

Characteristics of patients with viral infections of the lower respiratory tract

A retrospective study

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Abstract

While the impact of respiratory virus infections has been well researched in some respiratory diseases, no clinical studies have discussed the subject of who would be more likely to develop respiratory virus infections among patients with various respiratory illnesses who come from different backgrounds. This study aimed to identify respiratory diseases that are frequently associated with respiratory virus infections along with the characteristics of patients who develop such infections in clinical settings. Tested specimens were obtained from the lower respiratory tract by bronchoscopy to provide more accurate data. Data of bronchoscopies at Ryukyu University Hospital between August 2012 and September 2016 were reviewed, and patients who underwent multiplex polymerase chain reaction (PCR) tests for detecting respiratory viruses in bronchoscopy specimens were retrospectively recruited for descriptive statistics. Differences among patients' primary pulmonary diseases and backgrounds were compared between the PCR-positive and -negative patients, and multivariate statistical analysis was performed to analyze factors associated with a positive PCR test result. Overall, 756 bronchoscopies were performed during the study period and PCR tests were performed for 177 patients. Of them, 27 tested positive for respiratory viruses, mainly parainfluenza virus and rhinovirus, and out of those, 7 were hospitalized for >1 month. Overall, all patients did not experience typical upper respiratory infection symptoms. In positive patients, 13 and 7 had diagnoses of interstitial lung disease and bacterial pneumonia, respectively. The diagnoses of 3 bacterial pneumonia cases were changed to viral pneumonia after receiving their PCR-positive tests. Respiratory virus infections were confirmed in 14 patients on immunosuppressant therapy and 4 on maintenance dialysis. Multivariate analysis revealed that immunosuppressant therapy and maintenance dialysis were independently associated with respiratory virus infections. Viruses were commonly detected in patients with interstitial lung diseases and bacterial pneumonia, while few patients were diagnosed with pure viral pneumonia. These illnesses were considered to be induced by respiratory infections. Immunosuppressant therapy and maintenance dialysis were associated with respiratory virus infections. Multiplex PCR testing is an essential diagnostic tool for respiratory virus infections in immunocompromised patients.

Abbreviations: ILD = interstitial lung disease, PCR = polymerase chain reaction.

Keywords: bacterial pneumonia, corticosteroid, immunosuppressant therapy, interstitial lung disease, maintenance dialysis, respiratory virus, viral pneumonia

1. Introduction

Recently, innovative tools for the simultaneous detection of multiple viral pathogens have shown that respiratory virus infections are involved in respiratory diseases more often than expected. Respiratory virus infections often cause asthma and chronic obstructive pulmonary disease exacerbations.^[1] Furthermore, respiratory viruses are common pathogens in community-acquired pneumonia,^[2] with viral lower respiratory tract infections frequently occurring in patients who have undergone hematopoietic stem-cell transplantations.^[3] Although some studies have researched the association between viral infections and the exacerbations of interstitial

lung diseases (ILDs), a concrete association has not been identified.^[4]

While the impact of respiratory virus infections has been well researched in terms of some respiratory diseases, there have been no clinical studies of who is more likely to have respiratory virus infections among patients with unspecified respiratory diseases and different backgrounds. Therefore, it is unclear when respiratory virus infections should be considered in clinical settings. At our facility, in routine medical practice, we use multiplex polymerase chain reaction (PCR) as a diagnostic tool to determine the presence of viral pathogens. This study reviewed the data of patients with respiratory diseases who underwent bronchoscopies and multiplex PCR for respiratory viruses.

The authors have no funding and conflicts of interest to disclose.

All data generated or analyzed during this study are included in this published article [and its supplementary information files]

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How to cite this article: Nabeya D, Kinjo T, Ueno S, Setoguchi M, Nishiyama N, Kami W, Arakaki W, Haranaga S, Fujita J. Characteristics of patients with viral infections of the lower respiratory tract: A retrospective study. *Medicine* 2022;101:38(e30819).

Received: 28 April 2022 / Received in final form: 28 August 2022 / Accepted: 30 August 2022

<http://dx.doi.org/10.1097/MD.00000000000030819>

Then, we identified respiratory diseases that are frequently associated with respiratory virus infections along with the characteristics of patients who often develop such infections in clinical settings. Specimens were obtained from the lower respiratory tract of patients and were used for PCR testing. Therefore, the results of the present study provided a more accurate reflection of lower respiratory tract virus infections compared to those of other studies that relied on expectorated sputum or swab specimens instead.

