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Original Article

Respiratory etiological surveillance among quarantined patients with suspected lower respiratory tract infection at a medical center in southern Taiwan during COVID-19 pandemic

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Abstract *Background:* A comprehensive study of respiratory pathogens was conducted in an area with a low prevalence of COVID-19 among the adults quarantined at a tertiary hospital.
Methods: From March to May 2020, 201 patients suspected lower respiratory tract infection (LRTI) were surveyed for etiologies by multiplex polymerase chain reaction (PCR: FilmArray TM Respiratory Panel) test combination with cultural method, viral antigen detection and serologic surveys.
Results: Total 201 patients tested with FilmArray TM Respiratory Panel were enrolled, of which 68.2% had sputum bacterial culture, 86.1% had pneumococcus and Legionella urine antigen test. Their median age was 72.0 year-old with multiple comorbidities, and 11.4% were nursing

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home residents. Bacteria accounted for 59.7% of identified pathogens. Atypical pathogens were identified in 31.3% of total pathogens, of which viruses accounted for 23.9%. In comparison to patients with bacterial infection, patients with atypical pathogens were younger (median = 77.2 vs 67.1, years, P = 0.017) and had shorter length of hospital (8.0 vs 4.5, days, P = 0.007).

Conclusions: Patients with LRTI caused by atypical pathogens was indistinguishable from those with bacterial pathogens by clinical manifestations or biomarkers. Multiplex PCR providing rapid diagnosis of atypical pathogens enhance patient care and decision making when rate of sputum culture sampling was low in quarantine ward during pandemic.

Introduction

At the end of 2019, Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was rapidly spread worldwide, causing substantial morbidity and mortality.[1] In Taiwan, multiple policies in response to COVID-19 were implemented by Central Epidemic Command Center (CECC) and the Taiwan Centers for Disease Control (TCDC), such as border control, surveillance for case detection, public health education (mask wearing and handwashing), and suspension of classess.[2,3] Previous studies using the data reported to TCDC found the impact of these public health policies on preventing respiratory infectious disease, such as influenza, invasive *Streptococcus pneumoniae* disease, enterovirus, and scarlet fever in Taiwan.[3,4] Similarly, the decline of seasonal influenza activity was reported in other country.[5]

Several reports studied the epidemiology of viral infection during the pandemic of COVID-19,[6—9] and concurrent respiratory pathogens among COVID-19 patients.[10—16] A recent study by Leuzinger et al. found dominant seasonal community-acquired respiratory viruses were rapidly replaced by SARS-CoV-2 within three weeks after the pandemic, and competitive infection between SARS-CoV-2 and seasonal community-acquired respiratory viruses was suggested.[7] However, most of these studies were conducted in the areas of a high COVID-19 prevalence, but there were lack of similar data from the areas of a low prevalence rate of COVID-19. From this perspective, it is possible that the epidemiology of respiratory pathogens in the areas with a low prevalence of COVID-19, such as Taiwan, may be different from that in the high prevalence regions. Thus, we aimed to investigate the distribution of respiratory pathogens in Taiwan, and clinical characteristics and outcomes of adults with and without recognized respiratory etiologies were analyzed to reveal the clinical impact of comprehensive etiological studies for quarantined adults.

Materials and methods

Study design and setting

A quarantine ward for screening SARS-CoV-2-infected cases was implemented since March, 2020 at National Cheng Kung University Hospital (NCKUH), a tertiary medical center in southern Taiwan. The present study included the cases (aged >18 years) suspected lower respiratory tract infection (LRTI) visiting the Emergency Department of NCKUH from March 2020 to May 2020. A series of surveys for respiratory pathogens were performed, including real-time reverse-transcription polymerase chain reaction (RT-PCR) for SARS-CoV-2 RNA sampled from nasopharyngeal swab,[17] bacterial cultures of expectorated sputum, urine antigen tests for *Legionella pneumophila* serogroup 1 and pneumococcus (BinaxNOW™, Abbott Diagnostics Scarborough, USA). Besides, the FilmArray™ Respiratory Panel (BioFire Diagnostics, bioMérieux SA, France) sampled from nasopharyngeal swab was applied to detect adenovirus, human rhinovirus/enterovirus, influenza virus A (A/H1, A/H1 2009, and A/H3), influenza virus B, respiratory syncytial virus, parainfluenza viruses 1—4, human metapneumovirus, coronavirus 229E, coronavirus HKU1, coronavirus OC43, coronavirus NL63, *Chlamydia pneumoniae*, *Bordetella pertussis*, *Bordetella parapertussis*, and *Mycoplasma pneumoniae*. Other tests for specific pathogens, such as sputum *Mycobacterium* culture, influenza rapid antigen, *M. pneumoniae* serologic test, *Aspergillus* galactomannan antigen, and *Pneumocystis jirovercii* PCR could be performed by the discretion of attending physicians.

