Retrospective study of clinical characteristics and viral etiologies of patients with viral pneumonia in Beijing

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Abstract

Aims: The virus is common in patients with viral pneumonia. However, the viral etiology and clinical features of patients with viral pneumonia in China remain unclear. The main purpose of this study was to analyze the viral causes and epidemiology of patients with viral pneumonia in Beijing, which can significantly improve the pertinence and accuracy of clinical treatment of the disease.

Methods: Firstly, 1539 respiratory specimens of pneumonia (oropharyngeal swabs, nasopharyngeal swabs, saliva samples and bronchoalveolar lavage fluid) were collected from 19 hospitals in Beijing from September 2015 to August 2018. Then, TaqMan low-density microfluidic chip technology was used to detect viral pneumonia specimens in 1539 respiratory tract specimens of pneumonia and determine the types of viral bacteria in them. Lastly, the analysis of demographic, clinical and etiological data of patients with viral pneumonia was performed.

Results: The results showed that among the 1539 respiratory tract specimens with pneumonia, 760 were detected as viral pneumonia specimens, with a positive rate of 49.4%. Among which, 467 were infected with mono-viral and 293 were infected with multi-viral. Influenza A virus (Flu A), mycoplasma pneumoniae (MPn), Ebola virus (EBV) and herpes simplex virus type 1 (HSV-1) were the major viral components in the samples of these patients. Furthermore, these viral species were significantly associated with sample sources, onset season and certain clinical characteristics.

Discussion: Our findings may provide corresponding treatment strategies for viral pneumonia patients infected with specific viruses.

Keywords

viral pneumonia, respiratory tract, viral species, clinical characteristics, treatment

Introduction

Pneumonia is a serious global public health problem. Viral and bacterial pneumonia are the main leading causes of death worldwide.1 Viral pneumonia, caused by respiratory virus infection, leads to worsening of the disease, death and new outbreaks of infectious diseases.2 Therefore, accurate and rapid identification of pathogens is critical for effective antiviral therapy and control of infection transmission.3 However, a range of potential respiratory viruses can cause similar clinical symptoms, which are often difficult to diagnose.4,5 Although molecular diagnostic methods have made great progress, the cause of pneumonia remains uncertain.6,7 Since there are few vaccines against viral pneumonia caused by respiratory virus infection, the etiology of the epidemic virus of viral pneumonia is urgent to study.
It will be meaningful to prevention and control of the virus epidemic in the future. As we all know, the early and rapid molecular detection of respiratory viruses is of great value in preventing the development of viral pneumonia. However, due to high cost of viral testing, only a few patients with viral pneumonia have a chance to be detected. In addition, the etiology of viral pneumonia may be closely related to many factors such as age, geographic area, season, immune status and medical conditions. In order to identify potential viruses of viral pneumonia, we collected clinical and demographic data for patients with viral pneumonia at general hospitals in Beijing and conducted virus testing and viral load analysis on different respiratory samples. Rapid screening viruses through multiple detection techniques could be important for the early detection, diagnosis and treatment of patients with viral pneumonia caused by new mutations.

Methods

Patients and study design

The study was conducted in 2296 patients with pneumonia in 19 hospitals in Beijing from September 2015 to August 2018. These patients were enrolled according to the following clinical diagnosis criteria of pneumonia patients: (1) chest radiograph or computed tomography (CT) showed a new infiltrating shadow in the lungs (this diagnostic criterion is a necessary condition); (2) the newly developed cough or cough symptoms were aggravated with or without coughing; (3) fever (underarm temperature >37.0°C) or low body temperature (underarm temperature <35.6°C); (4) the total number of white cells in peripheral blood increased by >10^4/μl or decreased by <4000/μl, or the nucleus was on the left). In addition, patients with viral pneumonia judged by clinicians had at least one of the following symptoms: fever, cough and sputum, chest pain, shortness of breath or nasal congestion within seven days. Different respiratory samples (oropharyngeal swabs represented by TV, nasopharyngeal swabs represented by PV, sputum samples represented by SP and bronchoalveolar lavage fluid represented by BALF) and clinical information of these patients were collected and recorded, respectively. The specimen was stored in 3 ml UTMTM Viral Transport Media and stored at –80°C for further virus detection. Multi-viral detection was performed using TaqMan low-density microfluidic chip technology by TaqMan™ Fast Advanced Master Mix (Applied Biosystems, USA). After virus detection, all individuals were divided into negative group (patients without viral infection), mono-viral infection group and multi-viral infection group. The demographic, clinical and etiological data of these individuals were further analyzed.

