Pulmonary Function Tests in Infants Following SARS-CoV-2 Infection

Talia Benenson-Weinberg[1], Avigdor Hevroni[1], Laurice S. Boursheh[1], and Oded Breuer[1]

[1]Hadassah University Medical Center

October 6, 2023

Abstract

Introduction: The clinical spectrum of SARS-CoV-2 infection is well-established. However, understanding its long-term implications, especially in infants, remains limited. We aimed to evaluate pulmonary function tests in infants (iPFT) several months after a documented SARS-CoV-2 infection. **Methods**: An observational case-control study was performed. iPFT results in infants with persistent respiratory complaints several months after a SARS-CoV-2 infection were compared to a registry of patients assessed at our center between 2008 and 2019 using the Mann–Whitney U and Fisher's exact tests. Excluded from the study were infants with chronic diseases and extreme prematurity. **Results**: iPFT data from sixteen infants with respiratory complaints and a history of SARS-CoV-2 infection and 475 controls were evaluated in the study. The median time between the SARS-CoV-2 infection and iPFT evaluation was 5.5 months (IQR=2.8-8.0). There were no differences between cases and controls in clinical characteristics and reason for iPFT evaluation. iPFT results showed no significant differences between cases and controls in lung volumes, compliance, or resistance. Expiratory airflow limitation was observed in both groups, with better low lung volume flows in the SARS-CoV-2 group. Categorization according to iPFT physiologic alteration and bronchodilator responsiveness were similar in the two groups. **Conclusion**: This study provides the first comprehensive iPFT data in infants following a SARS-CoV-2 infection. The findings suggest that SARS-CoV-2 infection does not cause unique long-term effects on pulmonary function in infants with chronic respiratory symptoms. Further studies in larger cohorts, particularly in infants with severe acute SARS-CoV-2 infection, are warranted to validate these findings.

INTRODUCTION

Since emerging in November 2019, the severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) has rapidly spread worldwide, causing coronavirus disease 2019 (COVID-19). Although patients of all ages are affected, the illness among children and adolescents is generally milder compared to adults, with up to 66% being asymptomatic [1]. Unlike children and adolescents, the majority of infants have been reported to be symptomatic, with fever, upper respiratory symptoms, and decreased oral intake being the most common clinical features [2].

While the acute-phase illness of SARS-CoV-2 is well established, understanding its long-term consequence and its effect on chronic lung morbidity is still evolving. Previous studies have evaluated pulmonary function tests (PFT) in patients post SARS-Cov-2 infection to objectively assess the long-term respiratory influence of the virus. In adults, a reduction in diffusion capacity was the main finding, significantly correlated to the severity of the acute illness[3–5]. Only a limited number of studies evaluated PFT in pediatric patients following a SARS-Cov-2 infection. Unlike in adults, these studies did not identify any abnormality in expiratory flows, lung volumes or diffusion capacity [6–9].

To our knowledge, despite significant respiratory COVID-19-symptoms reported in infants, no study has explored PFT in this age group, following an infection. The aim of this study was to assess whether SARS-Cov-2 infection has long term effects on pulmonary functions in infants.

METHODS

Study population

After institutional review board approval (0204-23-HMO), an observational case-control study was conducted. Given the retrospective nature of the study involving existing data, informed consent was exempted. Cases included infants who were referred for iPFT by a pediatric pulmonologist due to persistent respiratory complaints with a documented SARS-CoV-2 infection during their course of illness.

Controls included all infants who underwent iPFT at our medical center prior to the COVID-19 era (between 2008 and 2019). Demographic and clinical parameters of these patients were retrieved from computerized database. Excluded from the study were subjects with any diagnosis of chronic or congenital disease, including; extreme prematurity, chronic lung disease, congenital heart disease, pulmonary hypertension, Down's syndrome, congenital diaphragmatic hernia, and infants who underwent iPFT testing prior to bone marrow transplant. We further excluded from the study infants in which the primary respiratory complaint for which they underwent a respiratory evaluation, was not documented in their medical file.

Infant Pulmonary Function Testing (iPFT)

All measurements were performed according to the ATS-ERS guidelines[10–12]. Infants were clinically stable for at least 4 weeks prior to testing. Prior to testing, parental written consent was obtained. Infants were sedated using 100–150mg/kg triclofos sodium syrup or the equivalent 50-75mg/kg chloral hydrate syrup.

