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Original Article

Comparative study on the incidence of non-COVID-19 viral pneumonia before and after the COVID-19 pandemic: A retrospective analysis based on respiratory non-COVID viral nucleic acid results

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ABSTRACT

Background: The impact of the coronavirus disease 2019 (COVID-19) pandemic on the etiology of non-COVID-19 viral pneumonia remains to be identified. We investigated the evolution of non-COVID-19 viral pneumonia in hospitalized patients before and after the COVID-19 pandemic.

Methods: This is a single-center retrospective study. Patients who came to West China Hospital of Sichuan University diagnosed with non-COVID-19 viral pneumonia from January 1, 2016 to December 31, 2021, were included and divided into pre- and post-COVID-19 groups according to the date of the COVID-19 outbreak in China. The results of 13 viral nucleic acid tests were compared between the two groups.

Results: A total of 5937 patients (3954 in the pre-COVID-19 group and 1983 in the post-COVID-19 group) were analyzed. Compared with the pre-COVID-19 group, the proportion of patients tested for respiratory non-COVID-19 viral nucleic acid was significantly increased in the post-COVID-19 group (14.78% *vs.* 22.79%, P <0.05). However, the non-COVID-19 virus-positive rates decreased from 37.9% to 14.6% after the COVID-19 outbreak (P < 0.001). Notably, non-COVID-19 viral pneumonia caused by the influenza A virus H1N1 (InfAH1N1) (2009) dropped to 0% after the pandemic. The top three viruses were InfAH1N1 (2009) (13.9%), human rhinovirus (7.4%), and human adenovirus (3.4%) in the pre-COVID-19 group, and human rhinovirus (3.8%), human respiratory syncytial virus (2.0%), human parainfluenza virus (1.1%) and InfAH3N2 (1.1%) in the post-COVID-19 group.

Conclusions: The proportion of non-COVID-19 viral pneumonia decreased significantly after the COVID-19 outbreak, among which InfAH1N1 (2009) pneumonia decreased the most dramatically.

Introduction

Data from before the coronavirus disease-2019 (COVID-19) pandemic suggest that the incidence of non-COVID-19 viral pneumonia was high, accounting for 12.3%–27.0% of pneumonia cases.[1,2] Specifically, in patients with severe community-acquired pneumonia requiring mechanical ventilation, the detection rate of non-COVID-19 viral pneumonia was as high as 50%.[3] In particular, the outcomes of influenza virus pneumonia.[4] were more serious. The WHO estimated that annual epidemics of influenza result in approximately 1 billion infections, 3–5 million cases of severe illness, and 300,000–500,000 deaths. The severity of pandemic influenza depends on several factors, including the virulence of the pandemic virus strain and the level of pre-existing immunity. The most severe influenza pandemic, in 1918, resulted in more than 40 million deaths worldwide.

However, after the outbreak of COVID-19, few studies were conducted on non-COVID-19 viral pneumonia. Only one study,[5] from Australia, reported that by the winter of 2020, the detection rates of respiratory syncytial virus and influenza in Western Australian children decreased by 98.0% and 99.4%, respectively, compared with the rates before the COVID-19 pandemic. However, the prevalence of other non-COVID-19 viral

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pneumonia under the influence of COVID-19 remains to be elucidated. The current study aimed to investigate the changes in viral pneumonia other than the novel coronavirus before and after the COVID-19 pandemic.

Methods

Study design

This study was a single-center retrospective study performed at West China Hospital of Sichuan University, which is a referral center in Western China with 4300 beds. It was a designated hospital for non-COVID-19 patients during the COVID-19 pandemic. Patients diagnosed with non-COVID-19 pneumonia upon admission from January 1, 2016 to December 31, 2021, were included. The study protocol was approved by the Ethics Committee of the West China Hospital. December 8, 2019, was selected as the cut-off date to define pre- and post-COVID-19, as the first COVID-19 patient officially confirmed in Wuhan occurred on this day. The patient's data were collected, including their sex, age, admission diagnosis, department distribution, length of hospital stay, and underlying diseases (including hypertension, diabetes, coronary heart disease, heart failure, chronic obstructive pulmonary disease [COPD], renal failure, and immunosuppression).

