

# Serum Mycoplasma Pneumoniae IgG in COVID-19: A Protective Factor

**Bobin Mi**

Wuhan Union Hospital

**Lang Chen**

Wuhan Union Hospital

**Adriana C. Panayi**

Brigham and Women's Hospital

**Yuan Xiong**

Wuhan Union Hospital

**Guohui Liu** (✉ [liuguohui@hust.edu.cn](mailto:liuguohui@hust.edu.cn))

Wuhan Union Hospital <https://orcid.org/0000-0002-2013-1396>

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## Research article

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# Abstract

A correlation between prior exposure to *Mycoplasma pneumoniae* (IgG positive) and better clinical response to COVID-19 was elusive. In the present study, a retrospective review of 133 COVID-19 infected patients treated at Wuhan Union Hospital from Feb 1 to Mar 20 was carried out. Our data showed that COVID-19 infected patients with mycoplasma IgG positivity had a higher lymphocyte count and percentage ( $p = 0.026$ ,  $p = 0.017$ ), monocyte count and percentage ( $p = 0.028$ ,  $p = 0.006$ ) and eosinophil count and percentage ( $p = 0.039$ ,  $p = 0.007$ ), and a lower neutrophil count and percentage ( $p = 0.044$ ,  $p = 0.006$ ) than COVID-19 infected patients without mycoplasma IgG. Furthermore, requirement and use of a nasal catheter or oxygen mask was significantly lower in COVID-19 infected patients with mycoplasma IgG positivity ( $p = 0.029$ ). Our findings indicate that mycoplasma IgG positivity is a potential protective factor for COVID-19.

## Introduction

Ever since its initial outbreak in Wuhan, Hubei province, China, in December 2019, the 2019 novel coronavirus disease (COVID-19) has quickly spread around the world. Currently, more than 1.3 million cases have been confirmed, with 76,420 deaths worldwide.<sup>1</sup> The clinical characteristics of patients with COVID-19 have been well described with some risk factors shown to increase the mortality of COVID-19 identified, including diabetes, cancer and aging.<sup>2,3</sup> Protective factors that may help patients with COVID-19 show fewer severe symptoms and better recovery remain elusive. As frontline medical personnel in the Wuhan Union Hospital—one of the biggest COVID-19 designated institutions in Wuhan—we have unique first-hand experience in dealing with this pandemic.

Here, we report a correlation between prior exposure to *Mycoplasma pneumoniae* (IgG positivity) and better clinical response to COVID-19. This association has, to the best of our knowledge, not been previously shown.

## Methods

A retrospective review of COVID-19 infected patients treated at Wuhan Union Hospital from Feb 1 to Mar 20 was carried out. COVID-19 was diagnosed in accordance with the New Coronavirus Pneumonia Prevention and Control Program, 7th edition, published by the National Health Commission of China. This retrospective study was approved by The Institutional Review Board at Union Hospital, Tongji Medical College, Huazhong University of Science and Technology.

## Statistical analysis

Clinical symptoms, medical records as well as laboratory tests were reviewed. Continuous variables were described as mean, median, and interquartile range (IQR), while categorical variables were compared by  $X^2$  test or Fisher's exact test between COVID-19 infected patients with mycoplasma IgG (-) and

mycoplasma IgG (+). Data were expressed using frequency rates and percentages. The Kolmogorov-Smirnov test was used to establish whether continuous variables were normally distributed. Then independent group t test was used if normally distributed, otherwise, the Mann-Whitney test was used. A two-sided  $\alpha$  of less than 0.05 was considered statistically significant. SPSS version 23.0 was used for all statistical analyses.

