Journal of Microbiology, Immunology and Infection xxx (xxxx) xxx

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.e-jmii.com

Correspondence

Fungal antigenemia in patients with severe Coronavirus disease 2019 (COVID-19): The facts and challenges

Dear Editor,

Since December 2019, an outbreak of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread globally. One of the complications observed in COVID-19 cases is secondary infection. When the burden of SARS-CoV-2 increases, the body's immune function decreases, and the probability of fungal infection increases.

The traditional detection methods used for fungal infection, such as culture methods and histopathology, might bring unpredictable biosafety issues, since the relevant specimens cannot be inactivated. Therefore, serological assays for fungal antigens, including (1,3)-β-D-glucan (G), galactomannan (GM), and mannan (Mn) tests commonly used for serological diagnosis fungal infection.[1,2] The sensitivity of G test in invasive Candida and *Aspergillus* infection is 70%—80%, and the specificity is 70%—80%. The serum GM detection is as sensitive as 70%—80%. The sensitivity of mannan detection is 58% and the specificity is 93%. When the combined detection of mannan antigen and antibody can improve the sensitivity of 83% and the specificity of 86%.[3]

In this study, we aimed to illustrate the existence of these fungal antigens from 181 patients with severe COVID-19 in at Hubei Provincial Hospital of Traditional Chinese Medicine (Wuhan, China) between December 31, 2019, and February 24, 2020., where was known for its severe outbreak of SARS-CoV-2. This study was approved by the ethics committee of Hubei Provincial Hospital of Traditional Chinese Medicine, and its protocols followed the Declaration of Helsinki.

In total, 181 residual serum samples originally collected during the routine examination of 181 patients with severe COVID-19 were investigated. Severe COVID-19 was defining according to guideline of diagnosis and treat for Coronavirus Disease 2019 (7th edition) awarded by National Health Commission of the People's Republic of China, the relevant characteristic symptoms including RR≥30 times/min, Oxygen saturation≤93% and so on. The serum samples were divided based on the different stages of disease during which they were collected: early-stage (1—7 days), middle-stage (8—14 days), and late-stage (≥15 days). The diagnostic criteria used for confirming COVID-19 was based on the guidelines issued by the National Health Commission of the People's Republic of China. All test kits for detection of G, GM, and Mn were provided by the manufacturer (Dynamiker Biotechnology (Tianjin) Co., Ltd, China) using an Automatic ELISA Workstation (A200). Rank and sum tests were performed, and count data were analyzed with a χ^2 test. Differences were considered statistically significant at $p < 0.05$. There was no significant difference in the mean values and positive rates of G, GM, and Mn between the early-, middle-, and late-stage COVID-19 patient samples ($P > 0.05$) (Table 1). However, the positive GM test rate tended to increase with age, i.e., the positive rate of the groups of patients 50—64 years old and aged ≥50 years old were higher than that of the group of patients aged 20—49 years old.

The main limitation of this retrospective study using the residual sera for analysis is the lack of clinical evaluation or other diagnostic approaches for possible fungal infection among these patients with severe COVID-19, particularly those with positive results for the three fungal antigen assays. However, this study suggests that concomitant fungal infection among patients with severe COVID-19 should not be ignored due to the high positive rate of fungal antigenemia. Chen et al. reported 99 patients with COVID-19 and 4 (4.0%) had fungal co-infections, including *Candida albicans* (n = 3) and *Candida glabrata* (n = 1).[4] Further clinical and microbiological investigations should be conducted to illustrate the reality of co-infection with fungi among patients with COVID-19.

https://doi.org/10.1016/j.jmii.2020.05.010

Please cite this article as: Lei Y et al., Fungal antigenemia in patients with severe Coronavirus disease 2019 (COVID-19): The facts and challenges, Journal of Microbiology, Immunology and Infection, https://doi.org/10.1016/j.jmii.2020.05.010

Table 1 Positive rates of (1,3)-β-D-glucan (G), galactomannan (GM), and Candida mannan (Mn) tests in different stages of disease and age groups in severe COVID-19 patients.