Hospitalized patients were quarantined in single rooms, and the quarantine was discontinued, if at least two consecutive respiratory specimens collected ≥12 h apart revealed negative results for SARS-CoV-2 RNA, or one etiological pathogen other than SARS-CoV-2 was identified plus one negative result for SARS-CoV-2 RNA. With quarantine discontinuation, the patient could be discharged or transferred to ordinary wards for further care. If clinical deterioration developed, the patient would be transferred to intensive care units, as usual medical practice. The study was approved by the NCKUH Institutional Review Board (A-ER-109-183).

Data collection

The data of included patients were obtained by reviewing electronic medical records. Clinical information including age, gender, site of care (including nursing home residence or home care) and physical status (such as bedridden status, nasogastric tube feeding, and pressure sores) before

admission, clinical manifestations related to respiratory tract infection at presentation (including fever, cough, dyspnea, and vomiting), and comorbidities (such as congestive heart failure, diabetes mellitus, structural lung disease, chronic kidney disease, end-stage renal disease with dialysis therapy, prior stroke, solid-organ or hematologic malignancies, etc.) were recorded in a predetermined case record form. Laboratory data, including white blood cell (WBC) with differential count, C-reactive protein (CRP), and procalcitonin (PCT) were also collected, if available.

For respiratory pathogen surveys, pathogens isolated from sputum or blood specimens obtained at emergent room or within 48 h after admission were regarded as significant pathogens. For sputum cultures, bacteria isolated from qualified sputum samples displaying >25 leukocytes and <10 epithelial cells per 100 × power field in Gram staining were referred as significant pathogens.[18] Microorganisms, except *Candida* species, obtained from bronchoalveolar lavage (BAL) fluid were regarded as pathogens. To diagnosis pulmonary tuberculosis (TB), the *Mycobacterium* growth in sputum or BAL fluid cultures would be confirmed by Xpert® MTB/RIF (Cepheid, Sweden). For nontuberculous mycobacteria (NTM) infection, the diagnosis was based on 2020 IDSA pulmonary NTM guideline[19] and the mycobacterial species was identified by the reverse dot-blot hybridization (BluePoint™ MycoID, BIO CONCEPT INC, Taiwan).

Respiratory failure was defined as a PaO2/FiO2 ratio of <200 and shock as systolic blood pressure <90 mmHg or mean arterial pressure <65 mmHg. For outcome assessment, the need of endotracheal intubation, ICU transferal, length of hospital stay (analysis only for survivors), and crude in-hospital mortality were recorded. Time to discontinue quarantine and total antibiotic prescription days (analysis only for survivors) were also recorded to assess the clinical benefits of FilmArray™ Respiratory Panel.

Measures and statistical analysis

For respiratory pathogen survey, patients with other concurrent infections (such as urinary tract or soft tissue infection) were excluded, because their clinical features may be complicated by infections other than LRTI. To analyze clinical outcomes and characteristics, for excluding the impact of LRTI caused by untested atypical pathogens, only patients tested with FilmArray™ Respiratory Panel were included for analysis. In the group of detected pathogens, clinical outcomes and characteristics of patients infected by atypical pathogens (including virus, *L. pneumophila*, *Mycoplasma pneumonia*, and *C. pneumoniae*)[20,21] and bacteria were further analyzed. Continuous variables with a normal distribution were expressed as means (±standard deviations [SD]) and those with a non-normal distribution as medians (interquartile range, IQR). To compare continuous nonparametric variables, Mann—Whitney U test is used. For the comparisons of categorical variables, chi-square test is used or Fisher's exact test is applied, if one or more expected values for the cells are less than five. A p value of less than 0.05 indicates statistical significance. All statistical analyses were performed using the statistical software IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., USA).

