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Clinical Research Study

Association Between COVID-19 Infection and Pulmonary Fibrosis: A Nested Case-Control Study

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Abstract

Background

Pulmonary fibrosis is associated with significant morbidity. Data are scarce on the link between coronavirus disease (COVID-19) and pulmonary fibrosis. We aimed to assess the association between COVID-19 with pulmonary fibrosis.

Methods

We conducted a nested case-control study in a cohort of 2,894,801 adults without a diagnosis of pulmonary fibrosis. The underlying cohort consisted of members of the largest healthcare provider in Israel aged 18 years or older as of May 1, 2020. Subjects were followed up from cohort entry until June 30, 2022, for the occurrence of pulmonary fibrosis. Ten randomly selected controls were matched to each case of pulmonary fibrosis on age, sex, and calendar time. To account for surveillance bias a lag time of 60 days was used for ascertainment of prior COVID-19 and COVID-19 severity.

Results

During follow-up 1284 patients were newly diagnosed with pulmonary fibrosis and matched with 12,840 controls. Multivariable conditional logistic-regression models showed that the odds ratio for pulmonary fibrosis was 1.80 (95% confidence interval, 1.47-2.19) in patients with COVID-19 compared with no COVID-19. The multivariable odds ratio for pulmonary fibrosis was 1.33 (1.06-1.68), 2.98 (1.16-7.65), and 9.30 (5.77-14.98) for mild, moderate, and severe COVID-19, respectively, compared with no COVID-19. The magnitude of the association was attenuated but remained statistically significant for severe disease when the lag time was extended to 180 days (1.08 [0.78-1.49], 2.37 [0.75-7.46], and 5.34 [2.75-10.36] for mild, moderate, and severe COVID-19, respectively).

Conclusions

COVID-19 appears to be associated with an increased risk of pulmonary fibrosis and the magnitude of the association increases with COVID-19 severity.

Introduction

Since the emergence of the coronavirus disease (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), in December 2019, it has become a leading cause of morbidity and mortality worldwide¹ with more than 600 million

cases globally and more than 6.5 million deaths.²

As the pandemic evolved and effective vaccines and treatments became available, it is important to acknowledge the long-term complications in patients infected with the SARS-CoV-2 virus. Due to the high prevalence of respiratory failure and the need for mechanical ventilation in patients with severe manifestations of the disease, there has been increasing concern about pulmonary sequelae, most notably pulmonary fibrosis.³

Bocchino et al, prospectively followed 84 previously hospitalized non-intubated COVID-19 patients with high-resolution computed tomography for up to 12 months.⁴ They showed that fibrotic-like changes were detected in 50% of patients at 3 months, 42% at 6 months, and only 5% at 12 months. Fibrotic changes were detected in 2% at 3-6 months and remained unchanged at 12 months. On the other hand, a meta-analysis showed that the prevalence of post-COVID-19 lung fibrosis is as high as ~45%.⁵

Large-scale population-based studies to evaluate the association between COVID-19 and pulmonary fibrosis are lacking. In this retrospective population-based nested case-control study we aimed to assess the association between COVID-19 and the onset of pulmonary fibrosis, using real-world data from the largest healthcare provider in Israel.

Section snippets

Materials and Methods

The study was approved by the institutional review board of Lady Davis Medical Centre and Data Utilization committee of Clalit Health Services. Owing to the retrospective nature of the study, a waiver of informed consent was granted by the Institutional Review Board. The current study followed the Strengthening Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline....

Results

A total of 3,094,176 adults aged 18 years or older were identified in the CHS database as being alive on May 1, 2020 (cohort entry date). We excluded 195,896 individuals with less than 1 year of continuous membership in the CHS before the study entry date, and 4019 with recorded pulmonary fibrosis prior to study entry date. The remaining 2,894,801 constituted the study cohort. Among this group 1284 had a new pulmonary fibrosis diagnosis during the follow-up period and were matched to 12,840...

Discussion

Pulmonary fibrosis is a feared complication of several respiratory infections. In this study, we show an association between COVID-19 and increased risk of pulmonary fibrosis. The magnitude of this association increases with increasing COVID-19 severity and persisted after extending the lag time for the ascertainment of prior exposure to COVID-19.

A previous in-vitro analysis of lung tissue and bronchoalveolar lavage fluid samples from severe COVID-19 patients has shown that exposure of human...

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