Detection of viruses

The TaqMan low density array (TLDA) method, through which viruses can be detected, is only used for the identification of the virus. Viruses that can be detected include: adenovirus, coronavirus_229E, coronavirus_NL63, coronavirus_OC43, CoV_HKU-1_OC43, entero-1_pool, enterovirus D, rhinovirus, influenza A virus (Flu-A)_pan, Flu-A_H3, Flu-A_H1-2009, Flu-A, human metapneumovirus (hMPV), parainfluenza virus (PIV)-1, PIV-2, PIV-3, PIV-4, respiratory syncytial virus (RSV)-A, RSV-B, Chlamydia pneumoniae, Mycoplasma pneumoniae (MPn), Boca, cytomegalovirus (CMV), parechovirus, Bordetella, Bordetella pertussis, Legionella pneumophila, epstein-barr virus (EBV), severe acute respiratory syndrome (SARS), middle east respiratory syndrome coronavirus (MERS-CoV), mumps virus (MuV), measles, herpes simplex virus (HSV)-1, HSV-2, human herpesvirus (HHV)-6, varicella zoster virus (VZV), Rickettsia burnetii, Moraxella catarrhalis, Streptococcus pneumoniae, Streptococcus pyogenes and Haemophilus influenzae (HIB). In summary, there were 30 kinds of viruses, 3 mycoplasma viruses and 8 fungal viruses.

Statistical analysis

Data analysis was performed using SPSS software. The ordinary chi-square test was used in the tests of the three groups. The Bonferroni method was used for pairwise comparative test. A two-tailed independent-samples t-test method was used to compare continuous variables between each group. The univariate analysis was conducted using logistic regression methods. Logistic regression analysis of the relationship between clinical symptoms and univariate and multivariate prognosis in patients with viral pneumonia was performed by calculating 95% CIs with odds ratio (ORs). Probability <0.05 was considered to be statistically significant.

Results

Clinical characteristics of patients with viral pneumonia infection

A total of 2296 specimens of pneumonia were enrolled from 19 different hospitals in Beijing. After further exclusion, 1539 (67% of 2296) samples of pneumonia were enrolled in the study. The TLDA detection results showed that 760 (49.4% of 1,539) viral pneumonia samples were positive viral infection. Among which, 467 were infected with mono-viral and 293 were infected with multi-viral (Fig. 1). The remaining 779 (50.6% of 1539) samples were negative viral infection. Table 1 presents the clinical characteristics
corresponding to 1539 samples. Among the 1539 samples, 891 samples were from male patients and 648 samples were from female patients. The results in Table 1 show that age distribution was correlated with positive detection rate ($\chi^2 = 25.268$, $P < 0.01$). In addition, 1539 samples of patients and positive detection rates have significant clinical characteristics, including expectoration ($c^2 = 6.25$, $P = 0.044$)/dyspnea ($t^2 = 14.859$, $P < 0.01$), diarrhea ($t^2 = 6.619$, $P = 0.037$) within 24 h. Meanwhile, the remarkable difference was observed in clinical symptoms of dyspnea ($\chi^2 = 20.497$, $P < 0.01$), diarrhea ($\chi^2 = 8.091$, $P = 0.018$) and chilly ($\chi^2 = 6.691$, $P = 0.035$) that occurred within 72 h. According to the clinical data, patients corresponding to 1539 samples were divided into two categories: improvement and death. We used clinical symptoms and patient outcome indicators to perform logistic univariate analysis. The univariate analysis showed that fever, expectoration, dyspnea, cyanosis, unconsciousness and swelling of both legs were associated with disease outcome (Fig. 2).

Compared with the negative group (represented by 0), multi-viral infection group (represented by 2) was significantly associated with four different clinical symptoms (expectoration, dyspnea, swelling of both legs and rhonchi). Mono-viral infection group (represented by 1) was significantly associated with two different clinical symptoms (fever and diarrhea) (Fig. 3). The expectoration and swelling of both legs were significantly associated with viral pneumonia (mono-viral infection group vs. multi-viral infection group).

