Pulmonary function in children post -SARS-CoV-2 infection: a systematic review and meta-analysis

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Abstract

Objective: There are some concerns regarding long-term complications of COVID-19 in children. A systematic review and meta-analysis was performed evaluating the respiratory symptoms and pulmonary function, post-SARS-CoV-2 infection. **Methods:** A systematic search was performed in databases up to 30 December 2022 **.** Studies evaluating respiratory symptoms and pulmonary function after COVID-19 infection in children were selected. The major outcomes were frequency of respiratory symptoms and mean of spirometry parameters. Pooled mean with 95% confidence intervals (CIs) was calculated. **Results:** A total of 6 articles with 272 patients were included in meta-analysis. Dyspnea and cough were the most common symptoms. The meta-mean of forced expiratory volume (FEV1) and forced vital capacity (FVC) was 101.72%, 95% CI= (98.72, 104.73) and 101.31 %, 95% CI= (95.44, 107.18) respectively. The meta-mean of FEV1/FVC and Forced expiratory flow at 25 and 75% was 96.16 %, 95% CI= (90.47, 101.85) and 105.05 %, 95% CI= (101.74, 108.36) respectively. The meta-mean of diffusing capacity for carbon monoxide was 105.30%, 95%CI= (88.12, 122.49). There was no significant difference in spirometry parameters before and after bronchodilator inhalation. **Conclusions:** Despite of some clinical respiratory symptoms, meta-results showed no abnormality in pulmonary function in follow-up of children with SARS-CoV-2 infection. Disease severity and asthma background had not confounded this outcome.

Introduction

The coronavirus disease 19 (COVID 19) which spread worldwide during few years ago, caused great challenge in health, economy, social and environment (1). This mysterious virus represents with very heterogeneous organ involvements. The most prevalent presentations are fever, cough and anosmia (2). In spite of most early reports considered mild infection in children, gradually increasing concerns was developed about long-term complications of disease (3, 4). Early in 2020, there were several reports of a disease mimicking Kawasaki in children, which present with fever and muco-cutaneous as well as multi-organ involvement. Majority of patients with this new emerging syndrome, represent with cardiac involvement and require intensive care unit (ICU) admission (5). After that, many data were released about severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in children with more morbidity and mortality.

Autopsy examination in patients who dead due to COVID 19 has shown different grades of fibro proliferative procedures and diffuse alveolar injury. Therefore, it seems that COVID 19 survivors might be at risk for respiratory sequel and persistent impaired pulmonary function tests. According to expected pathophysiology, restrictive pattern is more probable. Available data has revealed that abnormal diffusing capacity for carbon monoxide (DLCO), which is relevant with severity of acute illness, is the most prevalent result in pulmonary function test (PFT) of post-acute patients. While ground grass opacities is most common in high-resolution computed tomography (HRCT) of them (6, 7). A recent meta-analysis has shown that 77% of infected

patients with SARS-Cov2 had abnormal lung computed tomography (CT) in acute phase (2). Several studies reported persistent post-COVID 19 respiratory symptoms. In one study, 25-42% of patients reported moderate to severe dyspnea, 4-8 weeks after hospital discharge (8).

Because of continues growth and development of respiratory system in pediatrics especially during infancy and early childhood, they are more vulnerable to pulmonary sequel (9).

Pulmonary function test is one of methods, which can evaluate long-term pulmonary sequel in survived COVID 19 patients. This is safe, objective and more favorable than imaging. This tool is useful in assessment of degree of airway restriction and obstruction (9).

To the best of our knowledge, there is not any systematic review and meta-analysis regarding long-term respiratory outcome in pediatric population post-SARS-CoV-2 infection. Since future of pediatric survivors of COVID 19 is uncertain, we have conducted present systematic review and meta-analysis to summarize available evidence and define the gapes, which may initiate future studies.

