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Journal of Infection 81 (2020) e12–e15

Contents lists available at ScienceDirect

Journal of Infection

journal homepage: www.elsevier.com/locate/jinf

Letter to the Editor

## Clinical features and outcomes of adult COVID-19 patients co-infected with Mycoplasma pneumoniae

*Dear Editor*,

A recent review published by the Journal of Infection raised concerns towards co-infection with *Mycoplasma pneumoniae* (MP) in coronavirus disease 2019 (COVID-19) patients.[1] It is difficult to distinguish between COVID-19 with or without MP co-infection because of the overlapping manifestations and image features. Similar clinical characteristics, complications, and outcomes were reported for patients infected with either MP alone or with viral co-infection.[2] Until now, the morbidity of co-infection with MP in COVID-19 patients and whether co-infection with MP has worse clinical outcomes have not been reported yet and thus remain uncertain.

To answer these questions, we conducted a retrospective observational study in The Central Hospital of Wuhan from January 15, 2020, to March 15, 2020. For diagnosing COVID-19, a real-time reverse transcription-polymerase chain reaction (RT-PCR) assay was performed with sputum or throat swab samples. To establish MP infection, IgM chemiluminescence immunoassay was used (MP IgM positive and antibody titer $\geq$ 1:160[3]) or positive results for MP RT-PCR tests of throat swabs.[3] Comorbidity, clinical manifestation, laboratory findings, and outcomes were collected from all patients. The study was approved by the ethics committee of The Central Hospital of Wuhan (Ethics 2020-34).

Among a total of 874 patients with laboratory-confirmed COVID-19, the overall rate of *M. pneumoniae* co-infection was 2.5% (22 of the 874 patients). In this study, 88 patients with COVID-19 mono-infection were matched as the control group using the propensity score. Patients co-infected with influenza or other bacteria besides MP were excluded from both groups. The characteristics, treatment, and clinical outcomes are summarized in Tables 1 and 2.

The median age of COVID-19 mono-infection patients was 57.00 (46.50–65.00) years, which was similar to that of MP co-infection patients who were 56.50 (52.50–66.50) years. There were no significant differences in the major complaints on admission between the two groups. The major complaints on admission were fever (59.1%), cough (28.2%), dyspnoea (8.2%), fatigue (9.1%), and diarrhoea (3.6%) in all the patients. However, one patient (1.1%) in the mono-infection group reported chest pain and one patient in the co-infection group mentioned dizziness (4.5%). Likewise, most of the comorbidities were similar in both groups, except for rheumatoid arthritis (RA) that was reported in the MP co-infection group (9.1% vs 0.0%, $p = 0.05$). Wakabayashi et al.[4] reported that MP was one of the most frequent causative microbial agents of pneumonia in RA patients and the mortality was statistically higher in those patients than in non-RA patients suffering from pneumonia.

Patients coinfected with MP were more likely to have higher bilirubin levels compared with patients infected with COVID-19 alone ($14.67 \pm 28.72$ vs $8.03 \pm 4.07$, $p = 0.037$). Pooled analysis of six studies show that bilirubin concentration was significantly higher in patients with severe COVID-19 (SMD: 0.48 $\mu$mol/L; 95% CI, 0.11-0.85 $\mu$mol/L, $p = 0.012$).[5] In sepsis, a higher serum bilirubin level at ICU admission is associated with subsequent ARDS development and mortality.[6] However, there was no similar trend of ARDS development and mortality observed in this study. Previous studies reported that COVID-19 with liver injury is associated with poorer clinical outcomes. Alanine aminotransferase (AST) abnormality was associated with the highest mortality risk compared to other indicators. However, in our study, AST was almost at a normal level, hence there was no evidence to support co-infection with MP could lead to liver injury and increase mortality in COVID-19 patients.

Both *M. pneumoniae* pneumonia (MMP) and COVID-19 have been reported to induce hypercoagulability[7], Moreover, in children with MPP, complications as acute cerebral infarction and pulmonary embolism have been reported.[8] In patients with COVID-19, Zhang L. et al[7] reported that D-dimer on admission more than 2.0 μg/mL could effectively predict in-hospital mortality. In our study, Prothrombin Time ($11.60 \pm 0.84$ s vs $13.34 \pm 5.4$ s, $p = 0.004$) was shorter and Prothrombin Activity ($104.90 \pm 20.14$ s vs $89.78 \pm 30.65$ s, $p = 0.006$) was higher in the co-infection group. Therefore, COVID-19 co-infection with MP has an even higher risk of blood coagulation, and thrombosis than the mono-infected patients and routine anticoagulation prophylactics is strongly recommended.