**Sample source distribution**

In 1539 sample sizes for virus detection, four sample source types (TV, PV, SP and BALF) were included. The number of TV samples was 699, the number of PV sample was 563, the SP sample size was 273 and the BALA sample size was 4 (Fig. 4(a)). Among the 760 positive samples, mono-viral infections accounted for 467, of which 206 were TV samples, 161 were PV samples and 100 were SP samples. Multi-viral infections accounted for 293, of which 97 were TV samples, 70 were PV samples, 123 were SP samples and 3 were BALF samples (Fig. 4(b) and (c)). Based on the above results, in the TV and PV viral pneumonia samples, mono-viral infections are mainly type, while in SP viral pneumonia samples, multi-viral infections account for a larger proportion. Meanwhile, multi-viral infection is mainly distributed in the fewest BALF samples.

**Distribution of viral species in different sample sources**

Virus detection was performed by using the TLDA technology, which can detect 41 viruses at one time. TV, PV and SP were the main sources of respiratory specimens. Among the 303 positive TV samples, Flu A (25.06%) was found to be the highest proportion of the virus in the samples of viral pneumonia, followed by MPn (10.53%), HSV-1 (10.53%) and S. pneumonia (9.84%). In 231 positive PV samples, Flu A (18.38%) was the highest virus proportion, followed by MPn (11.11%), EBV (10.26%) and HSV-1(10.26%).
| Characteristic                  | Negative |     | Mono-viral infection |     | Multi-viral infection |     | \( \chi^2 \) | P  |
|--------------------------------|----------|-----|----------------------|-----|-----------------------|-----|-----------|----|
| Gender                         |          |     |                      |     |                       |     |           |    |
| Male                           | 442      | 28.72 | 266                  | 17.28 | 183                  | 11.89 | 3.096 | 0.213 |
| Female                         | 337      | 21.90 | 201                  | 13.06 | 110                  | 7.15  |          |    |
| Age                            |          |     |                      |     |                       |     |           |    |
| \( \leq 18 \)                  | 13       | 0.84 | 12                   | 0.78  | 2                    | 0.13  | 25.268 | <0.01 |
| 18–44                          | 176      | 11.44 | 112                  | 7.28  | 51                   | 3.31  |          |    |
| 45–64                          | 206      | 13.39 | 113                  | 7.34  | 51                   | 3.31  |          |    |
| \( \geq 65 \)                  | 384      | 24.95 | 230                  | 14.94 | 189                  | 12.28 |          |    |
| Fever within 24 h              |          |     |                      |     |                       |     |           |    |
| 0                             | 405      | 26.32 | 229                  | 14.88 | 143                  | 9.29  | 1.428 | 0.490 |
| 1                             | 374      | 24.30 | 238                  | 15.46 | 150                  | 9.75  |          |    |
| Hypothermia within 24 h        |          |     |                      |     |                       |     |           |    |
| 0                             | 722      | 46.91 | 433                  | 28.14 | 269                  | 17.48 | 0.271 | 0.873 |
| 1                             | 57       | 3.70 | 34                   | 2.21  | 24                   | 1.56  |          |    |
| Cough within 24 h              |          |     |                      |     |                       |     |           |    |
| 0                             | 129      | 8.38 | 58                   | 3.77  | 37                   | 2.40  | 5.104 | 0.078 |
| 1                             | 650      | 42.24 | 409                  | 26.58 | 256                  | 16.63 |          |    |
| Expectorate within 24 h        |          |     |                      |     |                       |     |           |    |
| 0                             | 216      | 14.04 | 108                  | 7.02  | 62                   | 4.03  | 6.251 | 0.044 |
| 1                             | 563      | 36.58 | 359                  | 23.33 | 231                  | 15.01 |          |    |
| Chest pain within 24 h         |          |     |                      |     |                       |     |           |    |
| 0                             | 727      | 47.24 | 431                  | 28.01 | 276                  | 17.93 | 1.084 | 0.582 |
| 1                             | 52       | 3.38 | 36                   | 2.34  | 17                   | 1.10  |          |    |
| Dyspnea within 24 h            |          |     |                      |     |                       |     |           |    |