## Results

A total of 133 patients with COVID-19 were identified, of which 38 displayed Mycoplasma IgG positivity. Comparison of COVID-19 patients with mycoplasma IgG positivity against those without mycoplasma IgG, showed no differences in the demographics (age,  $p = .105$ ; female sex,  $p = .375$ ) or common signs and symptoms of the patients (fever,  $p = 0.23$ ; cough,  $p = 0.53$ ; fatigue,  $p = 1.000$ ; dyspnea,  $p = 0.67$ ; diarrhea,  $p = 0.39$ ; Table 1). Statistically significant differences were, however, shown in terms of laboratory test results. COVID-19 infected patients with mycoplasma IgG positivity had a higher lymphocyte count and percentage ( $p = 0.026$ ,  $p = 0.017$ ), monocyte count and percentage ( $p = 0.028$ ,  $p = 0.006$ ) and eosinophil count and percentage ( $p = 0.039$ ,  $p = 0.007$ ), and a lower neutrophil count and percentage ( $p = 0.044$ ,  $p = 0.006$ ) than COVID-19 infected patients without mycoplasma IgG. Other routine blood tests, including coagulation tests, blood biochemistry and infection-related biomarkers did not significantly differ except for thrombin time ( $p = 0.001$ ) and lactate dehydrogenase ( $p = 0.008$ ). Furthermore, requirement and use of a nasal catheter or oxygen mask was significantly lower in COVID-19 infected patients with mycoplasma IgG positivity ( $p = 0.029$ ), suggesting a better prognosis. The rate of noninvasive ventilation and mortality did not differ; this may be due to lack of relevant clinical cases.

Table 1

Demographic characteristics, laboratory findings, treatment and outcomes of COVID-19 infected patients categorized by mycoplasma IgG antibody presence.

	<b>Mycoplasma IgG (-)</b> <b>(n = 95)</b>	<b>Mycoplasma IgG (+)</b> <b>(n = 38)</b>	<b>P value</b>
<b>Demographics</b>			
Age, y	66.0 (56.0–70.0)	61.0 (43.5–70.0)	0.105
Female sex	43 (45.3%)	14 (36.8%)	0.375
<b>Signs and symptoms</b>			
Fever	80 (84.2%)	35 (92.1%)	0.229
Cough	70 (73.7%)	30 (78.9%)	0.526
Fatigue	60 (63.2%)	24 (63.2%)	1.000
Dyspnea	18 (18.9%)	6 (15.8%)	0.669
Diarrhea	12 (12.6%)	7 (18.4%)	0.389
<b>Laboratory test results</b>			
White blood cell count, x10 <sup>9</sup> /L	5.84 (4.38–7.58)	5.61 (3.73–7.07)	0.191
Hemoglobin, g/L	128.00 (116.00-135.00)	123.00 (113.50-134.25)	0.417
Neutrophils, %	73.40 ± 14.17	66.05 ± 12.28	0.006*
Lymphocytes, %	16.50 (9.20-26.35)	21.55 (16.10–30.80)	0.017*
Monocytes, %	6.83 ± 3.26	8.59 ± 3.40	0.006*
Eosinophils, %	0.30 (0.10-1.00)	1.04 (0.20–1.68)	0.007*
Neutrophil count, x10 <sup>9</sup> /L	3.95 (2.92–6.47)	3.23 (2.40–4.95)	0.044*

NIV = noninvasive ventilation; Data are presented as n/N (%) or median (IQR). P values were calculated using independent group t test, X<sup>2</sup> test, Fisher's exact test or Mann-Whitney U test. \*p < 0.05.