Prior to 2019, flows and volumes were measured via a custom made iPFT device using a heated pneumotachograph (series 3700A, Hans Rudolph Inc., USA) connected via a low-dead-space Rendell Baker face mask to a differential pressure transducer and signal conditioner set to 100 Hz (SCIREQ TD-05 & SC-24), as previously described[13–16]. Subsequent to 2019, flows and volumes were measured using a commercial device MasterScreen BabyBody (JAEGER/Vyaire). Differences in flow and volume measurements between the two testing devices were normalized for all infants tested, regardless of inclusion in current study.

iPFT measurements were uniform and included: Tidal breathing analysis with measurements of respiratory rate (RR), tidal volume (Vt), and Minute ventilation (MV); Baby-body plethysmograph for the measurement of functional residual capacity (FRCpleth) and airway resistance (Raw); Measurement of respiratory system compliance (Crs) with the multiple breaths occlusion technique prior to 2019 (for the control group) and with the single breath occlusion technique after 2019 (for the SARS-CoV-2 group); and Tidal and raised rapid thoraco-abdominal compression techniques for the measurements of forced expiratory airway flows. Forced expiratory flow at FRC (VmaxFRC) was obtained from the tidal forced expiratory flow-volume curve, and the forced vital capacity (FVC), forced expiratory volume after 0.5 sec ($FEV_{0.5}$) and forced expiratory flows at 50%, 75% and 85% of vital capacity ($FEF_{50\%}$, $FEF_{75\%}$ and $FEF_{85\%}$) from the raised-volume expiratory flow-volume curve. Residual volume (RV) and total lung capacity (TLC) were calculated from the results of the plethysmography measurements and of maximal expiratory flow-volume curves.

Bronchodilator responsiveness (BDR) was defined positive if an improvement of 20% in the VmaxFRC was documented twenty minutes after an inhalation of nebulized salbutamol as previously described[17] or 4-5 puffs of Salbutamol inhaler (100mccg/puff) via valve holding chamber.

Pulmonary function results of all infants included in the study were categorized according to the physiological pattern diagnosed[18]: normal lung function pattern - VmaxFRC (%pred)$>$ 80%, and FRC(%pred) 80% - 110%, and FVC(% pred)$>$80%; Obstructive pattern - VmaxFRC(% pred) $<$80% and FRC(% pred)$>$ 80%; Restrictive pattern - VmaxFRC(%pred)$<$80% and FRC(% pred)$<$80%; Mixed pattern (obstructive and restrictive) - infants who do not meet any of the previous criteria.

Statistical Analysis

Results were summarized by standard descriptive statistics and shown as medians and interquartile range (IQR) for continuous variables, and percentages for nominal variables. Differences between groups were evaluated using the Mann–Whitney U test for continuous variables and chi-square tests for categorical

variables, as appropriate. Tests were conducted using Stata, version 17 (StataCorp) with p-values of less than 0.05 considered significant.

RESULTS

Study population

Eighteen infants were referred to perform iPFT at our institution due to persistent respiratory complaints with a documented SARS-CoV-2 infection. After exclusion of two infants (one infant due to Down's syndrome and a congenital heart defect, and the other due to extreme prematurity) sixteen infants were included as cases in the study (81% male), see figure 1 for patient selection and table 1 for additional patient characteristics.

The most common respiratory complaints for which these 16 infants were referred for further evaluation with iPFT were chronic or recurrent cough (56%), recurrent wheezing (19%), and noisy breathing and tachypnea (13% each). Of these sixteen infants, twelve (75%) experienced a symptomatic acute COVID-19 illness, most commonly fever (6/12 (50%)), cough (5/12 (42%)) and dyspnea (4/12 (33%)). In 11 infants, the symptoms were mild. One late-preterm infant suffered a severe neonatal COVID-19 disease with acute respiratory distress syndrome (ARDS), following vertical transmission. Four infants experienced an asymptomatic SARS-CoV-2 infection and were diagnosed following an exposure to a symptomatic individual. The median age at the time of the documented SARS-CoV-2 infection was 4.0 months, interquartile range (IQR)=1.1-7.3 months.

The median age of cases at the time of the iPFT was 10.5 months (IQR = 7.0-13.5), with a median time of 5.5 months (IQR=2.8-8.0) between the documentation of a SARS-CoV-2 infection and the respiratory evaluation with iPFT.