| 0                             | 622      | 40.42 | 366                  | 23.78 | 202                  | 13.13 | 14.859 | <0.01 |
| 1                             | 157      | 10.20 | 101                  | 6.56  | (21.63)              | 91    | 5.91   | (31.06) |
| Stuffy nose, runny nose, sore throat or sneezing within 24 h |          |     |                      |     |                       |     |           |    |
| 0                             | 693      | 45.03 | 409                  | 26.58 | 258                  | 16.76 | 0.576 | 0.750 |
| 1                             | 86       | 5.59 | 58                   | 3.77  | 35                   | 2.27  |          |    |
| Chilly within 24 h             |          |     |                      |     |                       |     |           |    |
| 0                             | 694      | 45.09 | 413                  | 26.84 | 255                  | 16.57 | 0.888 | 0.641 |
| 1                             | 85       | 5.52 | 54                   | 3.51  | 38                   | 2.47  |          |    |
| Weakness, muscle and joint pain, headache within 24 h |          |     |                      |     |                       |     |           |    |
| 0                             | 652      | 42.37 | 395                  | 25.67 | 239                  | 15.53 | 1.211 | 0.546 |
| 1                             | 127      | 8.25 | 72                   | 4.68  | 54                   | 3.51  |          |    |
| Diarrhea within 24 h           |          |     |                      |     |                       |     |           |    |
| 0                             | 770      | 50.03 | 453                  | 29.43 | 284                  | 18.45 | 6.619 | 0.037 |
| 1                             | 9        | 0.58 | 14                   | 0.91  | 9                    | 0.58  |          |    |
| Fever within 72 h              |          |     |                      |     |                       |     |           |    |
| 0                             | 630      | 40.94 | 369                  | 23.98 | 228                  | 14.81 | 1.442 | 0.486 |
| 1                             | 149      | 9.68 | 98                   | 6.37  | 65                   | 4.22  |          |    |
| Hypothermia within 72 h        |          |     |                      |     |                       |     |           |    |
| 0                             | 728      | 47.30 | 437                  | 28.40 | 266                  | 17.28 | 2.685 | 0.261 |
| 1                             | 51       | 3.31 | 30                   | 1.95  | 27                   | 1.75  |          |    |
| Cough within 72 h              |          |     |                      |     |                       |     |           |    |
| 0                             | 192      | 12.48 | 105                  | 6.82  | 63                   | 4.09  | 1.484 | 0.476 |
| 1                             | 587      | 38.14 | 362                  | 23.52 | 230                  | 14.94 |          |    |
| Expectorate within 72 h        |          |     |                      |     |                       |     |           |    |
| 0                             | 287      | 18.65 | 158                  | 10.27 | 91                   | 5.91  | 3.431 | 0.180 |
| 1                             | 492      | 31.97 | 309                  | 20.08 | 202                  | 13.13 |          |    |
| Chest pain within 72 h         |          |     |                      |     |                       |     |           |    |
| 0                             | 750      | 48.73 | 449                  | 29.17 | 288                  | 18.71 | 3.116 | 0.211 |
| 1                             | 29       | 1.88 | 18                   | 1.17  | 5                    | 0.32  |          |    |
(continued)
However, EBV (22.82%), Flu A (13.65%), MPn (13.41%) and HSV-1 (8.94%) accounted for most of the virus proportion in the 223 positive SP samples. In only three positive BALF samples, Flu A (18.18%) and MPn (18.18%) accounted for most of the virus proportion (Fig. 5). Overall, although samples of positive samples come from different sources, the main virus species of viral pneumonia samples are Flu A, MPn, EBV and HSV-1. Thus, it can be seen that Flu A, HSV-1 and MPn were the main virus species of viral pneumonia samples in the respiratory specimens of TV, PV and SP. In view of this, we performed difference and correlation analysis between Flu A, HSV-1, MPn and clinical symptoms in the samples of TV, PV and SP (supplementary Table 1). For Flu A virus, the clinical symptoms of hypothermia within 72 h and cough within 72 h showed significant differences in three samples. For HSV-1 virus, the clinical symptoms of cough within 72 h showed significant differences in three samples. For MPn virus, the clinical symptoms showed no significant differences in three samples.