Results

A total of 320 patients admitted to the quarantine ward during the study period. With the exclusion of 8 patients younger than 18 years old and 71 patients with concurrent infections other than respiratory tract infections, 201 patients with test of FilmArray™ Respiratory Panel were included for analysis (Fig. 1). Their median age was 72.0 year-old and male predominated, accounting for 68.2% of the included cohort. Among the included patients, nearly a half had pressure sores in varied dependent sites, and about one third were bedridden. Nasogastric tube was placed for feeding in 19.9% of the patients, and of which 11.4% were nursing home residents. As for the initial presentations of acute illness suspicious of respiratory tract infections, fever was most common as noted in 79.6% of all included patients, followed by cough (62.7%), dyspnea (52.5%). Vomiting was occasionally noted (Table 1).

Common underlying comorbidities included diabetes mellitus (32.8%), solid organ malignancy (31.8%), and

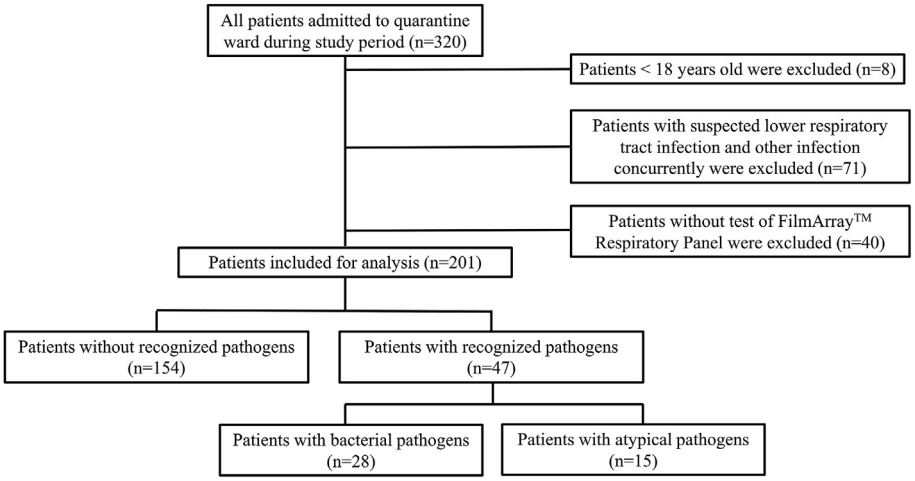

Figure 1. Study flow chart of included patients with suspected lower respiratory tract infection admitted to the quarantine ward.

chronic kidney disease (27.9%). Prior events of pulmonary infections and stroke were not uncommon, 23.9% and 21.4%, respectively. Of note, one sixth had clinical or sonographic evidence of congestive heart failure. The most common antibiotics prescribed on admission was ceftriaxone (n = 109, 54.2%), followed by cefoperazone/sulbactam (n = 28, 13.9%), cefepime (n = 26, 12.9%) and quinolones (including gemifloxacin, moxifloxacin and levofloxacin, n = 18, 9.0%). Doxycycline as combination was prescribed to 167 patients (83.1%), and 155 patients (77.1%) received oseltamivir. Among those participants, 13.4% developed acute respiratory failure and 9.5% needed intensive care.

Of 201 patients with comprehensive surveys for respiratory pathogens, 67 pathogens were detected in 47 (23.4%). Among those patients, 68.2% had sputum bacterial culture, and 86.1% had pneumococcus and *Legionella* urine antigen test. Clinical characteristics and outcomes were compared between those with and without recognized pathogens in Table 1. There were no significant differences in terms of age, gender, and physical status upon admission between the two groups. Fever, cough or dyspnea was presented dominant at a similar proportion of either group (Table 1). Underlying prior stroke was more common in the patients with recognized pathogens (32% *vs* 18%, $P = 0.044$). In contrast, chronic kidney disease (CKD) was more often found in those without recognized pathogens (33% *vs* 11%, $P = 0.003$). The risk of respiratory failure, transferal to ICUs, endotracheal intubation, or shock was

Table 1 Demographic and clinical characteristics of the patients tested by FilmArray™ Respiratory Panel with and without recognized pathogen admitted to the quarantine ward.