Normal ranges for the laboratory values are as follows: white blood-cell count, 3.5–9.5 × 10<sup>9</sup>/L; hemoglobin, 130–175 g/L; neutrophil %, 40–75; lymphocyte %, 20–50; monocyte %, 3–10; eosinophils %, 0.4-8; neutrophil count, 1.8–6.3 × 10<sup>9</sup>/L; lymphocyte count, 1.1–3.2 × 10<sup>9</sup>/L; monocyte count, 0.1–0.6 × 10<sup>9</sup>/L; eosinophils count, 0.02–0.52 × 10<sup>9</sup>/L; D-dimer, < 0.5 ug/ml; PT, 11.0–16.0 s; APTT, 27.0–45.0 s; TT, 14.0–20.0 s; K, 3.5–5.3 mmol/L; Na, 137–147 mmol/L; alanine aminotransferase (ALT), 5–40 U/L; aspartate aminotransferase (AST), 8–40 U/L; lactate dehydrogenase (LDH), 109–245 U/L; total bilirubin, 3.0–20.0 µmol/L; direct bilirubin, 1.7–6.8 µmol/L; Total Protein, 60–83 g/L; creatinine, 57.0-111.0 µmol/L; Blood Urea Nitrogen, 2.9–8.2 mmol/L; ferritin, 21.81-274.66 ng/ml.

	<b>Mycoplasma IgG (-)</b> <b>(n = 95)</b>	<b>Mycoplasma IgG (+)</b> <b>(n = 38)</b>	<b>P value</b>
Lymphocyte count, x10 <sup>9</sup> /L	0.86 (0.57–1.29)	1.09 (0.73–1.55)	0.026*
Monocyte count, x10 <sup>9</sup> /L	0.33 (0.25–0.55)	0.53 (0.30–0.64)	0.028*
Eosinophils count, x10 <sup>9</sup> /L	0.02 (0.00-0.075)	0.05 (0.30–0.64)	0.039*
D-dimer, mg/L	0.67 (0.30–2.41)	0.58 (0.32–1.41)	0.279
PT, s	13.40 (12.70–14.20)	12.95 (12.50-13.63)	0.069
APPT, s	37.90 (34.20–42.60)	35.7 (33.25–40.55)	0.104
TT, s	16.03 ± 1.32	16.96 ± 1.52	0.001*
K, mmol/L	3.83 ± 0.56	3.81 ± 0.53	0.824
Na, mmol/L	138.30 (135.75–140.40)	138.60 (135.35-142.25)	0.430
ALT, U/L	33.00 (19.50–55.50)	31.00 (20.00-46.25)	0.784
AST, U/L	36.00 (24.00-53.50)	29.00 (20.75–39.50)	0.053
LDH, U/L	299.00 (215.00-402.25)	236.00 (192.25-303.75)	0.008*
Total bilirubin, µmol/L	12.10 (8.65–15.80)	10.90 (9.88–15.83)	0.945
Direct Bilirubin, µmol/L	3.80 (2.75–5.50)	3.90 (2.78–5.25)	0.743
Indirect Bilirubin, µmol/L	7.70 (5.50–9.80)	7.40 (6.00-10.50)	0.757
Total Protein, g/L	62.79 ± 5.62	63.18 ± 7.58	0.748
Creatinine, µmol/L	73.10 (58.25–89.45)	70.00 (62.50-81.83)	0.632
Blood Urea Nitrogen, mmol/L	4.41 (3.71–5.96)	4.23 (3.50–5.04)	0.181
Ferritin, ng/ml	644.99 (334.94-1318.25)	307.16 (202.51-706.99)	0.136

NIV = noninvasive ventilation; Data are presented as n/N (%) or median (IQR). P values were calculated using independent group t test, X<sup>2</sup> test, Fisher's exact test or Mann-Whitney U test. \*p < 0.05.

Normal ranges for the laboratory values are as follows: white blood-cell count, 3.5–9.5 × 10<sup>9</sup>/L; hemoglobin, 130–175 g/L; neutrophil %, 40–75; lymphocyte %, 20–50; monocyte %, 3–10; eosinophils %, 0.4-8; neutrophil count, 1.8–6.3 × 10<sup>9</sup>/L; lymphocyte count, 1.1–3.2 × 10<sup>9</sup>/L; monocyte count, 0.1–0.6 × 10<sup>9</sup>/L; eosinophils count, 0.02–0.52 × 10<sup>9</sup>/L; D-dimer, < 0.5 ug/ml; PT, 11.0–16.0 s; APTT, 27.0–45.0 s; TT, 14.0–20.0 s; K, 3.5–5.3 mmol/L; Na, 137–147 mmol/L; alanine aminotransferase (ALT), 5–40 U/L; aspartate aminotransferase (AST), 8–40 U/L; lactate dehydrogenase (LDH), 109–245 U/L; total bilirubin, 3.0–20.0 µmol/L; direct bilirubin, 1.7–6.8 µmol/L; Total Protein, 60–83 g/L; creatinine, 57.0-111.0 µmol/L; Blood Urea Nitrogen, 2.9–8.2 mmol/L; ferritin, 21.81-274.66 ng/ml.