Laboratory testing

The sample types and collection methods used in this study included: (1) throat swabs (disposable sterile flocked swab + self-capped tube or a 1.5 mL centrifuge tube; sampling was performed at the isthmus, with the swab being broken from the sterile sampling tube and the tail discarded); (2) sputum (self-collected) using a disposable sterile sputum cup; morning sputum was preferred, and the sample volume was 21 mL; and (3) manual sputum suction (conventional sputum suction was performed using a suction tube + reservoir bottle). A viral nucleic acid detection[6] method was used to detect 13 common respiratory viruses. A total of 13 viral nucleic acid tests were performed using the GeXP Genetic Analysis platform combined with multiple reverse transcription-polymerase chain reaction methods to detect the following: influenza A virus, influenza A virus H1N1 (InfAH1N1) (2009), seasonal influenza virus H3N2, influenza B virus, human adenovirus, bocavirus, human rhinovirus (HRV), human parainfluenza virus, human coronavirus, human respiratory syncytial virus (HRSV), human metapneumovirus, mycoplasma pneumonia, and chlamydia.

Statistical analysis

The database was constructed using Excel, and the data analysis was performed using IBM SPSS version 26 (IBM SPSS Inc., Chicago, IL, USA). Measurement data that conform to a normal distribution are expressed as the mean±standard deviation. In addition, measurement data that did not conform to a normal distribution are described as median and interquartile range (IQR), rate, or composition ratio as a percentage. A chi-squared test was used to compare two rates or two constituent ratios; a *Z*-test was used for a statistical test of parameters, such as mean value and variance of sample data; and $P < 0.05$ (two-sided) was considered statistically significant.

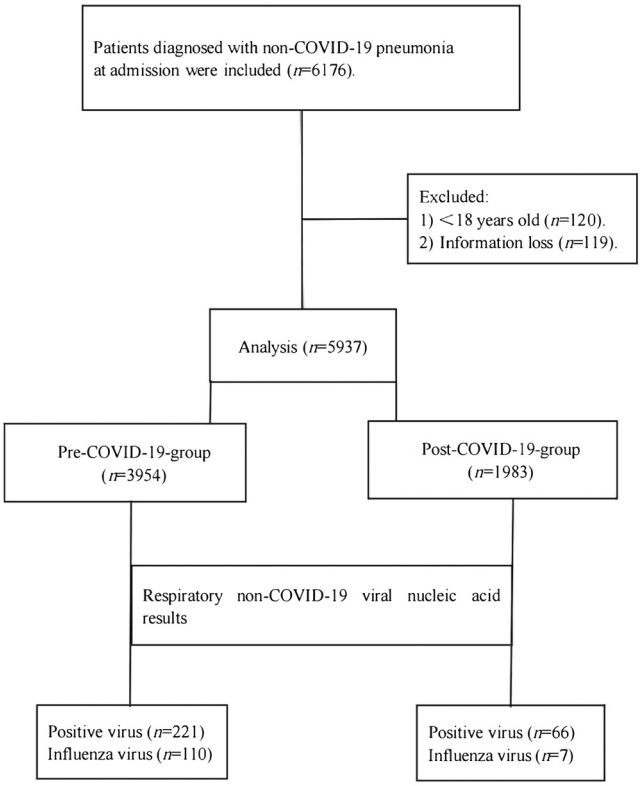

Figure 1. Research flowchart.
COVID-19: Coronavirus disease-2019.

Results

Patient selection

Patients diagnosed with non-COVID-19 pneumonia admitted from January 1, 2016, to December 31, 2021, were included. A total of 119 patients were excluded from the analysis due to information loss and 120 patients were excluded because they were less than 18 years old. Finally, a total of 5937 adult patients with non-COVID-19 pneumonia were analyzed (Figure 1).