Clinical variables	Total (n = 201)	Pathogens not recognized (n = 154)	Pathogens recognized (n = 47)	*P* value
Age, years (IQR)	72.0 (59.0–81.4)	71.6 (58.0–81.6)	72.0 (62.0–80.4)	0.958
Male gender	137 (68.2)	105 (68.2)	32 (68.1)	0.990
Microbiologic study				
Sputum bacterial culture	137 (68.2)	102 (66.2)	35 (74.5)	0.289
Pneumococcus urine antigen	173 (86.1)	130 (84.4)	43 (91.5)	0.220
Legionella urine antigen	173 (86.1)	130 (84.4)	43 (91.5)	0.220
Physical status upon admission				
Presence of pressure sores	96 (47.8)	70 (45.5)	26 (55.3)	0.236
Bedridden status	61 (30.3)	45 (29.2)	16 (34.0)	0.529
Long-term nasogastric tube feeding	40 (19.9)	28 (18.2)	12 (25.5)	0.269
Nursing home residency	23 (11.4)	20 (13.0)	3 (6.4)	0.213
Initial clinical manifestations				
Fever	160 (79.6)	122 (79.2)	38 (80.9)	0.808
Cough	126 (62.7)	92 (59.7)	34 (72.3)	0.118
Dyspnea	105 (52.2)	79 (51.3)	26 (55.3)	0.629
Vomiting	11 (5.5)	6 (3.9)	5 (10.6)	0.133
Comorbidity				
Diabetes mellitus	66 (32.8)	51 (33.1)	15 (31.9)	0.878
Solid organ malignancy	64 (31.8)	51 (33.1)	13 (27.7)	0.482
Chronic kidney disease	56 (27.9)	51 (33.1)	5 (10.6)	0.003
Recurrent pneumonia	48 (23.9)	32 (20.8)	16 (34.0)	0.062
Prior stroke	43 (21.4)	28 (18.2)	15 (31.9)	0.044
Congestive heart failure	32 (15.9)	24 (15.6)	8 (17.0)	0.814
Lung metastasis	21 (10.4)	16 (10.4)	5 (10.6)	1.000
Long-term dialysis therapy	19 (9.5)	17 (11.0)	2 (4.3)	0.254
Chronic obstructive pulmonary disease	20 (10.0)	14 (9.1)	6 (12.8)	0.577
Bronchiectasis	9 (4.5)	5 (3.2)	4 (8.5)	0.218
Previous pulmonary tuberculosis	6 (3.0)	6 (3.9)	0 (0)	0.339
Bronchial asthma	5 (2.5)	4 (2.6)	1 (2.1)	1.000
Hematological malignancy	6 (3.0)	4 (2.6)	2 (4.3)	0.626
Acute critical illness				
Respiratory failure	27 (13.4)	19 (12.3)	8 (17.0)	0.410
ICU transferal	19 (9.5)	11 (7.1)	8 (17.0)	0.082
Endotracheal intubation	17 (8.5)	10 (6.5)	7 (14.9)	0.079
Shock	10 (5.0)	9 (5.8)	1 (2.1)	0.458
Clinical outcome				
In-hospital mortality	17 (8.5)	11 (7.1)	6 (12.8)	0.237
Length of hospital stay, days (IQR)	7.0 (5.0–11.75)	7.0 (5.0–12.0)	7.0 (5.0–10.0)	0.899

Data are given as numbers (percentages), unless otherwise specified. IQR indicates interquartile range.
Only survivors included for comparison of length of hospital stay.

similar between the two groups. Though the crude in-hospital mortality rate in those with recognized pathogens was higher than that in those without recognized pathogens (13% *vs* 7%), the difference was not statistically significant ($P = 0.2$).

Pathogens identified among the 201 patients were summarized in Table 2. Bacteria accounted for 59.7% of identified pathogens. Atypical pathogens were identified in 31.3% of total isolates, of which viruses accounted for 23.9%. Five fungal pathogens (7.5%) and one *Mycobacterium tuberculosis* (1.5%) were also identified respectively. The most frequent isolated bacteria was *Pseudomonas aeruginosa* (17.9%), followed by *Klebsiella pneumoniae* (13.4%). Among identified atypical pathogens, *M. pneumoniae* (7.5%) was the most detected, followed by adenovirus (6.0%), human rhinovirus/enterovirus (6.0%) and parainfluenza viruses (6.0%, type 1, 3 and 4 respectively).

Table 2 Pathogens detected in respiratory specimens of 201 patients in the quarantine ward.