2. Methods

2.1. Data collection

Data of bronchoscopies at Ryukyu University Hospital between August 2012 and September 2016 were reviewed, and all patients who underwent multiplex PCR tests for respiratory viruses in bronchoscopy specimens were retrospectively recruited. PCR tests were performed using commercially available multiplex PCR kits (Seeplex RV15 OneStep ACE Detection, Seegene, Korea). These can detect 15 respiratory viruses (adenovirus, coronaviruses 229E/NL63 and OC43, parainfluenza viruses 1–4, rhinovirus A/B/C, respiratory syncytial viruses A and B, metapneumovirus, enterovirus, influenza A and B viruses, and bocavirus 1/2/3/4). The PCR results, diagnoses of lung lesions before considering PCR results, and medical histories were extracted for descriptive statistics. Diagnosis of pure viral pneumonia was based on the description in the medical records (no criteria for pure viral pneumonia in this study).

2.2. Statistical analysis

Differences among patients' primary pulmonary diseases and backgrounds were compared between the PCR-positive and -negative patients using the chi-square and Mann-Whitney *U* tests. A forward stepwise logistic regression was performed to analyze factors associated with a positive PCR test result. The independent variables were selected according to the results of the univariate analysis and the clinical importance of susceptibility to infection.^{15–81} All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY).

2.3. Ethics

The study was conducted in accordance with the Declaration of Helsinki, as revised in 2013. The requirement for informed consent was waived because this was a retrospective study. This study was reviewed and approved by the Clinical Research Ethics Committee of the University of the Ryukyus (Approval Number 1597).

3. Results

3.1. Overview of collected patient data

Overall, 756 bronchoscopies were performed during the study period, and PCR tests using bronchoscopic specimens were performed for 177 patients. Thus, 177 patients were included in the study (Fig 1). While PCR testing showed that 27 patients had respiratory viruses, their medical records showed that they had experienced no typical upper respiratory infection symptoms, such as rhinitis and sore throat. Parainfluenza viruses and rhinovirus accounted for more than half of the positive results (Fig 2). The clinical diagnoses of PCR-positive patients before considering PCR positivity are shown in Table 1. Almost all patients were diagnosed with acute diseases, such as ILD and bacterial pneumonia. ILDs consisted of acute exacerbation of interstitial pneumonia, organizing pneumonia, eosinophilic

pneumonia, and pulmonary alveolar hemorrhage. Other respiratory infections included mycosis, lung abscess, nocardiosis, and cytomegalovirus pneumonia. After PCR results were revealed,

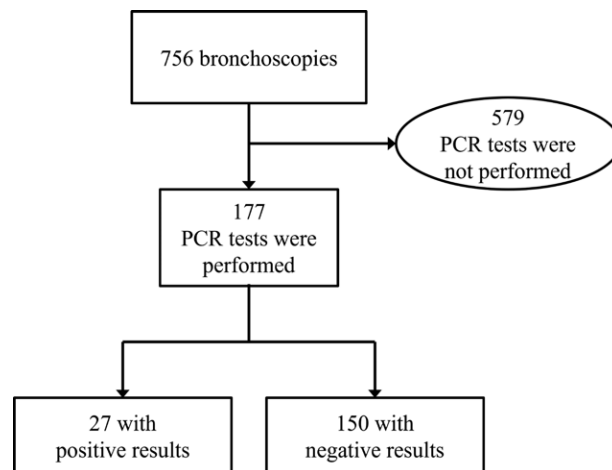


Figure 1. Flow diagram of the study. PCR = polymerase chain reaction.

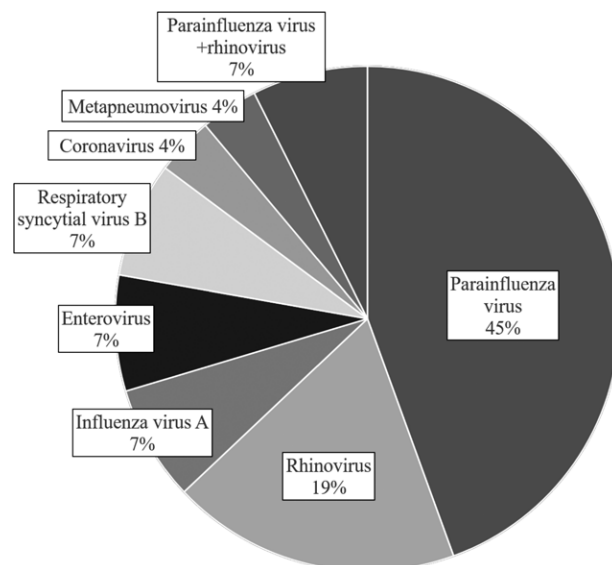


Figure 2. Viruses detected on polymerase chain reaction (PCR) testing of bronchoscopic specimens. A total of 27 patients had positive PCR results: 12 patients tested positive for parainfluenza virus, 5 for rhinovirus, 2 for influenza A virus, 2 for enterovirus, 2 for respiratory syncytial virus type B, 1 for coronavirus 229E/NL63, 1 for metapneumovirus, and 2 for co-infections of parainfluenza virus and rhinovirus.

