Responses to Participants' Questions

The overarching goal of the R3 Seminars is to catalyze a shared understanding of the research being conducted by the scientific stakeholder community within the RECOVER Consortium. The R3 Seminars and the Q&As typically feature highly scientific material intended for researchers and clinicians. For other audiences interested in these topics, a link to the National Library of Medicine's MedlinePlus medical dictionary is provided at the end of the Q&As as a resource to help in understanding the scientific terminology.

This document provides responses* to questions raised by seminar participants related to the following presentations at the R3 Seminar ***RECOVER in Action: PASC in Children and Adolescents, EHR Insights*** held on May 9, 2023:

- **Presentation 1: Clinical Features and Burden of Post-Acute Sequelae of SARS-CoV-2 Infection in Children and Adolescents**

  Suchitra Rao, MBBS, MSCS
- **Presentation 2: Identifying Pediatric Long COVID in Electronic Health Records Data**

  Vitaly Lorman, PhD
- **Discussant: Kelan Tantisira, MD, MPH**

* Responses may have been edited for clarity.

All Presenters: Questions and Responses

Q. This is a question to both our panelists about whether you have been able to look into the effects of possible interventions, such as looking at patients that may have been prescribed pharmaceutical interventions. We could name them, but you are aware of the possible interventions out there for Long COVID. Is that something that has been talked about? As far as you are aware, is that on the list of future things to do? Could you please speak to interventions and cohort data.

Responses:

Dr. Lorman: We're in the process of working on a study that's looking specifically at remdesivir and dexamethasone and their effect as COVID treatments on the risk of developing Long COVID. We've looked at Paxlovid in a query in the past, and I think there have been other treatments also discussed. So, there definitely is work in progress on a few different treatments. In the study that Dr. Rao presented on, we looked at which drugs tend to be prescribed to patients who are COVID positive as compared with patients who don't have COVID. So, not effectiveness so much, but more looking at which drugs tend to be prescribed in practice.

Dr. Rao: Based on that work, which was an adjunct to the work that I just presented, some of these medications were used to try to treat some of those PASC symptoms. So, it was more than just those supportive care measures; if patients had an ongoing cough, it was looking at cough suppressant medications or nonsteroidal medications and things that might be helping with those acute symptoms. We found that there was some association; however, there was not enough power to be able to show improved recovery or faster recovery.

The other thing I want to mention is the work that we've done in the first year of this RECOVER Initiative to look at detecting PASC and defining PASC, and then the next steps for us are going to be looking at treatments for PASC. Speaking of the work that Dr. Lorman is discussing, that is certainly going to be a main focus for us in the next year, as well as looking at preventive aspects. Are there other things that we can do to try and prevent these symptoms from occurring in the first place, or at least reduce symptom duration?

Q. How does the lack of testing in the first months of the pandemic affect inclusion/exclusion criteria for these studies?

Responses:

Dr. Rao: This question absolutely hits the nail on the head. We're really at the mercy of the EHR data, and we acknowledge that that is going to be one of the limitations of looking at things such as the incidence of PASC at the beginning phases of the pandemic. We know that testing at that time was very much restricted to sicker patients who might be more likely to be hospitalized and had access to the test centers that were built around those larger facilities. We certainly acknowledge these limitations and have taken them into account. Testing then became more widespread and more reliable. And then we went into the issue of at-home testing. So now people aren't going into those centers to get the tests, they are doing all their testing at home. The time period for our study was March of 2020 through October of 2021. So, we're less at the mercy of the at-home testing phenomenon, but we certainly are at risk of bias when we're looking at that early period. When we design studies, we need to think about these things. It's still better to try and explore these questions using what data we have, but there may be some caveats. We might not be able to give precise incidence estimates at the start of the pandemic, for example, for those very reasons.

We also need to think about a combination of approaches. It made sense to look at testing during that first period when it was more reliable. We couldn't use the U09.9 code because it didn't exist until October 2021. So, we need to evolve our study designs. For example, maybe we need to rely to a greater extent on other codes, or to acknowledge that there may be limitations with looking at SARS-CoV-2 PCR testing alone. Over time, we've had to take these factors into account and to look at a combination of different approaches. That's why it's good to do work in different ways because we can then look at similarities and differences, assess if something works, and then pursue that technique further.