Pathogens	Number of isolates (%)
Bacterial pathogens	
Gram-negative pathogens	**33 (49.3)**
Pseudomonas aeruginosa	12 (17.9)
Klebsiella pneumoniae	9 (13.4)
Acinetobacter species	3 (4.5)
Acinetobacter baumannii	2 (3.0)
Acinetobacter johnsonni	1 (1.5)
Stenotrophomonas maltophilia	2 (3.0)
Escherichia coli	1 (1.5)
Enterobacter cloacae complex	1 (1.5)
Chryseobacterium indologenes	1 (1.5)
Haemophilus influenzae	1 (1.5)
Proteus mirabilis	1 (1.5)
Serratia marcescens	1 (1.5)
Unidentified glucose-fermenting gram-negative bacillus	1 (1.5)
Gram-positive pathogens	**7 (10.4)**
Staphylococcus aureus	4 (6.0)
Streptococcus pneumoniae	2 (3.0)
Streptococcus dysgalactiae	1 (1.5)
Mycobacterial pathogens	**1 (1.5)**
Mycobacterium tuberculosis	1 (1.5)
Fungal pathogens	**5 (7.5)**
Pneumocystis jirovecii	2 (3.0)
Aspergillosis	3 (4.5)
Atypical bacterial and viral pathogens	**21 (31.3)**
Mycoplasma pneumoniae	5 (7.5)
Adenovirus	4 (6.0)
Human rhinovirus/enterovirus	4 (6.0)
Parainfluenza virus	4 (6.0)
Parainfluenza virus 1	2 (3.0)
Parainfluenza virus 3	1 (1.5)
Parainfluenza virus 4	1 (1.5)
Influenza A	1 (1.5)
Coronavirus HKU1	1 (1.5)
Coronavirus NL63	1 (1.5)
Human metapneumovirus	1 (1.5)

The bold indicated a group of pathogens with common characteristics, such as bacteria, fungus and mycobacterium.

With the exclusion of one patient who had mixed infection of bacteria and atypical pathogen, clinical characteristics and outcomes compared between patients with identified bacterial and atypical pathogens were shown in Table 3. Among patients with atypical pathogens infection, six patients had extrapulmonary manifestations, including four had sore throat, three had concomitant gastrointestinal symptoms, and one had myalgia. There was no statically significant difference of sex, physical status upon admission, initial clinical manifestations, WBC, CRP, neutrophil to lymphocyte ratio (N/L ratio), PCT and comorbidity. Patients with atypical pathogens was younger than those with bacteria (median = 77.2 *vs* 67.1, $P = 0.017$). The risk of respiratory failure, shock, transferal to ICUs, endotracheal intubation, time to discontinue quarantine, total antibiotic prescription days or crude in-hospital mortality rate was similar between the two groups. Only one mortality case among patients with atypical pathogens. Shorter hospital stay was noted among patients with atypical pathogens (8.0 *vs* 4.5 days, $P = 0.007$) than those with bacterial pathogens.

Discussion

With test of FilmArray™ Respiratory Panel combination with cultural method, viral antigen detection and serologic surveys, our study provided a comprehensive investigation of respiratory pathogens among patients with suspected LRTI in southern Taiwan during COVID-19 pandemic. All 201 patients in study were tested by FilmArray™ Respiratory Panel, and of which 68.2% had sputum bacterial culture, and 86.1% had pneumococcus and *Legionella* urine antigen test. Rate of pathogens detection was 23.4%, and bacteria was in majority (59.7%) under our study design.

The *S. pneumoniae* has remained to be the most frequently detected bacterial etiology from worldwide perspective among patient with community-acquired pneumonia (CAP).[18,22–24] Among the patients with COVID-19 during pandemic, the identified pathogens were complex including *Acinetobacter baumannii*, *P. aeruginosa*, *S. pneumoniae*, *Staphylococcus aureus*, *Haemophilus influenzae* and *K. pneumoniae*.[11–13,25,26] In contrast, previous epidemiologic study which enrolled both CAP and healthcare-associated pneumonia in Taiwan revealed *Klebsiella* spp. (24.4%) was the most frequent isolated pathogens, followed by *Pseudomonas* spp. (23.1%). Current study showed lower rate of *S. pneumoniae* (3.0%) was similar to previous survey (3.9%).[27]

Hsih et al., revealed influenza virus and adenovirus as the most common etiologies among patients with flu-like symptoms tested with FilmArray™ Respiratory Panel during the period from January 24th 2020 to February 28th 2020.[9] However, there was only one patient infected by influenza A in our study. Such reduction of influenza infection during COVID-19 pandemic had been reported, which would be related to strengthening public health policies for COVID-19 control.[3–5]

Current study showed lower detection rate of pathogens (23.4%) compared with previous survey among patients with

Table 3 Demography and clinical characteristics of the patients infected by bacterial and atypical pathogens in the respiratory tract.

