. Does anyone have any other, sorry, comments on that one? Okay. This is another question for the panel. Can the panel comment on potential causes of post-exertional fatigue and malaise in passe in the absence of objective findings on routine workup, including ECG echo, cardiac MRI, and PFTs? Has cardiopulmonary exercise testing been performed in this context? And if so, have you seen impaired oxygen consumption?

Dr. Alope Finn

I'll comment a little bit on that. I think fatigue after COVID-19 acute infection, in my experience, just my personal experience with some people that I know around me who have had COVID, it's very common to have fatigue after COVID-19, and some of that fatigue persists for a long time. Now, what that's caused by, I think is still not clear. But I do think that the cardiopulmonary exercise testing will begin to give us some idea whether there's objective evidence of some issue with the cardiopulmonary system in terms of ability to exercise. And that's a mandated test. That's one of the tests that actually is mandated in the RECOVER clinical cohort. So I think we'll begin to learn something about it. Some people may want to add something about that. Anu may have some

comments.

Dr. Anu Lala

Yeah, thanks Alope. I can just speak from our Mount Sinai experience. We published a study just a few months ago on 41 patients that we did at a mean of nine months after COVID-19 infection. All of these patients had normal echos, normal CTs, normal PFTs, I said already echos, ejection fraction, et cetera. But interestingly enough, 80% still had changes that represented circulatory impairment, or some cardiopulmonary impairment. And so, I think we're just scratching the surface at this point, as Alope mentioned. And I think, having a lot of the CPAT data is really, really going to uncover a wealth of information, because, the unexplained dyspnea after COVID is a very frequent symptom that we're hearing. And we just don't fully understand the mechanism of it yet. So I think more to come on that, and hopefully RECOVER will be one of the main vehicles to allow us to understand more.

Dr. Matt Oster

Yeah, I'll echo that. It's important to look at and learn more, especially in the long COVID, for people who are having this long-term fatigue. It's a very real thing. And I think it certainly transcends into their exercise capacity as well. I will mention, I didn't have time to present, we did a recent study in our MIC patients. So we were having a number of those who had poor function, come back for exercise tests three months afterwards. They all did great, and that might be unique to MIC, but I was very surprised at how well they did. But again, these are people who tend to recover and feel better after a couple of months. People who have lingering symptoms, I think are in a different bucket, and can certainly benefit as a part of their evaluation.

Beth Linas

Great. And then just to... Oh sorry, Dr. Sue.

Dr. Jennifer Su

No, I didn't have anything else to add. Thank you.

Beth Linas

All right. Sure thing. Just to clarify, the question, was it about fatigue? The question was about post-exertional malaise. Just want to clarify if there's any different response from panelists.

Dr. Jennifer Su

I don't know, but I would speculate that it may be more in line with the dysautonomia than specific cardiac or pulmonary, especially if this particular patient or this situation has normal echocardiogram and pulmonary function tested. Just because, although there may be subclinical findings of cardiac risk for this COVID population later on, in the setting of a normal echocardiogram and EKG, you do have enough perfusion that you would not expect to have these symptoms directly related to the heart.

Beth Linas

Thank you. We got a lot of extra questions, and I will note that we will have our panelists answer them for the FAQ and we will post them. But today, I just want to give a big thank you to our presenters, and thank you to our audience for attending this seminar and engaging with the Q&A. A reminder, a recording of today's seminar will be available on recovercovid.org within a few weeks, and we will also be posting a Q&A document that has responses to the questions we received today, including those that we didn't have time to answer.

And then last slide, this slide list the topics for future sessions. Our three seminars, a reminder are on the second and fourth Tuesday of the month, from 12:00 to 1:30 Eastern. We have some exciting topics coming up, and hope to see you at future sessions. Thank you very much, and have a great day.

Webinar Slides

To request a copy of the R3 Webinar slides, please email RECOVER_ACC@rti.org.

To Learn More

- Information about RECOVER research and to volunteer for studies: <https://recovercovid.org/research>
- Frequently Asked Questions about RECOVER and PASC: <https://recovercovid.org/faqs>
- CDC information: Information for the general public and for healthcare providers about post-Covid conditions: <https://www.cdc.gov/coronavirus/2019-ncov/long-term-effects/>