Table 1. Continued.

| Characteristic                  | Negative |     |     |     |     |     |     |     |     |     |     |     |
|--------------------------------|----------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
|                                | N   | %  | N   | %  | N   | %  | £²  | P   |     |     |     |     |
| Dyspnea within 72 h            |     |     |     |     |     |     |     |     |     |     |     |     |
| 0                              | 691 | 44.90 | 415 | 26.97 | 231 | 15.01 | 20.497 | <0.01 |     |     |     |     |
| 1                              | 88  | 5.72 (11.3°) | 52  | 3.38 (11.13°) | 62  | 4.03 (21.16b°) |     |     |     |     |     |     |
| Stuffy nose, runny nose, sore throat or sneezing within 72 h |     |     |     |     |     |     |     |     |     |     |     |     |
| 0                              | 742 | 48.21 | 454 | 29.50 | 277 | 18.00 | 3.961 | 0.138 |     |     |     |     |
| 1                              | 37  | 2.40 | 13  | 0.84 | 16  | 1.04 |     |     |     |     |     |     |
| Chilly within 72 h             |     |     |     |     |     |     |     |     |     |     |     |     |
| 0                              | 765 | 49.71 | 460 | 29.89 | 281 | 18.26 | 6.691 | 0.035 |     |     |     |     |
| 1                              | 14  | 0.91 | 7   | 0.45 | 12  | 0.78 |     |     |     |     |     |     |
| Weakness, muscle and joint pain, headache within 72 h |     |     |     |     |     |     |     |     |     |     |     |     |
| 0                              | 741 | 48.15 | 443 | 28.78 | 270 | 17.54 | 3.793 | 0.150 |     |     |     |     |
| 1                              | 38  | 2.47 | 24  | 1.56 | 23  | 1.49 |     |     |     |     |     |     |
| Diarrhea within 72 h           |     |     |     |     |     |     |     |     |     |     |     |     |
| 0                              | 774 | 50.29 | 462 | 30.02 | 285 | 18.52 | 8.091 | 0.018 |     |     |     |     |
| 1                              | 5   | 0.32 | 5   | 0.32 (1.07b°) | 8   | 0.52 (2.73b°) |     |     |     |     |     |     |

Note: 0 and 1 represented “no” and “yes”, respectively. P values represented the comparison between all three groups in term of clinical features. P < 0.05 was statistically significant.

*aSignificant difference between negative group and multi-viral infection group.

*bSignificant difference between mono-viral infection group and multi-viral infection group.

Fig. 2. Prevalence and odds ratios (OR) of clinical symptoms in patients with pneumonia in terms of disease outcomes. OR < 1 or OR > 1 was statistically significant.
Correlation analysis between different types of viral species and clinical characteristics

The multiple linear logistic regression method was used to analyze the clinical characteristics and the infection of various bacterial species. The results showed that patients with viral pneumonia infected with Flu A viruses had obviously clinical symptoms, such as chilly/rigor and fever. However, patients with viral pneumonia infected with EBV may have distinct clinical symptoms, such as dyspnea and stethalgia. Patients with viral pneumonia infected with multi-viral were significantly associated with clinical symptoms, such as dyspnea, fever, rhonchi and swelling of both legs (Fig. 6).

Discussion

Virus infection is the main cause of the high incidence of respiratory tract infection.\textsuperscript{13,14} Many reports describe the etiology and epidemiology of hospitalized patients (including children and/or adults) with severe viral pneumonia around the world.\textsuperscript{15,16} In this study, enrolled sample with pneumonia had significant associations with some clinical features, such as the expectoration, dyspnea, diarrhea, chilly with 24 h and 72 h. The logistic univariate analysis showed that fever, expectoration, dyspnea, cyanosis, unconsciousness and swelling of both legs were associated with disease outcome. Compared with the negative group, multi-viral infection was significantly associated with the expectoration, dyspnea, swelling of both legs, rhonchi clinical symptoms. Mono-viral infection was significantly associated with the fever and diarrhea. These finding suggested the association between collected samples, clinical features and disease outcome.