Four hundred and seventy-five subjects were included as controls in the study (65% male, median age at the time of iPFT = 9.4 months, IQR=7.0-13.1) (see figure 1 for patient selection). No statistically significant differences were found between cases and controls in baseline clinical characteristics and the reason for referral to perform iPFT (table 1).

iPFT performance

Included in the study were iPFT measurements that met the American Thoracic Society/European Respiratory Society criteria[11,12,19]. In all SARS-CoV-2 cases included in the study, all iPFT performed were acceptable. Tidal breathing measurements and tidal forced expiratory flow-volume curves for VmaxFRC measurements were acceptable in 471 (99%) of control subjects. Raised-volume rapid thoracoabdominal compression allowing measurements of maximal expiratory flow-volume loops (FVC, $FEV_{0.5}$ $FEF_{75\%}$and $FEF_{85\%}$) were acceptable in 455 (96%) of control subjects and calculation of RV and TLC were acceptable in 428 (90%) of control subjects.

iPFT results

As a group, iPFT results in the SARS-CoV-2 group showed normal lung volumes, normal lung compliance (Crs) and normal airway resistance (Raw) (table 2). Expiratory flows in the SARS-CoV-2 group were mildly decreased, mainly when assessing flows from the tidal expiratory flow-volume curve (median (IQR) VmaxFRC=60 (37-80) %predicted).

When comparing the SARS-CoV-2 group to controls, no differences in tidal breathing measurements, lung volumes, compliance nor resistance were found. The SARS-CoV-2 group demonstrated slightly better expiratory flows when compared to the control, mainly for low lung volumes (median (IQR) $FEF_{85\%}$=75 (48-98) in the SARS-CoV-2 group Vs. $FEF_{85\%}$=58 (43-77) in controls, p=0.035) (table 2).

Categorization according to iPFT pattern and bronchodilator responsiveness, showed no significant difference between the SARS-CoV-2 group and the controls, neither in the occurrence of different iPFT patterns, nor in the iPFT results (table 3). The majority of infants tested in both groups demonstrated an obstructive iPFT

pattern (63% of the SARS-CoV-2 group and 66% of the controls, p=0.776) and only a minority showed normal iPFT results (31% of the SARS-CoV-2 group and 15% of the controls, p=0.074). Infants in the SARS-CoV-2 group with an obstructive lung disease pattern had similar iPFT results to controls.

Assessment of bronchodilator responsiveness (BDR) was available in 335 infants from our cohort (7 from the SARS-CoV-2 group and 328 controls). A positive BDR was present in 21% of the SARS-CoV-2 group and 22% of controls (p=0.904), see table 3.

In the SARS-CoV-2 group, abnormal pulmonary function tests were not associated with a personal or familial history of atopy nor with exposure to second-hand smoke. Data regarding atopy and second-hand smoke exposure were not sufficiently available for the control group.

The association between iPFT results and acute COVID-19 respiratory symptoms

Of the sixteen included cases, 7 infants (44%) experienced respiratory symptoms (cough and/or dyspnea) during their COVID-19 illness. There was no association between the presence of respiratory symptoms during the acute COVID-19 illness and iPFT results (p>0.05 for all evaluated indices). The one infant who had postnatal acute COVID-19 related ARDS had normal iPFT results at 2.7 months of age (VmaxFRC=119%predicted, $FEV_{0.5}$=98%predicted, FVC=93%predicted and TLC=105% predicted).

DISCUSSION

In this case control study, we present iPFT data in infants with persistent respiratory complaints and a history of SARS-CoV-2 infection. Our results show that when compared to a large control group of infants who were evaluated at our center prior to the COVID-19 era, infants who suffered an acute SARS-CoV-2 infection have very similar iPFT results. This suggests that a SARS-CoV-2 infection does not have lasting impact on pulmonary function in infants. Results from this study add data in infants to the already present data in children regarding the minimal long-term effect of SARS-CoV-2 infection on pulmonary function.

No prior study has evaluated pulmonary function tests in infants recovering from a SARS-CoV-2 infection. Most studies that have evaluated pulmonary function tests in children and adolescents with respiratory symptoms following a SARS-CoV-2 infection, found no significant differences in spirometry, body plethysmography, impulse oscillometry, lung clearance index and diffusion lung capacity for carbon monoxide (DLCO) results between the study groups and healthy children and adolescents [6–9]. One study found evidence of a mild obstructive pattern, in 45% of school age children with ongoing cardiorespiratory symptoms following a SARS-CoV-2 infection[20]. We evaluated children with persistent respiratory complaints several months after a SARS-CoV-2 infection and found evidence of mild expiratory airflow limitation present in 63% of cases. However, in some of the included cases the respiratory complaints were present also prior to the SARS-CoV-2 infection, thus not necessarily a result of the SARS-CoV-2 infection itself.