Clinical variables	Bacterial pathogens (n = 28)	Atypical pathogens (n = 15)	P value
Age, years (IQR)	77.2 (66.5—85.9)	67.1 (43.0—76.0)	0.017
Male sex	22 (78.6)	7 (46.7)	0.046
Microbiologic study			
Sputum bacterial culture	19 (67.9)	11 (73.3)	1.000
Pneumococcus urine antigen	27 (96.4)	13 (86.7)	0.275
Legionella urine antigen	27 (96.4)	13 (86.7)	0.275
Physical status upon admission			
Presence of pressure sores	18 (60.0)	5 (43.8)	0.052
Bedridden status	11 (39.3)	3 (20.0)	0.308
Long-term nasogastric tube feeding	8 (28.6)	3 (20.0)	0.719
Nursing home resident	1 (3.6)	1 (6.7)	1.000
Initial clinical manifestations			
Fever	21 (75.0)	13 (86.7)	0.458
Cough	20 (71.4)	12 (80.0)	0.719
Dyspnea	16 (57.1)	6 (40.0)	0.284
Vomiting	3 (10.7)	2 (13.3)	1.000
Laboratory data			
White blood cell count, 1000/uL (IQR)	9.8 (7.3—13.2)	8.3 (5.4—11.3)	0.262
Neutrophil to lymphocyte ratio (IQR)	7.4 (3.7—17.7) (n = 27)	6.2 (3.0—15.6) (n = 15)	0.703
C-reactive protein (IQR)	97.6 (13.8—353.0) (n = 7)	37.5 (13.1—37.5) (n = 3)	0.425
Procalcitonin (IQR)	0.47 (0.18—0.72) (n = 4)	0.08 (0.05—0.08) (n = 2)	0.064
Comorbidity			
Diabetes mellitus	12 (42.9)	4 (26.7)	0.295
Recurrent pneumonia	11 (39.3)	4 (26.7)	0.408
Prior stroke	11 (39.3)	2 (13.3)	0.096
Solid organ malignancy	9 (32.1)	4 (26.7)	1.000
Congestive heart failure	7 (25.0)	2 (13.3)	0.458
Bronchiectasis	5 (17.9)	0 (0)	0.145
Chronic obstructive pulmonary disease	5 (17.9)	0 (0)	0.145
Lung metastasis	1 (3.6)	2 (13.3)	0.275
Chronic kidney disease	2 (7.1)	2 (13.3)	0.602
Previous pulmonary tuberculosis	1 (3.6)	0 (0)	1.000
Hematologic malignancies	1 (3.6)	0 (0)	1.000
Long-term dialysis therapy	0 (0)	1 (6.7)	0.349
Bronchial asthma	0 (0)	1 (6.7)	0.349
Acute critical illness			
ICU transferal	5 (17.9)	1 (6.7)	0.403
Endotracheal intubation	4 (14.3)	1 (6.7)	0.643
Shock	1 (3.6)	0 (0)	1.000
Respiratory failure	4 (5.7)	2 (0)	1.000
Clinical outcome			
Time to discontinue quarantine, hours	25.2 (21.0—28.8)	24.4 (21.9—26.9)	0.789
Total antibiotic prescription days	12.0 (8.0—16.0)	11.0 (7.0—15.0)	0.396
In-hospital mortality	5 (17.9)	1 (6.7)	0.403
Length of hospital stay, days (IQR)	8.0 (6.0—12.0)	4.5 (2.5—8.0)	0.007

Data are given as numbers (percentages), unless otherwise specified. IQR indicates interquartile range.
Only survivors included for comparison of total antibiotic prescription days and length of hospital stay.

CAP ranged 36.6—65.2%.[18,22,23,27,28] In a large prospective study enrolled 3104 adults with LRTI in 11 European countries, a potential pathogen was detected in 59% of patients.[29] There were several reasons of the low pathogen detection rate in our study. First, the sputum bacterial culture rate was low in the quarantine ward. While quarantine ward is important for preventing nosocomial transmission during pandemic, it may carry a potential negative

effect on patient care.[30] Decrease of visiting and education may result in low rate of cultural sampling and quality of specimens. Second, low accuracy for diagnosis of LRTI based only on patients' clinical symptoms and radiological findings. Previous studies conducted in emergent department reported that accurate diagnosis of pneumonia in elderly is difficult, and discordant diagnosis between emergent department and internal ward is common.[31,32] Third, the limitations of diagnostic tools. Specific tests for *Mycobacterium*, fungus and viruses not included in FilmArray™ Respiratory Panel were not performed routinely in our study. While the most of participants in our study were elderly with multiple comorbidities, the etiologies of LRTI may be more complicated and not detected under our study design.