Patient characteristics

Post-COVID-19 patients were more likely to be male (66.52% *vs.* 62.08%, P=0.001) and older (59.4±17.6 *vs*. 57.6±19.8 years, P=0.014) than pre-COVID-19 patients. Post-COVID-19 patients exhibited higher comorbidity rates with hypertension, diabetes, COPD, heart failure, and immunosuppression compared to pre-COVID-19 patients (P <0.05). In terms of laboratory testing, there were no statistical differences in platelet count, procalcitonin levels, and percentage of neutrophils between pre-COVID-19 and post-COVID-19 patients. However, the $CD4^+$ count significantly decreased from median 344.6 pre-COVID-19 to 338.5 post-COVID-19 (P=0.002) in cellular immune testing. Post-COVID-19 patients required invasive mechanical ventilation support (P <0.001) and intensive care unit admission (P <0.001) more frequently. Regarding culture results, post-COVID-19 patients exhibited a lower proportion of Gram-negative bacteria, with a decrease from 26.98% to 18.76% (P < 0.001); similar trend were observed with fungus, with a rate of 4.39% decreasing to 2.77%, P=0.003 (Table 1).

Table 1
Patients' characteristics before and after the COVID-19 pandemic.

Variable	Pre-COVID-19 (*n*=3945)	Post-COVID-19 (*n*=1983)	*P*-value
Male	2449 (62.08)	1319 (66.52)	0.001
Age (years)	57.6±19.8	59.4±17.6	0.014
Chronic comorbidity	2125 (53.87)	1127 (56.83)	0.030
Hypertension	1058 (26.82)	600 (30.26)	0.005
Diabetes	717 (18.17)	405 (20.42)	0.037
Coronary disease	283 (7.17)	119 (6.00)	0.961
COPD	782 (19.82)	327 (16.49)	0.002
Heart failure	373 (9.46)	70 (3.53)	<0.001
Kidney failure	161 (4.08)	77 (3.88)	0.714
Immunosuppression	285 (7.22)	295 (14.88)	<0.001
Virus screening	583 (14.78)	452 (22.79)	<0.001
Positive viral test	221 (37.9)	66 (14.6)	<0.001
HRV	43 (7.4)	17 (3.8)	0.670
HADV	20 (3.4)	2 (0.4)	0.470
HRSV	5 (0.9)	9 (2.0)	0.519
HPIV	8 (1.4)	5 (1.1)	0.485
Influenza virus	110 (18.9)	7 (1.6)	<0.001
InfAH1N1	81 (13.9)	0 (0.0)	<0.001
InfAH3N2	12 (2.1)	5 (1.1)	0.464
Influenza B	8 (1.4)	2 (0.4)	0.356
Laboratory testing			
WBC count (10^9/L)	8.2±9.4	8.6±10.6	0.029
N	71.7±15.3	71.4±14.8	0.331
PCT (ng/mL)	1.4±5.9	1.5±6.0	0.645
PLT count (10^9/L)	217.5 (140.0–279.0)	220.4 (143.0–279.0)	0.127
ALT (U/L)	37.7 (13.0–39.0)	37.1 (12.0–38.0)	0.002
AST (U/L)	41.0 (18.0–39.0)	45.3 (16.0–36.0)	<0.001
CB (μmol/L)	6.3±11.8	5.4±11.9	<0.001
IBIL (μmol/L)	6.5±5.2	6.7±4.5	0.016
Cr (μmol/L)	80.8 (51.0–80.0)	90.8 (59.0–90.0)	<0.001
$CD4^+$ count (cell/μL)	344.6 (120.0–495.0)	338.5 (169.0–551.0)	0.002
$CD8^+$ count (cell/μL)	300.0 (124.5–403.0)	302.3 (116.0–396.0)	0.662
Microbiological culture	3169 (80.33)	1514 (76.35)	<0.001
Sputum	2339 (73.81)	974 (64.33)	<0.001
The alveolar lavage fluid	116 (3.66)	181 (11.96)	<0.001
Tracheal secretions	74 (2.34)	64 (6.34)	0.001
Blood	291 (9.18)	121 (8.00)	0.069
Other	349 (11.01)	174 (11.49)	<0.001
PCR screening	150 (3.80)	351 (17.70)	0.057
PCR positive	71 (47.3)	156 (44.4)	0.098
Culture results			
Gram-negative bacteria	855 (26.98)	284 (18.76)	<0.001
Gram-positive bacteria	99 (3.12)	39 (2.58)	0.191
Fungus	139 (4.39)	42 (2.77)	0.003
Mechanical ventilation	280 (7.10)	277 (13.97)	<0.001
ICU admission	91 (2.31)	81 (4.08)	<0.001
Length of hospital day	15.3±13.2	15.5±14.8	0.316