Laboratory diagnosis of viruses is usually performed by using traditional methods, such as culture or antigen detection. Real-time and multiplex real-time-polymerase chain reaction assays are important tools for identifying the cause of viral pneumonia infection.\textsuperscript{9} In recent years,
TLDA technology has been used to accurately identify the virus infected by pneumonia.\textsuperscript{17,18} The method adopted in this study was to detect the virus infection of 1539 pneumonia sample by TLDA technique. The result showed that 760 samples were viral pneumonia samples. Among which, 467 were infected with mono-viral and 293 were infected with multi-viral. The expectoration and swelling of both legs were significantly associated with viral pneumonia (mono-viral infection vs. multi-viral infection). These findings suggested that pneumonia, especially viral pneumonia, may cause acute lung infections and clinical symptoms. Some similar results are also found in previous reports.\textsuperscript{19,20}

In patients with severe viral pneumonia, respiratory specimens from different sources have different virus types and numbers. Our results also reflected this difference. Nasopharyngeal swabs and oropharyngeal swab samples are easy to collect and have been studied in respiratory diseases.\textsuperscript{21} The sputum specimens and alveolar lavage fluids are relatively difficult to collect. If possible, we will try to use the sputum sample as the research object. This study explored the distribution of viruses in patients with viral pneumonia in different hospitals and specimens, as well as the distribution of age, onset season and clinical characteristics of patients. Our results showed that in

Fig. 4. Distribution of viral pneumonia samples in different sample sources. Distribution of viruses in patients with viral pneumonia. (a) Distribution of 1539 pneumonia samples in different sample sources. (b) Distribution of 760 positive samples in different sample sources. (c) Distribution Non-viral pneumonia (negative), mono-viral infection and multi-viral infection samples in different sample sources.
patients with viral pneumonia, patients with mono-viral infections accounted for the majority. Previous studies have reported that Flu-positive patients have severe pneumonia. Several previous studies have linked the Flu virus to the severity of community-acquired pneumonia, and many studies have shown that the virus rapidly impairs lung function. The Flu A has caused major epidemics and epidemics around the world. For example, the H1N1 subtype in 2009 led to a high hospitalization rate for pneumonia. In this study, the main source of respiratory specimens for viral patients was TV, PV and SP. In the distribution of sample sources, the virus species of Flu A, MPn, HSV-1 and EBV were the main infection sources. Several studies have shown that nasopharyngeal swab specimens are used for rapid and accurate detection of Flu A, Flu B and respiratory syncytial virus.

In our study, patients with viral pneumonia infected with Flu A virus appeared obvious clinical symptoms such as chilly/rigor and fever. However, patients with EBV may have distinct clinical symptoms, such as dyspnea and steathalgia. Viral pneumonia patients infected with multi-viral were significantly associated with clinical symptoms, such as dyspnea, fever, rhonchi and swelling of both legs. These findings may be helpful in providing corresponding treatment strategies for patients with viral pneumonia infected with specific viruses.

There are still many limitations and deficiencies in our research. Firstly, because we lack the clinical information of some specimens, we cannot carry out subsequent research and analysis. Secondly, the small number of samples will bring some errors. Thirdly, the sampling time is not complete, which leads to the lack of some analysis. Fourthly, some specimens have poor sampling quality. Therefore, our data on viruses causing viral pneumonia infection are not comprehensive, which also affects the relationship between viruses and the severity of disease in patients with viral pneumonia. In summary, our findings could have certain reference value for the evaluation of patients with viral pneumonia and clinical treatment. In summary, this study provided important epidemiological data on the clinical features, viral profiles and age distribution of patients with viral pneumonia in hospitals in Beijing. These findings could help to assess the burden of viral infection in patients. Timely and
accurate diagnosis of viruses in patients with viral pneumonia infection is needed to alleviate the burden of these diseases.

Conflict of interest
The author(s) declare that there is no conflict of interest.

Ethical approval
This study was approved by the ethics committee of WHO Collaborating Centre for Reference and Research on Influenza, Chinese National Influenza Centre, National Institute for Viral Disease Control and Prevention, Chinese Centre for Disease Control and Prevention. Written consent was obtained from these patients.

Guarantor
Not applicable.

Contributorship
Conception and design: Xiang Zhao and Dayan Wang; Administrative support: Dayan Wang; Supply of materials and samples: Yao Meng and Duo Li; Data collection and collation: Zhaomin Feng, Weijuan Huang and Xiyuan Li; Data analysis and interpretation: Hejiang Wei and Xiaoxu Zeng; All authors approve and revise the manuscript.

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Supplemental material
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