Methods :

Literature Search strategy and Study selection

Relevant databases including Medline, Web of sciences, Embase and Scopus were searched comprehensively to assess literature up to 30 December 2022 in English language. The search terms were including "COVID-19 or corona virus 2019" or "SARS-CoV-2" AND ("pulmonary function" OR "pulmonary diseases" OR "lung problem") AND "children" and "pediatrics". They were used separately or/and in combinations to obtain the eligible documents. The references of eligible articles were searched manually to find additional relevant papers. This study was conducted in adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement (10). The current study was based on published articles. Therefore, consent form was not needed. Two researchers (EB and NM) independently reviewed titles and abstracts of all studies to identify relevant articles. Articles were including according to following criteria: (1) English language, longitudinal or cross-sectional studies evaluating the pulmonary function and clinical symptoms of children after COVID 19 infection (2) spirometry parameters have been measured (3) the study population were pediatrics. Case reports, case series, letter to editors, unpublished reports, duplications and laboratory studies were excluded. In duplicate articles, the recent and more informative one was included. Included articles were assessed using Newcastle-Ottawa Quality Assessment Scale (NOS) for cohort and cross-sectional studies (11) if a study obtained five stars it was considered as good quality.

Data extraction

Two independent researchers (EB and NM) extracted data from eligible studies. A data collection sheet was used for data extraction. A third author (SGh) judged disagreement between EB and NM. Data from each study were including: author's name, year of publication, county of study, study design, number of studied patients, age range of children, interval between COVID 19 and pulmonary function assessment, mean$\pm$ standard deviation (SD) of spirometry parameters and frequency of respiratory symptoms.

Statistical analysis

The meta-mean with 95% confidence interval (CI) was calculated based on the mean and SD of spirometry parameters. If a study only reported the median, range and/or inter-quartile range (IQR); mean and SD were estimated, according to Hozo et al (12). The Cochran Q statistic and inconsistency index (I^2) were used to assess the heterogeneity among studies. If I^2 was more than 50%, and p value was lesser than 0.05, heterogeneity was considered significant. The random effect model was used in significant heterogeneity, whereas the fixed effect model was applied for non-significant heterogeneity. To assess the stability of the results, sequential omitting of individual studies in the meta-analysis was performed using sensitivity analysis. Subgroups were analyzed based on disease severity. Probable confounders were verified using meta regression. The standardized mean difference (SMD) was calculated in studies, which measured spirometry parameters twice. Publication bias was assessed using Egger's linear regression test. Agreement between

authors in data selection and extraction was assessed using Cohen's kappa statistic. Statistical analysis was performed using Comprehensive Meta-Analysis (CMA) computer program (Biostat, Englewood, NJ). A p value less than 0.05 was considered as statistically significant.

Results:

Literature search

A diagram of study selection is presented in figure 1. In primary search, 5834 papers were obtained evaluating the respiratory function and symptoms subsequent to COVID-19 in children. During screening process, some studies were excluded because they were review article or case series. Some studies were excluded because they studied adults, or evaluated respiratory function and symptoms during COVID-19 infection. Some studies were excluded because of duplication. Finally, seven articles including 345 patients were enrolled in the present review (13-18). Eligible studies were including 5 cross sectionals (13, 14, 16, 17, 19) and 2 longitudinal studies (15, 18). In one study the z score of spirometry parameters were reported. It only included in systematic review (16). Details of eligible studies are presented in table 1. Cohen's kappa statistic for interrater agreement in data selection and extraction was 0.98, p value$<$0.0001.

Systematic review of respiratory symptoms and spirometry parameters

Seven studies from Italy, Turkey, Germany and USA evaluated the clinical symptoms and respiratory functions in children post COVID-19 infection. Sample size ranged from 16 to 82 participants. The age of patients was varying from 7 to 15 years. Respiratory function was evaluated at least 6 weeks after infection. The most common clinical symptoms were cough, dyspnea, exercise intolerance and fatigue. In two studies no respiratory symptoms were reported (14, 19). Regarding spirometry parameters, four studies reported that COVID-19 did not affect respiratory functions (13-16) and three studies reported that it could affect pulmonary function (17-19). In four studies patients with a history of asthma were excluded (13, 14, 17, 19). In two studies spirometry parameters were measured before and after bronchodilator inhalation (13, 18). In five studies all types of COVID-19 were included (15, 17-19) and in two studies only mild or asymptomatic patients were enrolled (13, 14). Among 7 eligible studies, one study reported the z score of spirometry parameters (16). So it not included to meta-analysis.