Table 1

Clinical diagnoses of PCR-positive patients before considering PCR positivity

	n = 27
Interstitial lung diseases	11
Bacterial pneumonia	7 ^a
Other respiratory infections	5
Drug-induced lung injury	1
Acute respiratory distress syndrome	1
Lung cancer	1
Chronic atelectasis	1

PCR = polymerase chain reaction. ^aincluding 3 viral pneumonia cases diagnosed after the polymerase chain reaction test.

diagnoses in 3 patients who had been diagnosed with bacterial pneumonia were changed to pure viral pneumonia. The patient data collected are shown in Table 2. Seven of the PCR-positive patients were hospitalized for >1 month. Immunosuppressant therapy was the most common item of medical history in the PCR-positive group. Univariate analysis showed that PCR-positive patients were more likely to use immunosuppressants and be under maintenance dialysis treatment.

3.2. Risk factors for PCR-positive results

The results of the multivariate analysis are shown in Table 3. A forward stepwise logistic regression was performed. The independent variables were from the following backgrounds: immunosuppressant therapy, maintenance dialysis, hematological malignancy, lymphocytopenia, hematopoietic stem-cell transplant, solid organ transplant, anticancer cytotoxic chemotherapy, and human immunodeficiency virus infection. The final multivariate analysis included immunosuppressant therapy and maintenance dialysis. The results showed that immunosuppressant use and maintenance dialysis treatment were associated with positive PCR results.

4. Discussion

4.1. Detected viruses

Previous studies have shown that rhinovirus and influenza virus are common causative pathogens of community-acquired pneumonia,^[2] while parainfluenza virus infections are common in hospital-acquired pneumonia.^[9,10] The patients included in the present study were a mixture of inpatients and outpatients, and parainfluenza virus and rhinovirus accounted for most cases, with influenza virus cases being a minority. Most patients with influenza virus infection were diagnosed using rapid antigen tests without bronchoscopies; therefore, they were not included in the present study.

4.2. Respiratory virus infections and respiratory diseases

A systematic review has shown that respiratory viruses are detected in 22% of patients with community-acquired pneumonia,^[2] while other studies have shown that respiratory viruses are detected in approximately 20% of patients with hospital-acquired pneumonia.^[9,10] Moreover, the clinical importance of bacterial-viral co-infection in pneumonia has been researched.^[11] Respiratory virus infections can induce bacterial infections in the airways.^[12] These reports have indicated that respiratory virus infections are more common in pneumonia cases than expected. In the present study, the PCR positivity rates of pneumonia cases were higher than those in previous reports, which may have been due to the inclusion of many immunocompromised patients.

A prospective study and a meta-analysis have shown that respiratory virus infections do not increase interstitial pneumonia rates^[4,13]; however, a limited number of case reports have shown that respiratory virus infections induce acute exacerbations of interstitial pneumonia.^[14-16] Therefore, respiratory virus infections are among several possible triggers of exacerbations of interstitial pneumonia. Several case reports have shown an association of organizing pneumonia with influenza virus and non-influenza respiratory virus infections.^[17-19] Regarding other

Table 3
Factors associated with a positive PCR from the multivariate analysis

	Odds ratio	95% confidence interval	P value
Use of immunosuppressant therapies ^a	2.57	1.11–5.99	.028
Chronic kidney disease requiring maintenance dialysis	4.10	1.04–16.19	.044

PCR = polymerase chain reaction.
aCorticosteroids, cytotoxic drugs, or biological drugs.

Table 2
Patient demographic characteristics.

	PCR-positive group	PCR-negative group	P value
n = 177	27	150	
Male/female sex	15/12	98/52	.330
Median age (range)	57 (24–78)	66 (14–91)	.008
Underlying disease			
Diabetes mellitus	8	32	.343
Solid cancer	4	41	.169
Hematological disease	6	29	.729
Autoimmune disease	7	31	.540
Human immunodeficiency virus infection	1	5	.635
Lung structural disease ^a	11	44	.238
Chronic kidney disease requiring maintenance dialysis	4	6	.048
Medical history			
Hospitalized patient ^b	7	21	.104
Current smoking	3	26	.314
Acute respiratory failure	14	53	.103
Post-hematopoietic stem cell transplant	3	7	.182
Post-solid organ transplant	0	3	.607
During anticancer chemotherapy	6	27	.604
Lymphocytopenia (<200/μL)	4	8	.090
Use of immunosuppressant therapies	14	44	.022
Corticosteroids	11	36	.070
Cytotoxic drugs	8	20	.038
Biological drugs	3	4	.073
Prognosis			
Died within 1 mo	5	14	.140