When comparing iPFT results of cases included in the study, to a large group of infants evaluated at our center by iPFT prior to the COVID-19 pandemic, our study did not find any significant differences between the two groups. Cases and controls had similar demographic features and underwent a respiratory evaluation for similar persistent respiratory complaints. Cases showed a similar distribution in the pattern of pulmonary function tests results as the controls, with similar rates of obstructive, restrictive, and normal iPFT results. A mild but statistically significant difference in expiratory flow limitation was observed, with greater prominence in the control group. However, this difference lost significance when comparing only infants with an obstructive pattern. Thus, our results do not show evidence of a long-lasting effect of SARS-CoV-2 infection on iPFT. These findings are clinically relevant in view of the limited available evidence regarding the long-term sequela of SARS-CoV-2 infection in children and due to the ongoing reports of chronic residual symptoms following a SARS-CoV-2 infection, collectively termed Long-COVID.

Long-COVID is an ill-defined sequela of SARS-CoV-2 infection. It includes a wide range of ongoing, new or recurring symptom and there is currently little agreement worldwide in its definition and categorization [21]. Only a few studies have investigated persistent symptoms in young children and infants following a SARS-CoV-2 infection, making the categorization and diagnosis of long-COVID in young children difficult.

Data that is available show that preschool aged children take longer to recover from a SARS-CoV-2 infection when compared to older children and that the ongoing respiratory conditions may persist up to six months among children aged 1-5 years [22]. Epidemiological studies further report an increase in the prevalence of respiratory symptoms, mainly cough and difficulty breathing, in young children recovering from SARS-CoV-2 infection[6–9,23–26].

We evaluated infants with persistent respiratory complaints and a history of SARS-CoV-2 infection. Some of the included cases presented with respiratory symptoms prior to the SARS-CoV-2 infection, while others only following the infection. However, the occurrence of a SARS-CoV-2 infection in infants suffering from persistent respiratory complaints, present for months, calls for consideration that these ongoing symptoms are a manifestation of long-COVID. Furthermore, the anxiety surrounding a SARS-CoV-2 infection and its unknown long-term outcomes in children and infants [27], further augments the attention for an association between the persistent respiratory complaints and the SARS-CoV-2 infection. We did not find any distinct clinical or physiological features in cases included in our study which may characterize them as a group and differentiate them from infants with persistent respiratory complaints never infected by SARS-CoV-2. This suggests that the SARS-CoV-2 infection did not uniquely influence the disease course in included cases. This is further supported by the finding that no association was present between the severity of the acute SARS-CoV-2 infection and the iPFT results. Indeed, many controversies exist regarding the diagnosis of long-COVID and it is not currently established whether the long-term effects of COVID-19 are specific to a SARS-CoV-2 infection or are similar to other post-viral syndromes frequent in infancy [27].

A main strength of our study is the comprehensive data of PFT in infants following documented SARS-CoV-2 infection, which, to the best of our knowledge, has not been previously reported in the literature. However, our study has several limitations. The primary concern is that the iPFT were conducted in infants with pre-existing respiratory complaints, which in some were present before their SARS-CoV-2 infection. This means that the assessment was not focused on testing previously healthy infants with symptoms following a SARS-CoV-2 infection. To address this bias, we did not compare our cases to controls with normal iPFT results but to a large control group of infants who underwent iPFT due to respiratory complains prior to the COVID-19 era, speculating that the SARS-CoV-2 infection may cause characteristic clinical and physiological abnormalities if associated with the ongoing symptoms. Other limitations include the retrospective design with missing clinical information regarding the control group and the inclusion of a small number of cases.

In conclusion, we present iPFT results in infants following a SARS-CoV-2 infection. Our study demonstrates that pulmonary function tests (PFT) in infants evaluated for various respiratory complaints, a few months after a SARS-CoV-2 infection, are comparable to infants who underwent iPFT prior to the COVID-19 era. These findings suggest that SARS-CoV-2 infection may not have a lasting impact on lung function in infants. However, further studies are required, particularly in infants who suffered a severe respiratory COVID-19 illness, to validate and strengthen these findings.

REFERENCES

1. Forrest CB, Burrows EK, Mejias A, Razzaghi H, Christakis D, Jhaveri R, Lee GM, Pajor NM, Rao S, Thacker D, et al. Severity of Acute COVID-19 in Children <18 Years Old March 2020 to December 2021. Pediatrics 2022;149(4):e2021055765.