Data are expressed as *n* (%), mean±standard deviation, and median (interquartile range).
PCR analysis has been carried out in our hospital since January 2019.
ALT: Glutamic-pyruvic transaminase; AST: Glutamic-oxalacetic transaminase; CB: Direct bilirubin; $CD4^+$: $CD4^+$ T-cell; $CD8^+$: $CD8^+$ T-cell; COPD: Chronic obstructive pulmonary disease; COVID-19: Coronavirus disease-2019; Cr: Creatinine; HADV: Human adenovirus; HPIV: Human parainfluenza virus; HRSV: Human respiratory syncytial virus; HRV: Human rhinovirus; IBIL: Indirect bilirubin; ICU: Intensive care unit; InfAH1N1: Seasonal influenza A virus H1N1; InfAH3N2: Seasonal influenza virus H3N2; IQR: Interquartile range; N: Neutrophil percentage; PCR: Polymerase Chain Reaction; PCT: Procalcitonin; PLT: Platelet; SD: Standard deviation; WBC: White blood count.

Microbiological results based on respiratory non-COVID viral nucleic acid testing

The non-COVID-19 respiratory viral nucleic acid detection ratio increased significantly, from 14.78% pre-COVID-19 to 22.79% post-COVID-19 (Table 1). However, the virus-positive (non-COVID-19) rates decreased from 37.9% to 14.6% after the COVID-19 outbreak, while the InfAH1N1 (2009) positive detection ratio decreased dramatically, from 13.9% pre-COVID-19 to 0% post-COVID-19 (Table 1).

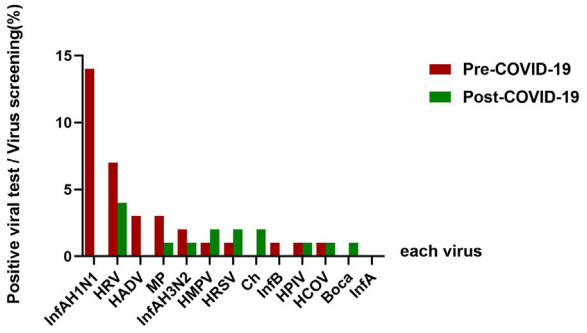

Figure 2. Positive virus screening of each virus before and after the COVID-19 pandemic. Pre-COVID-19: from January 1, 2016, to December 8, 2019; post-COVID-19: from December 9, 2019, to December 31, 2021.
Boca: Bocavirus; Ch: Chlamydia; COVID-19: Coronavirus disease-2019; HADV: Human adenovirus; HCOV: Human coronavirus; HMPV: Human metapneumovirus; HPIV: Human parainfluenza virus; HRSV: Human respiratory syncytial virus; HRV: Human rhinovirus; InfA: Influenza A virus; InfAH1N1: Influenza A virus H1N1; InfAH3N2: Seasonal influenza virus H3N2; InfB: Influenza B virus; MP: Mycoplasma pneumonia.

The proportion of the top three detected non-COVID-19 viruses was InfAH1N1 (2009) (13.9%), HRV (7.4%), and human adenovirus (3.4%) pre-COVID-19, and HRV (3.8%), HRSV (2.0%), and human parainfluenza virus (1.1%) post-COVID-19. In addition, post-COVID-19, mainly HRV, HRSV, and human metapneumovirus were detected (Figure 2).

Examining trends over the years, in 2020 and 2021, the positive detection of viruses (non-COVID-19) and influenza decreased compared to pre-COVID-19 levels. Examining trends over quarters, viruses (non-COVID-19) and influenza were generally detected higher in the first and fourth quarters both pre-COVID-19 and post-COVID-19 (Figure 3).

Discussion

Pneumonia[7,8] is a serious medical condition with a high rate of morbidity and short- and long-term mortality, and it remains the most common infectious disease worldwide across all ages. To our knowledge, this is the first study to compare non-COVID-19 viral pneumonia before and after the COVID-19 pandemic in hospitalized adult pneumonia patients. The results indicated that the proportion of non-COVID-19 viral pneumonia cases significantly decreased from 37.9% to 14.6% after the COVID-19 outbreak, especially for InfAH1N1, which decreased from 13.9% to 0%. This study describes the epidemiology of viral pneumonia other than COVID-19 before and after the pandemic period. This finding offers insights into strategies for preventing non-COVID-19 viral pneumonia in the future, emphasizing the importance of widespread influenza vaccination among the general population. In addition, they provide a basis for empirically selecting appropriate drugs for treatment.