Meta-analysis of spirometry parameters

The spirometry parameters were reported in seven articles (13-18). In Knoke study the z score of parameters were reported (16). So, it does not include to meta-analysis. In two studies, spirometry parameters were reported pre- and post-bronchodilator inhalation (13, 18). In five studies, spirometry parameters were reported without bronchodilator inhalation (14-17, 19). The FEV1, FVC and FEV1/FVC were reported in 345 patients. According to random effect modeling in meta-analysis, the mean of FEV1 was 101.72%, 95% CI= (98.72, 104.73), I^2=81.7. Forest plot is shown in figure2.

The pooled mean of FVC was 101.31 %, 95% CI= (95.44, 107.18), I^2=93.38. Forest plot is shown in figure3. The pooled mean of FEV1/FVC was 96.16 %, 95% CI= (90.47, 101.85), I^2=96.86. Forest plot is shown in figure 4. The pooled mean of FEF25-75 was reported in four studies (14, 15, 18, 19). The pooled mean of FEF25-75 was 105.05 %, 95% CI= (101.74, 108.36), I^2=26.93. Forest plot is shown in figure5. The mean of DLCO was reported in four studies (13, 15, 17, 18). The pooled mean of DLCO was 105.30 %, 95% CI= (88.12, 122.49), I^2=98.10. Forest plot is shown in figure 6. In two studies, FEV1, FVC and FEV1/FVC were reported before and after bronchodilator inhalation (13, 18). Meta- analysis confirmed that there was no significant difference in spirometry parameters before and after bronchodilator inhalation. The SMD for FEV1 was -0.21, 95% CI= (-0.65, 0.23), p value= 0.35, I^2=38.3. The SMD for FVC1 was -0.07, 95% CI= (-0.35, 0.21), p value= 0.14, I^2=zero. The SMD for FEV1/FVC was -0.29, 95% CI= (-0.58, 0.01), p value= 0.07, I^2= zero.

Heterogeneity analysis

Subgroup analysis according to severity of disease and sensitivity analysis were carried out evaluating the

possible source of heterogeneity. In two studies (13, 14) patients with asymptomatic COVID-19 were studied and in four studies all types of disease (asymptomatic and symptomatic) were studied (15, 17-19). According to meta-analysis the pooled mean of FEV1 in asymptomatic subgroup was 98.59%, 95%CI= (96.96, 100.23), I^2=zero. The pooled mean of FEV1 in symptomatic subgroup was 103.91%, 95%CI= (101.08, 106.74), I^2=53.27. The pooled mean of FVC in asymptomatic subgroup was 95.17%, 95%CI= (92.80, 97.54), I^2=zero. The pooled mean of FVC in symptomatic subgroup was 104.62%, 95%CI= (98.00, 111.24), I^2=91.17. The pooled mean of FEV1/FVC in asymptomatic subgroup was 98.28, 95%CI= (86.25, 110.31), I^2=zero. The pooled mean of FEV1/FVC in symptomatic subgroup was 94.99%, CI= (88.19, 101.79), I^2=95.65.

Meta regression showed neither disease severity nor asthma comorbidity had a significant effect on pooled mean of FEV1 (p value= 0.35 and 0.21 respectively) and FVC (p value= 0.80 and 0.51 respectively). In sensitivity analysis, the effect of each study on the pooled mean was assessed. There was no major deviation from pooled mean by omitting studies in FEV1, FVC FEV1/FVC, FEF25-75 and DLCO outcomes, indicating the stability and robustness of the results (Data not shown).

Publication bias

Egger's regression asymmetry test was used to explore the probable publication bias for FEV1, FVC and DLCO parameters. The Egger's test result provided no significant bias across the included studies (p value= 0.39, 0.69 and 0.53 respectively).