Quinolone antibiotics were more frequently administered to the patients with MP co-infection (81.8% vs. 35.2%, $p < 0.001$), and corticosteroids were more frequently administered to patients with MP co-infection (63.6% vs. 28.4%, $p = 0.005$). However, different antibiotics and corticosteroids strategy showed no associations with a better outcome.

Previous studies reported that children with MMP co-infected with human bocavirus, human rhinovirus, or respiratory syncytial virus had a longer fever process, higher leukocyte count, higher C-reactive protein, higher percentage of pneumothorax and diffuse large area of inflammation in chest X-ray compared with mono-infection.[9] However, in our study the severity of disease was comparable in the two groups, and most patients were categorized as having moderate pneumonia (95.5% vs. 95.5%) in both groups. The overall clinical outcome was good in this study; only one fatal case in co-infection group and two fatal case in mono-infection group were reported (4.5% vs. 2.3%, $p = 1.00$). The length of cough was longer in the MP co-infection group [20.00 (12.00–25.75) vs 16.25 (12.25–22.50), $p = 0.043$], while the length of hospital stay was slightly longer [16.00 (10.00–22.25) vs 14.00 (7.25–18.25), $p = 0.145$], but without statistical significance. In previous study,[2] a similar association of length of hospital stay and length

https://doi.org/10.1016/j.jinf.2020.07.010

**Table 1**
Baseline characteristics of coronavirus disease 2019 (COVID-19) and *M. pneumoniae* co-infection patients.

| Characteristics | COVID-19 mono-infection patients ($n = 88$) | COVID-19 patients co-infection with *M. pneumoniae* ($n = 22$) | $p$ |
|---|---|---|---|
| **Baseline** | | | |
| Age (years) | 57.00 (46.50–65.00) | 56.50 (52.50–66.50) | 0.726 |
| Male | 45 (51.1) | 11 (50.0) | 1.000 |
| Time from illness onset to hospital admission (days) | 10.50 (7.00–20.00) | 14.50 (5.50–20.00) | 0.666 |
| **Comorbidities** | | | |
| Diabetes | 20 (22.7) | 5 (22.7) | 1.000 |
| Hyperlipemia | 3 (3.4) | 1 (4.5) | 1.000 |
| Hypertension | 16 (18.2) | 4 (18.2) | 1.000 |
| Chronic heart failure | 2 (2.3) | 1 (4.5) | 1.000 |
| Liver cirrhosis | 2 (2.3) | 2 (9.1) | 0.373 |
| Anemia | 6 (6.8) | 2 (9.1) | 1.000 |
| Chronic kidney diseases | 1 (1.1) | 1 (4.5) | 0.858 |
| Rheumatoid arthritis | 0 (0.0) | 2 (9.1) | 0.05 |
| Cerebrovascular disease | 1 (1.1) | 1 (4.5) | 0.858 |
| Myasthenia Gravis | 1 (1.1) | 1 (4.5) | 0.858 |
| Deep venous thrombosis | 0 (0.0) | 1 (4.5) | 0.451 |
| COPD | 6 (6.8) | 1 (4.5) | 1.000 |
| **Symptoms** | | | |
| Fever | 55 (62.5) | 10 (45.5) | 0.226 |
| Cough | 27 (30.7) | 4 (18.2) | 0.368 |
| Dyspnea | 7 (8.0) | 2 (9.1) | 1.000 |
| Fatigue | 6 (6.8) | 4 (18.2) | 0.214 |
| Diarrhea | 2 (2.3) | 2 (9.1) | 0.373 |
| Chestpain | 1 (1.1) | 0 (0.0) | 1.000 |
| Dizzy | 0 (0.0) | 1 (4.5) | 0.451 |
| other | 11 (12.5) | 4 (18.2) | 0.728 |
| **Signs** | | | |
| Respiratory rate | 36.70 (36.50–37.02) | 36.50 (36.30–36.98) | 0.096 |