The reasons behind the proportion of non-COVID-19 viral pneumonia cases significantly decreasing after the COVID-19 pandemic are unclear. After the COVID-19 pandemic, we found one study from Australia that reported that by the winter of

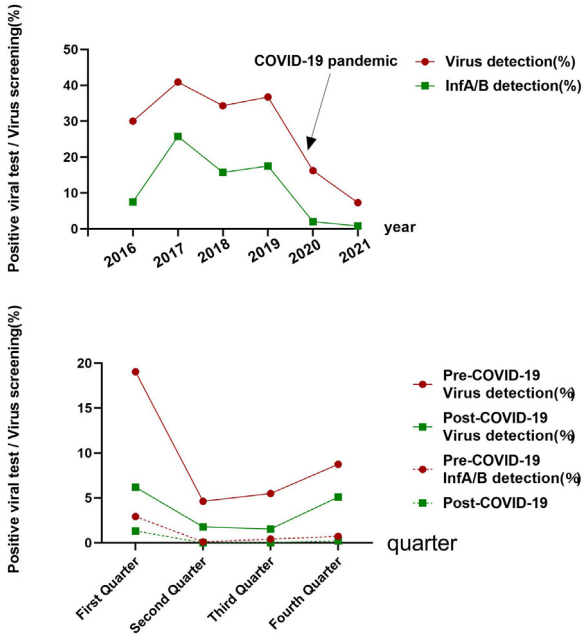

Figure 3. Positive Virus and Influenza virus A/B of screening changes by years and quarters.
COVID-19: Coronavirus disease-2019; First quarter: January–March; Second quarter: April–June; Third quarter: July–September; Fourth quarter: October–December.

2020, the detection rate of influenza, as determined by positive tests in Western Australian children, decreased by 99.4%.[5] However, a clear explanation for this phenomenon was not found, and because the study was centered on children, school closures were speculated to be the reason. However, it might be associated with measures such as wearing masks [9] and the reduced presence of people in public areas[10] for adults. In the future, we hope to control more confounding factors, deeply explore certain homeostatic relationships between microorganisms, and obtain rigorous and scientific conclusions. Larger and additional studies are needed to confirm the results.

In addition, our study identified that post-COVID-19, patients with pneumonia seemed to be more critically ill, and more patients required invasive mechanical ventilation support. This might be because after the COVID-19 outbreak, admitted patients tended to be older and more patients were admitted with underlying conditions. Other possible reasons were that fewer patients were admitted to the hospital after the outbreak. This is consistent with the research of Marriott et al.[11] and Kadambari et al.[12]

There are limitations regarding this study. First, this study is a single-center retrospective study. The results may not be generalizable to other regions. However, our sample size was relatively large, which can truly reflect the local epidemiological characteristics. A population-based study is needed to confirm the results. In the future, we expect to complete a national multicenter study. Second, data quality is vital in a retrospective study, but all our data were automatically extracted from an electronic medical record system. Furthermore, all the data on nucleic acid was objective, and therefore the quality of the data is relatively good. Third, the results of our study could only represent the current situation and cannot reflect possible changes in the future.

Conclusion

The proportion of viral pneumonia other than COVID-19 decreased significantly after the COVID-19 outbreak, among which InfAH1N1 (2009) pneumonia decreased most dramatically. Population-based surveillance studies of non-COVID-19 viral pneumonia are imperative for guiding future efforts in the prevention and control of non-COVID-19 viral pneumonia.

Author Contributions

Xiaojiao Tan: Writing review & editing, Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Zheng Zhang:** Formal analysis, Data curation. **Huan Zhang:** Visualization, Validation. **Jianbo Li:** Methodology. **Xuewei Yang:** Supervision, Software. **Lijie Wang:** Formal analysis. **Xuelian Liao:** Project administration, Methodology, Investigation, Funding acquisition.

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Ethics Statement

The study protocol was approved by the Ethics Committee of the West China Hospital, Ethics Approval No. 2021 (WCH2021-1548).

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

The data sets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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