Discussion

After widespread distribution of COVID 19 in pediatric patients, one of the most important issues was long-lasting complications in our next generation. Current evidences have mentioned increased risk of diabetes mellitus type I and severe diabetes ketoacidosis in children infected by SARS-CoV-2 (20). Autoimmune disorders might be more expected in coming years due to impact of COVID 19 on immune system (21). One of the most prevalent symptoms in children infected by SARS-CoV-2 is respiratory manifestation (22). There are increasing evidences of pulmonary sequel especially in adult population after infection (23). To the best of our knowledge present study is the first systematic review and meta-analysis evaluating the impact of COVID 19 on respiratory system of younger generation in long-term. In six eligible studies, 272 pediatric patients (143 females and 129 males) were evaluated with the mean age of 12.68 years. The mean of recovery time after SARS-CoV-2 infection was 3.94 months.

Infection generally was mild and most of patients had no or only mild symptoms. All spirometry parameters were in normal range. Two studies were evaluated post bronchodilator parameters. Their results showed no reversible obstructive changes in airways of children with history of COVID 19. Fortunately, all studies reported FEF 25-75%. It is one of the most sensitive measures of obstructive diseases in peripheral airways (24-27). The meta-mean of FEF25-75% was 105.05%, which was in normal range. According to our meta-results, no obstructive disease in studied population was detected.

One of the most expected involved areas in respiratory system during COVID 19 is alveolar epithelial cells (28, 29). It seems that peripheral airways with an internal diameter less than 2 millimeters are more prone to impair after SARS-CoV-2 infection. While these parts of respiratory system represent 90% of total lung capacity but only have role in less than 20% of airflow (30, 31). So, simple spirometry which measuring FEV1 and FVC hardly might detect early stages of pulmonary involvement after COVID 19. Measuring diffusion capacity is more sensitive in detection of pulmonary diseases especially in early stages (32). Unfortunately, only 177 out of 238 participants had DLCO values. However, according to meta-results the mean of DLCO was within normal range (108.97 %, 95%CI: (86.15, 131.79)). A meta-analysis in adults was evaluated pulmonary function post-COVID 19 infection. Results showed decreased DLCO in nearly 40% of survivors (33, 34). Decreased DLCO might be an early indicator of interstitial lung diseases even before change in lung volumes (35, 36). Chronic interstitial pneumonia and diffuse alveolar hemorrhage are demonstrated in few studies, which have reported histological finding in autopsy (37-39). Patients with SARS-CoV-2 may had pulmonary fibrosis, which is considered as defined sequel of barotrauma. All of these pathologies can impair carbon monoxide diffusion capacity (40). In present study, one explanation for normal DLCO may

be none-severe infection in most of studied children. We have tried to evaluate impact of disease severity in spirometry parameters. However, there were not significant difference between the result in symptomatic and asymptomatic patients. Future studies with longer period of follow-up and evaluating patients with more severe respiratory presentation are needed. We had also heterogeneity in atopy and asthma background of our included studies. However, according to meta-regression chronic pulmonary disease (such as asthma) had not a significant effect on pooled mean of major outcomes.

Less severity of respiratory system involvement in children infected by SARS-CoV-2 comparing with adult, might be possible explanation for different outcome between them (3). In addition, preexisting diseases in adults like chronic respiratory diseases, cardiac diseases and diabetes mellitus may induce impairment in pulmonary function. On the other hand, children during infancy and preschool age usually have more severe course during infection (41, 42). Because majority of our included participants were teenage, more studies which can evaluate pulmonary sequel in infants and young toddlers, should be designed. In addition, different variants of SARS-CoV-2 like Delta or Omicron had resulted to different presentation and probably different outcomes. Therefore, studies, which determine type of variants, may be useful. It is possible that pulmonary sequel of survived children is so tiny and routine pulmonary function test cannot detect abnormalities. It is useful to design exercise-challenging studies in survived children after COVID 19 to detect subtle or mild changes in pulmonary function.