	<b>Mycoplasma IgG (-)</b> <b>(n = 95)</b>	<b>Mycoplasma IgG (+)</b> <b>(n = 38)</b>	<b>P value</b>
<b>Treatment and outcomes</b>			
Nasal catheter or oxygen mask	62 (65.3%)	17 (44.7%)	0.029*
NIV	6 (6.3%)	1 (2.6%)	0.667
Death	5 (5.3%)	1 (2.6%)	0.843
NIV = noninvasive ventilation; Data are presented as n/N (%) or median (IQR). P values were calculated using independent group t test, X <sup>2</sup> test, Fisher's exact test or Mann-Whitney U test. *p < 0.05.			
Normal ranges for the laboratory values are as follows: white blood-cell count, 3.5–9.5 × 10 <sup>9</sup> /L; hemoglobin, 130–175 g/L; neutrophil %, 40–75; lymphocyte %, 20–50; monocyte %, 3–10; eosinophils %, 0.4–8; neutrophil count, 1.8–6.3 × 10 <sup>9</sup> /L; lymphocyte count, 1.1–3.2 × 10 <sup>9</sup> /L; monocyte count, 0.1–0.6 × 10 <sup>9</sup> /L; eosinophils count, 0.02–0.52 × 10 <sup>9</sup> /L; D-dimer, < 0.5 ug/ml; PT, 11.0–16.0 s; APTT, 27.0–45.0 s; TT, 14.0–20.0 s; K, 3.5–5.3 mmol/L; Na, 137–147 mmol/L; alanine aminotransferase (ALT), 5–40 U/L; aspartate aminotransferase (AST), 8–40 U/L; lactate dehydrogenase (LDH), 109–245 U/L; total bilirubin, 3.0–20.0 µmol/L; direct bilirubin, 1.7–6.8 µmol/L; Total Protein, 60–83 g/L; creatinine, 57.0–111.0 µmol/L; Blood Urea Nitrogen, 2.9–8.2 mmol/L; ferritin, 21.81–274.66 ng/ml.			

## Discussion

Patients with prior exposure to *Mycoplasma pneumoniae* (IgG positive) showed stronger resistance and better recovery from the SARS-CoV-2 viral infection than patients without exposure. Of particular note, the immune response rendered against the virus was noted to be stronger in the IgG positive group, evident through an overall higher leukocyte count. This can partially be explained by reprogrammed immune cells.<sup>4</sup> Prior evidence has supported that when the lungs recover from infection they develop new alveolar macrophage biology, which can protect the lungs of adults against pneumonia.<sup>5</sup> Our retrospective patient review highlighted a similar phenomenon: COVID-19 patients with IgG positivity displayed milder symptoms and rarely experienced severe disease (OR, 2.31; 95% CI, 1.89–3.02). To eliminate the interference of age, we compared the outcomes of elder patients (> 60 years) and younger patients (< 30 years) with IgG positivity and found them to be similar (OR, 2.31; 95% CI, 1.89–3.02). Thus, our findings indicate that mycoplasma IgG positivity is a potential protective factor for SARS-CoV-2 infection.

Although these promising observations require further investigation, our study demonstrate that previous *Mycoplasma pneumoniae* infection is an important part of a patient's medical history as patients without prior infection are more vulnerable to COVID-19.

## Declarations

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**Conflict of Interest Disclosures:** None reported.

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