PCR = polymerase chain reaction.
aPulmonary emphysema, fibrosis, bulla, or bronchiectasis.
bHospitalization >1 month after admission.

diseases, few reports have associated respiratory virus infections with eosinophilic pneumonia, pulmonary alveolar hemorrhage, and acute respiratory distress syndrome.^[20–23] From a different perspective, some of these patients with ILD may have viral pneumonia. A previous study showed that many cases of viral pneumonia were misdiagnosed as ILDs, and the multiplex PCR test was an effective diagnostic tool.^[24]

Although 27 patients were PCR-positive in the present study, only 3 were diagnosed with pure viral pneumonia. As mentioned above, the relationship between respiratory virus infections and some respiratory diseases has been reported; therefore, bacterial pneumonia, ILDs, and acute respiratory distress syndrome were considered to be induced by respiratory virus infections. However, no relationship has been proved between respiratory virus infections and other diseases. It is, therefore, concluded that respiratory viruses cause incidental infections. It should also be mentioned that most of the cases in this study were immunocompromised. Despite asymptomatic individuals, respiratory viruses were often detected.^[25] Thus, clinical findings are essential for diagnosing significant respiratory virus infections, even if the viruses were detected in the lower respiratory tract.

4.3. Risks of respiratory virus infections

Immunocompromised patients have a risk of severe infection with respiratory viruses^[3]; however, the risk of contracting respiratory virus infections has not been clear. Corticosteroids, cytotoxic agents, and biological agents are immunosuppressants that impair cellular immunity and increase the risk of infectious diseases.^[8,26–29] Patients with end-stage renal disease on maintenance dialysis treatment are also susceptible to certain infections owing to the impaired immune system.^[6] In addition, maintenance hemodialysis is performed for inpatients and outpatients in a hemodialysis unit, and frequent contact with other patients in the unit may increase opportunities for respiratory virus infections. Some reports have indicated that respiratory infections spread through the hemodialysis unit.^[30,31] In this study, immunosuppressant therapy and maintenance dialysis, both of which impair cellular immunity, were associated with PCR-positive results. Thus, patients with impaired cellular immunity are likely to develop respiratory virus infections. Although the results were specific to the risk of respiratory virus infections, they may offer guidance in preventing respiratory infections in immunocompromised patients.

4.4. Impact of multiplex PCR

PCR-positive cases in the present study showed no apparent common cold symptoms. A possible explanation for this is that most were immunocompromised, with a suppressed inflammatory response to viral pathogens. In the absence of multiplex PCR tests, patients' viral infections had not been noticed. Hematopoietic stem-cell transplant patients often have asymptomatic respiratory virus infections.^[3] Our results also showed that hospitalized patients had been infected with respiratory viruses. Based on incubation periods of respiratory virus infections, they may have been infected with the viruses during hospitalization.^[32] Recent studies have demonstrated that respiratory viruses are often detected in hospital-acquired pneumonia and spread in hospital wards without being identified.^[9,10] Thus, healthcare providers should consider that respiratory virus infections can be present in immunocompromised patients with lung lesions, even while hospitalized. The multiplex PCR test is an essential tool for diagnosing respiratory virus infections in these situations.

4.5. Limitations

First, this was a retrospective study. Many healthcare providers were involved in patient care, and patients' clinical findings

were not screened; therefore, the database would probably be less accurate. Second, the number of PCR-positive cases was small and inadequate for the performance of a multivariate statistical analysis. Third, our results did not represent every respiratory disease because of selection bias. This study included only patients who required bronchoscopies and excluded the cases diagnosed using routine testing. In addition, patients with severe respiratory failure were not included because bronchoscopies could not be performed. Fourth, the results of this study are not extremely innovative. As noted in the discussion, the association between respiratory viruses and respiratory diseases, the risk of respiratory virus infection, and the usefulness of PCR testing are to be expected and several studies exist. However, this study examines these matters in a real clinical setting. We believe that the results of this study will assist clinicians in the diagnosis of respiratory infections.

5. Conclusion

Bronchoscopic specimens were used to detect respiratory viruses, and parainfluenza virus and rhinovirus were the most commonly detected viruses. Viruses were commonly detected in patients with bacterial pneumonia or ILDs, and some were infected during hospitalization. In most patients, respiratory diseases were induced by respiratory virus infections, while few patients had pure viral pneumonia. Immunosuppressant therapy and maintenance dialysis were associated with respiratory virus infections. Multiplex PCR testing is an essential diagnostic tool for respiratory virus infections in immunocompromised patients, even those hospitalized without common cold symptoms.

Acknowledgments

We would like to thank Editage (www.editage.com) for providing English language editing assistance.

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