| Heart rate | 86.00 (79.75–97.25) | 94.00 (79.25–98.50) | 0.437 |
| Systolic pressure (mmHg) | 20.00 (18.00–20.00) | 19.50 (18.00–20.00) | 0.273 |
| Diastolic pressure (mmHg) | 130.00 (120.00–139.25) | 127.00 (116.00–143.25) | 0.672 |
| Peripheral oxygen saturation (%) | 80.00 (73.50–87.00) | 82.50 (72.75–88.50) | 0.624 |
| **Laboratory tests** | | | |
| White blood cell count ($\times$ 109/L) | 5.63 (4.90–7.08) | 5.81 (5.13–6.84) | 0.627 |
| Neutrophil count ($\times$ 109/L) | 3.55 (2.91–5.19) | 3.35 (2.64–5.43) | 0.725 |
| Lymphocyte count ($\times$ 109/L) | 1.35 (0.91–1.73) | 1.63 (1.20–2.04) | 0.167 |
| Monocyte count ($\times$ 109/L) | 0.39 (0.31–0.51) | 0.38 (0.33–0.56) | 0.257 |
| Hemoglobin (g/L) | 131.00 (119.00–142.00) | 123.00 (118.50–130.50) | 0.087 |
| Platelet count ($\times$ 109/L) | 204.00 (165.75–258.25) | 187.50 (144.00–250.25) | 0.269 |
| Albumin (g/L) | 39.90 (36.90–43.85) | 41.65 (36.12–43.05) | 0.858 |
| Alanine aminotransferase (ALT) (U/L) | 22.70 (15.10–33.15) | 23.15 (13.98–33.23) | 0.949 |
| Aspartate aminotransferase (AST) (U/L) | 19.60 (15.00–26.25) | 19.30 (14.53–23.70) | 0.834 |
| Direct Bilirubin ($\mu$mol/L) | $3.28 \pm 2.15$ | $19.19 \pm 72.26$ | 0.039 |
| Indirect Bilirubin ($\mu$mol/L) | $8.03 \pm 4.07$ | $14.67 \pm 28.72$ | 0.037 |
| Creatine ($\mu$mol/L) | 68.15 (55.82–88.95) | 56.70 (50.48–72.72) | 0.057 |
| Urea (mmol/L) | 4.50 (3.83–5.60) | 4.21 (3.34–4.54) | 0.151 |
| Creatine kinase (U/L) | 70.50 (49.75–115.75) | 66.00 (48.75–78.75) | 0.279 |
| Creatine kinase -MB (U/L) | 6.00 (5.00–9.00) | 7.15 (5.00–11.40) | 0.324 |
| Troponin (ng/mL) | 0.00 (0.00–0.01) | 0.01 (0.00–0.03) | 0.12 |
| Brain Natriuretic Peptid (pg/mL) | 32.50 (14.88–85.75) | 58.50 (20.75–126.85) | 0.245 |
| Lactate dehydrogenase (U/L) | 156.00 (138.00–194.75) | 177.00 (141.00–208.25) | 0.52 |
| Blood glucose (mmol/L) | 5.29 (4.70–6.99) | 5.55 (5.12–7.25) | 0.358 |
| Sodium (mmol/L) | 140.00 (137.57–142.00) | 139.50 (138.00–140.90) | 0.386 |
| Potassium (mmol/L) | 4.21 (3.97–4.50) | 4.16 (4.01–4.39) | 0.572 |
| Calcium (mmol/L) | 2.29 (2.19–2.45) | 2.38 (2.28–2.45) | 0.188 |
| Chloride (mmol/L) | 103.30 (102.02–106.40) | 104.20 (101.17–106.48) | 0.934 |
| Phosphorus (mmol/L) | 1.09 (0.93–1.22) | 1.11 (0.98–1.22) | 0.731 |
| Prothrombin Time (s) | $13.34 \pm 5.40$ | $11.60 \pm 0.84$ | 0.004 |
| International Normalized Ratio | $1.16 \pm 0.50$ | $1.00 \pm 0.08$ | 0.005 |
| Prothrombin Activity (%) | $89.78 \pm 30.65$ | $104.90 \pm 20.14$ | 0.006 |
| Activated Partial Thromboplastin Time (s) | $31.07 \pm 8.88$ | $28.53 \pm 5.15$ | 0.082 |
| Thrombin Time (s) | $16.95 \pm 1.79$ | $16.88 \pm 1.54$ | 0.86 |
| Fibrinogen (g/L) | 2.52 (2.17–3.05) | 2.37 (2.09–2.60) | 0.121 |
| D-dimer (ug/mL) | 0.45 (0.25–1.02) | 0.72 (0.44–1.61) | 0.062 |
| Interleukin-6 (pg/mL) | 4.49 (2.26–12.34) | 2.90 (2.08–5.89) | 0.138 |
| Procalcitonin (ng/ml) | 0.05 (0.04–0.08) | 0.05 (0.03–0.07) | 0.382 |
| C Reactive Protein (mg/dl) | 0.36 (0.12–2.63) | 0.24 (0.10–2.08) | 0.452 |