Conclusion:

Although more evidences are needed, our review showed no abnormality in pulmonary function test in follow-up of children with a SARS-CoV-2 infection history. Disease severity and asthma background had not confounded this outcome.

Limitation:

There are some limitations regarding present study: A) in spite of an attempt for a comprehensive search, it maybe that some eligible articles were missed. B) Eligible studies were observational and they were threatened with bias in different levels. It may affect the meta-results.

Conflict of interest

There is no conflict of interest.

Data availability statement

The data that support the findings of this study are openly available at the web space (as original articles)

Contributors' Statement

Dr Bakhtiari and Dr Moazzen designed the data collection instruments, collected data, carried out the initial analyses, and reviewed and revised the manuscript.

Dr Ghahremani and Dr Moazzen conceptualized and designed the study, coordinated and supervised data, drafted the initial manuscript, and reviewed and revised the manuscript.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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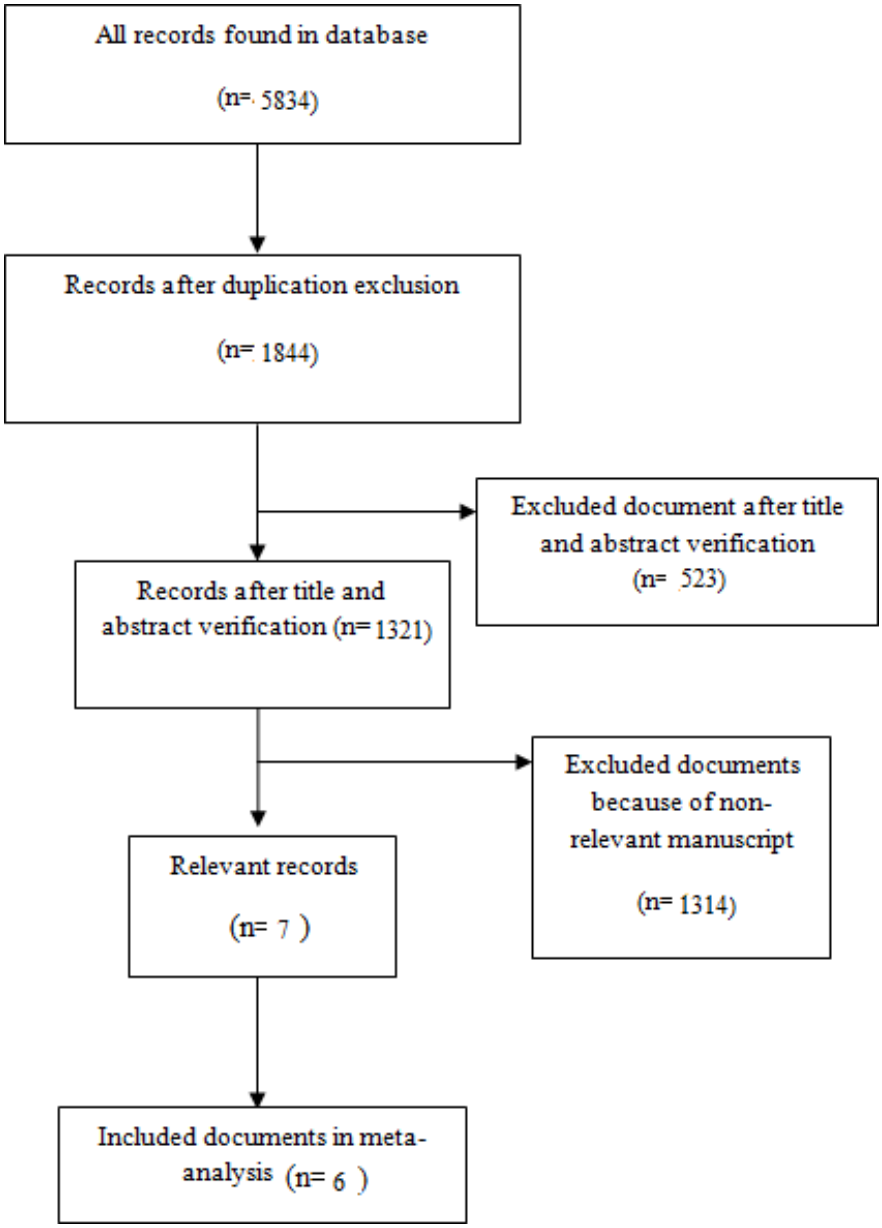