2. Xiao F, Tang M, Yan K, Zhou W. Clinical features of infants with SARS-CoV-2 infection: a systematic review and meta-analysis. Ann Palliat Med 2022;11(11):3394408–3393408.

3. Wu X, Liu X, Zhou Y, Yu H, Li R, Zhan Q, Ni F, Fang S, Lu Y, Ding X, et al. 3-month, 6-month, 9-month, and 12-month respiratory outcomes in patients following COVID-19-related hospitalisation: a prospective study. Lancet Respir Med 2021;9(7):747–754.

4. Bellan M, Soddu D, Balbo PE, Baricich A, Zeppegno P, Avanzi GC, Baldon G, Bartolomei G, Battaglia M, Battistini S, et al. Respiratory and Psychophysical Sequelae Among Patients With COVID-19 Four Months After Hospital Discharge. JAMA Netw Open 2021;4(1):e2036142.

5. Huang C, Huang L, Wang Y, Li X, Ren L, Gu X, Kang L, Guo L, Liu M, Zhou X, et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. Lancet Lond Engl 2023;401(10393):e21-33.

6. Bogusławski S, Strzelak A, Gajko K, Peradzyńska J, Popielska J, Marczyńska M, Kulus M, Krenke K. The outcomes of COVID-19 pneumonia in children-clinical, radiographic, and pulmonary function assessment. Pediatr Pulmonol 2022 Dec 23.

7. Palacios S, Krivchenia K, Eisner M, Young B, Ramilo O, Mejias A, Lee S, Kopp BT. Long-term pulmonary sequelae in adolescents post-SARS-CoV-2 infection. Pediatr Pulmonol 2022;57(10):2455–2463.

8. Leftin Dobkin SC, Collaco JM, McGrath-Morrow SA. Protracted respiratory findings in children post-SARS-CoV-2 infection. Pediatr Pulmonol 2021;56(12):3682–3687.

9. Knoke L, Schlegtendal A, Maier C, Eitner L, Lücke T, Brinkmann F. Pulmonary Function and Long-Term Respiratory Symptoms in Children and Adolescents After COVID-19. Front Pediatr 2022;10:851008.

10. Frey U, Stocks J, Coates A, Sly P, Bates J. Specifications for equipment used for infant pulmonary function testing. ERS/ATS Task Force on Standards for Infant Respiratory Function Testing. European Respiratory Society/ American Thoracic Society. Eur Respir J 2000;16(4):731–740.

11. Bates JH, Schmalisch G, Filbrun D, Stocks J. Tidal breath analysis for infant pulmonary function testing. ERS/ATS Task Force on Standards for Infant Respiratory Function Testing. European Respiratory Society/American Thoracic Society. Eur Respir J 2000;16(6):1180–1192.

12. Sly PD, Tepper R, Henschen M, Gappa M, Stocks J. Tidal forced expirations. ERS/ATS Task Force on Standards for Infant Respiratory Function Testing. European Respiratory Society/American Thoracic Society. Eur Respir J 2000;16(4):741–748.

13. Shavit S, Cohen S, Goldman A, Ben-Dov L, Avital A, Springer C, Hevroni A. Bronchodilator responsiveness in wheezy infants predicts continued early childhood respiratory morbidity. J Asthma Off J Assoc Care Asthma 2016;53(7):707–713.

14. Breuer O, Boursheh L, Bar-Yishay E, Hevroni A. Infant pulmonary function tests in individuals with Down syndrome. Respir Med 2022;204:107028.

15. Breuer O, Cohen-Cymberknoh M, Picard E, Bentur L, Bar-Yoseph R, Shoseyov D, Tsabari R, Kerem E, Hevroni A. The Use of Infant Pulmonary Function Tests in the Diagnosis of Neuroendocrine Cell Hyperplasia of Infancy. Chest 2021;160(4):1397–1405.

16. Hevroni A, Goldman A, Springer C. Infant pulmonary function testing in chronic pneumonitis of infancy due to surfactant protein C mutation. Pediatr Pulmonol 2015;50(6):E17-23.

17. Hevroni A, Goldman A, Blank-Brachfeld M, Abu Ahmad W, Ben-Dov L, Springer C. Use of tidal breathing curves for evaluating expiratory airway obstruction in infants. J Asthma Off J Assoc Care Asthma 2018;55(12):1331–1337.

18. Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, Coates A, van der Grinten CPM, Gustafsson P, Hankinson J, et al. Interpretative strategies for lung function tests. Eur Respir J 2005;26(5):948–968.

19. American Thoracic Society, European Respiratory Society. ATS/ERS statement: raised volume forced expirations in infants: guidelines for current practice. Am J Respir Crit Care Med 2005;172(11):1463–1471.

20. Ashkenazi-Hoffnung L, Shmueli E, Ehrlich S, Ziv A, Bar-On O, Birk E, Lowenthal A, Prais D. Long COVID in Children. Pediatr Infect Dis J 2021;40(12):e509–e511.

21. Akbarialiabad H, Taghrir MH, Abdollahi A, Ghahramani N, Kumar M, Paydar S, Razani B, Mwangi J, Asadi-Pooya AA, Malekmakan L, et al. Long COVID, a comprehensive systematic scoping review. Infection

2021;49(6):1163–1186.

22. Magnusson K, Skyrud KD, Suren P, Greve-Isdahl M, Størdal K, Kristoffersen DT, Telle K. Healthcare use in 700 000 children and adolescents for six months after covid-19: before and after register based cohort study. BMJ 2022;376:e066809.

23. Kikkenborg Berg S, Palm P, Nygaard U, Bundgaard H, Petersen MNS, Rosenkilde S, Thorsted AB, Ersboll AK, Thygesen LC, Nielsen SD, et al. Long COVID symptoms in SARS-CoV-2-positive children aged 0-14 years and matched controls in Denmark (LongCOVIDKidsDK): a national, cross-sectional study. Lancet Child Adolesc Health 2022;6(9):614–623.

24. Miller F, Nguyen DV, Navaratnam AM, Shrotri M, Kovar J, Hayward AC, Fragaszy E, Aldridge RW, Hardelid P, VirusWatch Collaborative. Prevalence and Characteristics of Persistent Symptoms in Children During the COVID-19 Pandemic: Evidence From a Household Cohort Study in England and Wales. Pediatr Infect Dis J 2022;41(12):979–984.

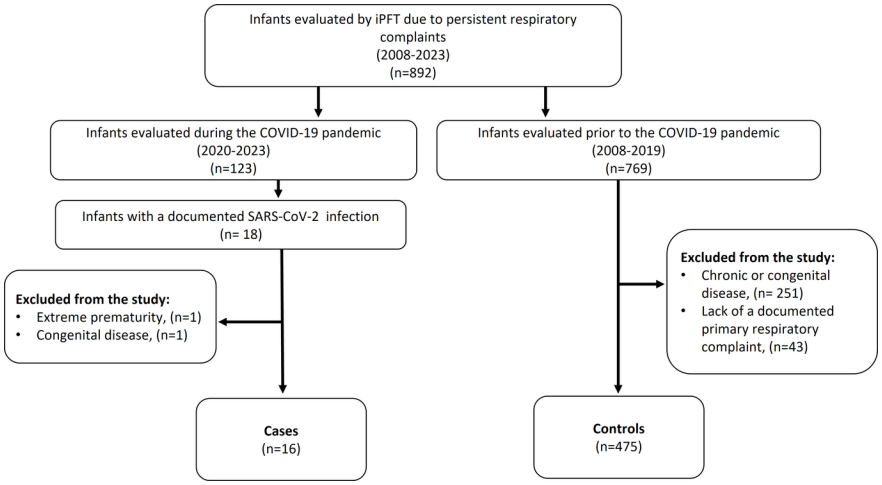
25. Borch L, Holm M, Knudsen M, Ellermann-Eriksen S, Hagstroem S. Long COVID symptoms and duration in SARS-CoV-2 positive children - a nationwide cohort study. Eur J Pediatr 2022;181(4):1597–1607.

26. Roessler M, Tesch F, Batram M, Jacob J, Loser F, Weidinger O, Wende D, Vivirito A, Toepfner N, Ehm F, et al. Post-COVID-19-associated morbidity in children, adolescents, and adults: A matched cohort study including more than 157,000 individuals with COVID-19 in Germany. PLoS Med 2022;19(11):e1004122.

27. Zimmermann P, Pittet LF, Curtis N. Long covid in children and adolescents. BMJ 2022;376:o143.

FIGURE LEGENDS

Figure 1: study population selection from the Hadassah infant pulmonary function tests (iPFT) database**.**



Hosted file

`Tables 0210.docx` available at https://authorea.com/users/671837/articles/671191-pulmonary-function-tests-in-infants-following-sars-cov-2-infection