**Table 2**
Treatments and clinical outcomes in COVID-19 and *M. pneumoniae* co-infection patients.

| Treatments and outcomes | COVID-19 mono-infection patients ($n=88$) | COVID-19 patients co-infection with M. pneumoniae ($n=22$) | $p$ |
|---|---|---|---|
| **Treatments** | | | |
| **Antivirals** | | | |
| Umifenovir | 74 (84.1) | 16 (72.7) | 0.354 |
| Ribavirin | 58 (65.9) | 18 (81.8) | 0.235 |
| Interferon alpha inhalation | 1 (1.1) | 0 (0.0) | 1.000 |
| Lopinaviritonavir | 2 (2.3) | 1 (4.5) | 1.000 |
| Oseltamivir | 11 (12.5) | 4 (18.2) | 0.728 |
| **Antibiotics** | 24 (85.7%) | 47 (87%) | |
| Fluoroquinolones | 31 (35.2) | 18 (81.8) | <0.001 |
| Cephalosporins | 23 (26.1) | 11 (50.0) | 0.056 |
| Amoxicillin and Clavulanate Potassium | 0 (0.0) | 3 (13.6) | 0.005 |
| **Corticosteroids** | 25 (28.4) | 14 (63.6) | 0.005 |
| **Outcomes** | | | |
| Discharge | 86 (97.7) | 21 (95.5) | 1.000 |
| Death | 2 (2.3) | 1 (4.5) | .. |
| Length of cough | 16.25 (12.25–22.50) | 20.00 (12.00–25.75) | 0.043 |
| Length of hospital stay (days) | 16.00 (10.00–22.25) | 14.00 (7.25–18.25) | 0.145 |
| **Severity of disease** | | | |
| Mild | 84 (95.5) | 21 (95.5) | 1.000 |
| Moderate | 4 (4.5) | 1 (4.5) | .. |

of cough was found in MMP children co-infected with viruses like adenovirus, influenza A, respiratory syncytial virus and bacteria like *Streptococcus pneumoniae*

There are some limitations in our study. First, using IgM to diagnose MP co-infection may lead to false negative, the sensitivity of IgM serology was 81.82%.[10] Second, our study may have the selective bias because children were not included in our study.

In conclusion, our study is the first to describe the clinical features and outcomes of COVID-19 patients co-infected with MP. There were no significant associations between MP co-infection and major complaints on admission, but an approximate of 4 days increasement in the length of cough was reported. Importantly, the already elevated risk of thrombosis in COVID-19 patients is significantly increased by the co-infection with MP.

## Authors' contributions

Lu, Wang and Xu, the corresponding author, were responsible for the conceptualization of the study, the revision and approval of this manuscript. Lei and Shen participated in the design and drafted the manuscript, collected data and were responsible for its accuracy. Tefsen helped to revise the manuscript. All authors contributed to the data analysis and interpretation. All authors read and approved the final manuscript.

## Declaration of Competing Interest

None.

## Acknowledgments

Not applicable.

## Funding

This work was supported, in part, by the Anhui Provincial Special Project of Central Government Guiding Local Science and Technology Development of China (201907d07050001) and the special fund for coronavirus disease 2019 of Wuhu (no. 2020dx2-1).

## Availability of data and materials

Data are available on request.

## Ethics approval

The study was approved by the ethics committee of the Central Hospital of Wuhan (Ethics 2020-34).

## Consent for publication

All authors have approved the manuscript and its publication.

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