Dr. Lorman: I totally agree with everything that Dr. Rao said. One specific issue that we've discussed a lot has been that of patients who are diagnosed with Long COVID with the U09.9 code, as more than half of them don't have a prior viral positive test result recorded in their EHR. So, it may be a test that was conducted at home or outside of the network that feeds into the EHR data. And that makes it challenging, for example, to figure out the time at which patients had COVID, which is important for some studies.

There are some things in the case control comparison studies that we've done to try to mitigate these limitations. For example, often our control groups have been patients with a negative SARS-CoV-2 test result and using that to determine the index date. So at least there is some greater confidence that the patients didn't have COVID at the time of the index date, even if we didn't capture the positive COVID test results at other times.

There have also been some studies where we've looked at non-contemporaneous control cohorts, such as patients with respiratory illness in 2019, so that the presence of patients with COVID in our control cohort isn't a concern. However, that comes with its own difficulties concerning differences in utilization prior to the pandemic as opposed to during the pandemic.

Q. Are there other countries that have Long COVID codes, and is this an approach that could also be replicated in other EHR datasets across the world?

Response:

Dr. Rao: That's a great question. We know that some countries do have diagnostic codes for Long COVID and Long COVID conditions. I don't have a list of all the different countries, but that does afford some opportunity for us to take a similar approach and explore that in another setting. But the use of codes has varied across the board, and they've been instituted at different times. It's a good way to highlight some of the challenges of trying to do cross-country collaborations; there may be different utility of codes used across different settings.

Q. How do individual symptoms such as tinnitus or sleep disruptions factor into the study? Recognizing that there is a wide range of symptoms, what about those symptoms that might be less common or those that we didn't see on the slides listed today?

Responses:

Dr. Rao: There is such a wide spectrum of manifestations of PASC. You saw in those earlier slides that based on even just a review of the literature, clinical adjudication, and sharing our experience in terms of taking care of these patients, we had 441 clusters of potential diagnoses of symptoms or conditions associated with PASC. So, we didn't report out all of them and we focused on the ones with the strongest association. But yes, absolutely there are going to be other conditions and other findings that have been reported and new ones that might continue to be reported.

So those symptoms do factor in when we're trying to investigate incidence rates of PASC. Those symptoms become very important when we're trying to characterize the full spectrum of PASC and may be relevant too when

we're doing prospective studies. We make sure that we're asking questions about symptoms such as tinnitus, memory problems, or skin rashes. I think these then get factored into other studies down the road. The study that we were doing was trying to look at those stronger associations, but we acknowledge that there's a whole spectrum of things that may not necessarily be in the highest risk category.

Dr. Lorman: To add to that, I think this is one place where the tree-based scan statistic approach might provide some additional signals. For example, I did look to see whether there were ear-infection-related codes that occurred disproportionately among the cases in our comparison, and when we compared patients with COVID to patients without COVID, so that sensitivity analysis I described, there we saw some signal for some ear-infection-related codes. That's the value of doing multiple comparisons and trying to synthesize them. In our manuscript, there is a table that lists clusters of specific codes that all seem to be associated with PASC diagnoses or with COVID positivity in the post-acute period. We think that having studies specific to those conditions down the road would be very important.

Q. How do the different variants of COVID-19 play into the analysis?

Responses:

Dr. Rao: When we think about the whole course of the COVID-19 pandemic, we need to be thinking in terms of different waves. However, we also need to be careful not to assume that the patterns that we're seeing are related to a variant and its inherent virological properties. It could also be other factors. It could be that over time we end up with a population that gets immunity through exposure from infections and from vaccinations. With EHR data, there are also changes in people's practices in terms of how they code data and new codes that develop. We talked about the U09.9 code. When we conduct these studies, we need to think about not only the inherent properties of the virus, the changes of immunity over time, the ways that the healthcare system has been managing cases with new therapeutics, etc., but also about how patterns of healthcare seeking and healthcare reporting change over time.

In our study, we were looking at the early phase before the Omicron variant period hit, and then Dr. Lorman's study looked at periods of time beyond that. So, we do a lot of work where we try to break things down into phases to assess any differences across different time periods. But we need to acknowledge that it may not just be because of that variant that we're seeing these signals.

Some other work that you've heard Dr. Lorman talk about is temporal trends, looking at different presentations of PASC and how they change over time. We did something similar with MIS-C (multisystem inflammatory syndrome in children). We wanted to see what was happening with the severity of MIS-C over different time periods. We found that the severity was in fact going down, but that's not to say that Omicron is necessarily less virulent; it's just there may be more population immunity.