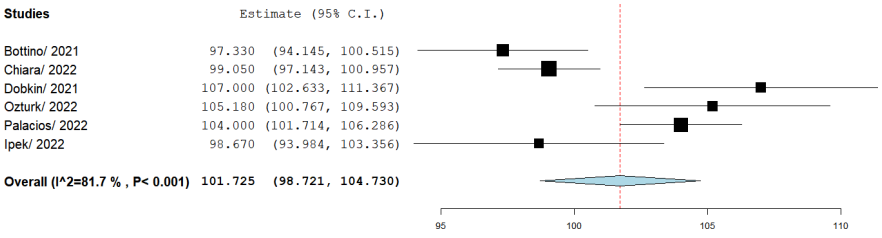

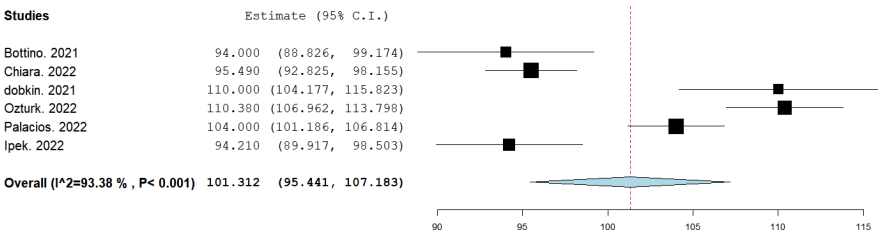

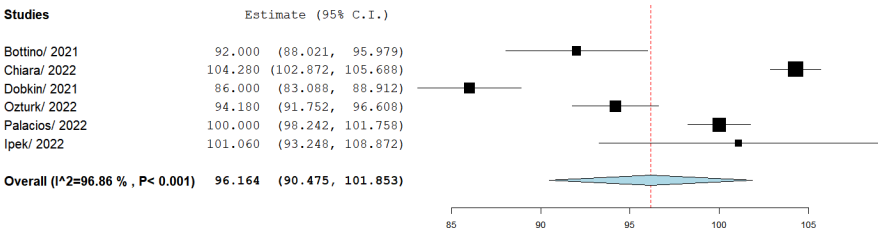

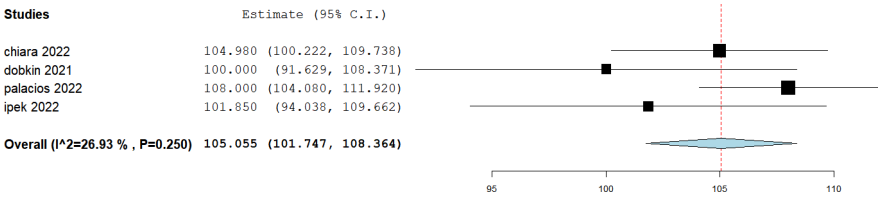

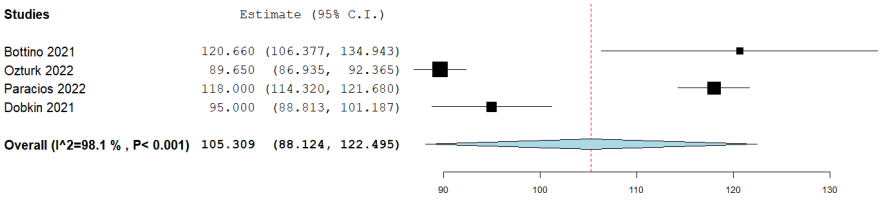

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