Previous studies has reported that CAP caused by *M. pneumoniae*, *C. pneumoniae* and *L. pneumophila* generally have similar symptoms of bacterial pneumonia.[21,33] Although studies reported biomarkers such as CRP and PCT were useful in differentiating between CAP caused by viral and bacterial etiologies in children,[34,35] there was no statistically significant difference of initial clinical manifestations, physical status upon admission, WBC, CRP, N/L ratio, PCT and comorbidities between patients infected by bacteria or atypical pathogens in our study. Patients infected by atypical pathogens were younger in our study. Previous studies have reported younger age and less comorbidities among patients with CAP due to atypical pathogens in comparison to patients hospitalized due to non-atypical pathogen CAP.[20]

Pneumonia caused by atypical pathogens is generally mild or moderate; however, it can cause severe disease and would be fatal especially when drug resistance and extrapulmonary complications presented.[21] In our study, one patient with atypical pathogens infection expired during hospitalization. While the benefit of empirical antibiotic coverage for atypical pathogens was still controversial,[20,21] some studies suggested multiplex PCR such as FilmArray™ Respiratory Panel provides rapid and accurate diagnosis with impact on decision of antibiotics prescription.[36,37] In our study, although there was no difference of total antibiotic prescription days between patients infected by bacterial or atypical pathogens, patients infected by atypical pathogens had shorter length of hospital stay (8.0 *vs* 4.5, $P = 0.007$), which may be benefit from rapid diagnosis provided by FilmArray™ Respiratory Panel. Lee et al. showed that combined use of procalcitonin and FilmArray™ Respiratory Panel would shorten the length of hospital stay among patients with severe acute respiratory infection.[38]

There were several limitations in our study. First, the numbers of sputum bacterial culture were lower than our expectation. As discussion in the previous paragraph, the low rate of sputum bacterial culture sampling may be resulted from the quarantine ward setting. Second, our study was conducted in a single medical center in southern Taiwan through the period from March to May 2020. Previous studies had shown the epidemiology of pneumonia pathogens may varied from evolution of pandemic, seasons and geography.[5,7,27] This limitation may have effect to our study result. Third, our study is a clinical observative design, some tests, such as sputum culture of *Mycobacterium*, influenza rapid antigen test, *M. pneumoniae* serologic test, aspergillus galactomannan antigen test and *P. jirovercii* PCR, were performed by the discretion of attending physicians. Our study may not establish the comprehensive epidemiology because of this limitation of diagnostic tools, especially when our participants were elderly with multiple comorbidities and diverse physical status. Fourth, because large of proportion of patients loss follow-up after discharge in our study, long-term clinical outcomes, such as 30 days mortality was not investigated in our study. Fifth, the patients included in this study were based on symptoms they presented. Most patients had diagnosis of CAP and health-care associated pneumonia after admission, but it was difficult to classify all patients into a specific disease spectrum. However, we thought the symptom-based inclusion was more practical and correlated to real-world condition during pandemic period. Further studies would be needed to establish the comprehensive epidemiology and clinical outcomes in patients with LRTI during pandemic.

Conclusions

Patients with LRTI caused by atypical pathogens was indistinguishable from those with bacterial pathogens by clinical manifestations or biomarkers. In comparison to patients with bacterial infection, patients with atypical pathogens infection were younger and had shorter length of hospital stay. While rate of sputum bacterial culture was low in quarantine ward because of the infectious control policies, multiplex PCR providing rapid diagnosis of atypical pathogens enhance patient care and decision making in quarantine ward during pandemic.

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Transparency declarations

None to declare.

Author contributions

C.P.H, C.S.T and N.Y.L conceived the study. C.P.H, C.S.T, T.H.H and P.L.S provided data collection, statistical and analytic support. C.P.H, C.S.T, N.Y.L and W.C.K analyzed the data. C.P.H prepared the manuscript. All authors reviewed and edited the manuscript.

Declaration of competing interest

All authors: no conflicts.

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