To summarize, it's something we're looking at with a lot of the research we're doing here, but we're trying to be mindful of what some of those changes and variations across the time periods truly represent.

Dr. Lorman: I second everything Dr. Rao said. To give one more example, in our study, in our preprints on kids with diabetes and their trajectories over time, we did look a little bit at pre-Omicron and Omicron effects. We saw some potential differences there. However, as Dr. Rao said, it's not just the variant. There's potentially a lot of confounding from utilization patterns alone. For example, in summer 2021, when patients started coming in for other things, that can throw a wrench into a lot of analyses. Also, other respiratory illnesses, such as flu and RSV, were being diagnosed more frequently, potentially confusing symptoms of those illnesses with COVID. All of these things become more potentially confounding later in the pandemic.

Q. Circling back to one of the earlier questions about the comorbidities and risk to children and adolescents with preexisting conditions, could you speak to what you're seeing within these populations and whether there are disease types or other confounding factors that may be increasing the risk of PASC?

Response:

Dr. Lorman: We conducted a study that took a broad look at this, comparing patients with existing chronic conditions who had COVID to patients with chronic conditions who did not have COVID. And what we saw is that patients with chronic conditions were somewhere around twice as likely to be hospitalized following COVID infection compared with patients who had chronic conditions who did not have COVID. However, it's hard to disentangle how often there's a causal effect; that is, some biological mechanism between COVID infection and something that exacerbates the chronic condition as compared with just increased surveillance, such as patients who have a chronic condition and then have COVID being more likely to see the doctor or be admitted to the hospital by virtue of having the chronic condition and COVID at the same time, but not necessarily a causal relationship.

It's very challenging to disentangle these things. In our work on Long COVID subtypes, we're definitely seeing some differences between COVID subtypes based on patients who have existing chronic conditions. There seem to be subtypes involving patients who have a high volume of utilization, have chronic conditions affecting multiple body systems, and have a lot of laboratory testing. And to the extent to which it's the existence of the chronic condition that's driving this as compared with something about how PASC interacts with this is certainly a challenging question that we're trying to look into to differentiate these further.

Q. Is a child with epilepsy at any greater risk of long-term neurological complications due to COVID?

Response:

Dr. Rao: That's a great question regarding the risk of PASC in people with medical comorbidities. In our study, we found that children with complex medical conditions have a 3.5 times higher risk of having Long COVID symptoms than children without complex medical conditions.

Q. Have you found that Paxlovid or remdesivir is helpful in reducing the incidence of Long COVID in children?

Response:

Dr. Lorman: We're currently working on a study of remdesivir and risk of Long COVID and we hope to have more to share soon.

Q. Does the aHR (Adjusted Hazard Ratio) calculation take into consideration the time from positive PCR test to symptom onset? What's the average time?

Response:

Dr. Rao: We looked at any PASC feature in the time window from 1 month to 6 months after the test date and most of these presented within the first 1 to 2 months after infection.

Q. Have you noticed clusters of Long COVID within families? Also, are you noticing different symptoms and conditions in teens as compared with younger children?

Response:

Dr. Lorman: Patients in families are not linked in our data, but this is an area where there could be more potential for investigation in prospective study cohorts.

Q. Many people were diagnosed with "Post Viral Syndrome" in 2020 before there were Long COVID specific codes. Is that another diagnosis you're looking for?

Response:

Dr. Lorman: It is and there are codes in other vocabularies, such as SNOMED, that we've also incorporated.

Q. Do many countries have Long COVID codes, so the patients can easily be identified? This is not the case in my country (Netherlands).

Response:

Dr. Rao: Many countries do not have Long COVID codes. Without a standardized definition of Long COVID, it is challenging to improve data sharing and comparison across countries.

Q. I'm wondering if there are indeed fewer PASC patients with a young age or if it's possible that PASC manifests in a different way and we don't recognize it yet. Any thoughts on that?

Response:

Dr. Rao: It's likely that PASC manifests differently in children than adolescents and younger adults. We saw that children younger than 5 years were more likely to seek healthcare visits for respiratory illnesses and symptoms and were less likely to present with fatigue and pain. This pediatric population is a very important group to explore further in studies.

Q. The data presented/collected are for those that sought medical care, had medical insurance, etc., and thus have diagnostic codes in their EHR. That said, given this knowledge, what can we hypothesize of the phenotype of Long COVID for those with socioeconomic disparities who are uninsured/uncared for?

Response:

Dr. Rao: That's right, our study provides data regarding the post-acute sequelae of COVID among people seeking healthcare, and so EHR-based studies are less able to explore Long COVID manifestations among people with socioeconomic disparities, such as decreased access to healthcare and those without insurance. While many of our findings are similar to other pediatric prospective studies, more work needs to be done to explore the impact in these populations.

Q. Are the speakers aware of any whole genome sequencing studies to see if there are specific genetic variants in children that may differ between PASC as compared with SARS-CoV-2 subjects with no PASC? If not, do you think that this is a worthwhile future possibility?

Response:

Dr. Rao: The prospective branch of the RECOVER Initiative will be exploring this question and is collecting samples for genomic analyses to see whether there are any underlying genetic characteristics that make individuals susceptible to Long COVID.

Q. Has the data included people who have experienced (multiple) reinfection with COVID?

Response:

Dr. Lorman: Both studies only looked at the earliest evidence of COVID for each patient. We are currently in the process of studying reinfections, particularly to what extent we can capture them in the EHR given the rise of at-home testing.

Q. Are there any autoimmune diseases that patients are at risk of in the future, near or distant, for children that have a history of Long COVID?

Response:

Dr. Rao: There have been reports of new autoimmune conditions developing in the weeks to months after acute SARS-CoV-2 infection, including immune thrombocytopenic purpura (ITP), Graves' disease, systemic lupus erythematosus, antiphospholipid antibody syndrome, vasculitis, myocarditis, uveitis, and Sjogren's syndrome.

Q. How long do you keep checking for new diagnoses?

Response:

Dr. Lorman: In both studies, we looked primarily during a post-acute infection period defined as between 28 and 180-days following infection.

Q. Is RECOVER looking into the common incidences of hypermobility and Ehlers Danlos syndrome in pediatric populations as well as the higher occurrences of PANS/PANDAS (Pediatric Acute-onset Neuropsychiatric Syndrome/Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections) among pediatric Long Haulers?

Response:

Dr. Lorman: Hypermobility syndrome was one of the conditions diagnosed more frequently among patients with PASC in our main analyses (compared with the non-PASC COVID-positive and COVID-negative cohorts), and we saw the diagnosis code for Ehlers Danlos syndrome occurring most frequently among patients with PASC compared with the COVID-negative cohort. Being the only specific congenital diagnosis that we saw a signal for in our main analysis, this is interesting and warrants further investigation. One hypothesis is that what we're seeing is patients who had this before COVID, but after COVID it rose to the level of requiring clinical care in some patients. With PANDAS, I think there are questions about how reliably it's diagnosed, especially given the recency of the diagnosis code, so it might be harder to detect in the EHR. But we did see a signal for the D89.89 diagnosis code in our main comparison.

Q. Is Long COVID a possible autoimmune disease? Are there long-term effects of the virus on the brain? Are Long COVID patients' EEGs showing abnormal slowing of waves with no other cause to explain findings?

Response:

Dr. Rao: New-onset autoantibodies have been detected following acute infections, and a broad autoantibody response can occur even in the absence of severe clinical disease. Despite the high frequency of autoantibodies in studies of patient with acute infection—with some studies demonstrating up to 50% of people hospitalized with severe COVID-19 having at least one type of autoantibody as compared with 15% of healthy controls, and another study showing up to 52% of hospitalized COVID-19 patients with antiphospholipid antibodies—only a relatively few

patients develop autoimmune disease during the follow-up period. This suggests that other factors are contributing to the pathogenesis of disease and the need for longer-term follow-up spanning several years.

Q. What types of mood issues are you seeing in children with Long COVID?

Response:

Dr. Rao: While many different mental health conditions have been seen with increased frequency among children infected with COVID-19 as compared with noninfected children, the most common mental health conditions observed among children and adolescents diagnosed with COVID-19 have been ADHD and disorders related to trauma or stressors. However, this is a very challenging area to study, and carefully conducted studies with adequate control subjects are required to explore whether these conditions arose secondary to the situational context of the pandemic (such as social distancing, school closures, cancelled extracurriculars, loss of loved ones) as compared with direct pathobiology resulting from SARS-CoV-2 infection.

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