Stage of disease	No. of patients tested	No (%) of patients with positive results in each indicated test			
		G	GM	Mn	Total (Positive in any of G, GM, MN test)
Early (1–7 days)	15	3 (20.0)	1 (6.7)	0.00 (0)	20.00[3]
Middle (8–14 days)	28	14.28 (4)	7.14 (2)	3.57 (1)	14.28[4]
Late (≥15 days)	138	18.11 (25)	7.97 (11)	1.45 (2)	25.3 (35)
Age (years)	No. of patients	G % (No)	GM % (No)	Mn % (No)	Total % (No)
20–49	25	24 (6)	0.00 (0)	4.00 (1)	24.00 (6)
50–64	57	12.28 (7)	8.77 (5)	1.75 (1)	21.05 (12)
≥65	99	19.19 (19)	9.09 (9)	1.01 (1)	24.24 (24)

Declaration of Competing Interest

The authors declare that they have no competing interests.

Acknowledgements

We acknowledge Dynamiker Biotechnology (Tianjin) Co., Ltd for providing the reagent of the three assays and for donating the Automatic ELISA Workstation (A200) to Hubei Provincial Centers for Disease Control and Prevention for fighting the COVID-19 pandemic.

References

1. Wang H, Wang Y, Yang QW, Ni YX, Lin LK, Luo YP, et al. A national survey on fungal infection diagnostic capacity in the clinical mycology laboratories of tertiary care hospitals in China. *J Microbiol Immunol Infect* 2020;**20**:30076–81.
2. Kung HC, Huang PY, Chen WT, Ko BS, Chen YC, Chang SC, et al. 2016 guidelines for the use of antifungal agents in patients with invasive fungal diseases in Taiwan. *J Microbiol Immunol Infect* 2018;**51**:1–17.
3. Ahmad S, Khan Z. Invasive candidiasis: a review of nonculture-based laboratory diagnostic methods. *Indian J Med Microbiol* 2012;**30**:264–9.
4. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* 2020;**395**:507–13.

Yake Lei[1]
Influenza Reference Laboratory, Institute of Health Inspection and Testing, Hubei Provincial Center for Disease Control and Prevention, Wuhan 430079, China
E-mail address: leiaik@163.com

Yinggai Song[1]
Department of Dermatology, Peking University First Hospital, Beijing, 100034, China
Beijing Key Laboratory of Molecular Diagnosis on Dermatoses, Beijing, 100034, China
Research Center for Medical Mycology, Peking University, Beijing, 100034, China
National Clinical Research Center for Skin and Immune Diseases, Beijing, China
E-mail address: syg3515@163.com

Yilin Shu[1]
Influenza Reference Laboratory, Institute of Health Inspection and Testing, Hubei Provincial Center for Disease Control and Prevention, Wuhan 430079, China
E-mail address: sjshuyilin@163.com

Youyun Zhao[1]
Department of Clinical Laboratory, Hubei Provincial Hospital of Traditional Chinese Medicine, China
E-mail address: zhaoyy206@163.com

Xixiang Huo[1]
Influenza Reference Laboratory, Institute of Health Inspection and Testing, Hubei Provincial Center for Disease Control and Prevention, Wuhan 430079, China
E-mail address: xixianghuo@163.com

He Wang
Dynamiker Sub-Center of Beijing Key Laboratory for Mechanisms Research and Precision Diagnosis of Invasive Fungal Disease, Tianjin, 300467, China
E-mail address: Raulshiny@163.com

Yingchun Zeng
Xiao Yu
Xiang Li
Guojun Ye
Bin Fang
Shi Han
Influenza Reference Laboratory, Institute of Health Inspection and Testing, Hubei Provincial Center for Disease Control and Prevention, Wuhan 430079, China
E-mail addresses: biojoy@163.com, fish-yuxiao@hotmail.com, li_xiang75@yeah.net, gjy0822@sina.comv, nicolfang@163.com, qzicha@163.com

Ruoyu Li**
Department of Dermatology, Peking University First Hospital, Beijing, 100034, China
Beijing Key Laboratory of Molecular Diagnosis on Dermatoses, Beijing, 100034, China

[1] These authors have equal contribution to this study.

Research Center for Medical Mycology, Peking University, Beijing, 100034, China
National Clinical Research Center for Skin and Immune Diseases, Beijing, China

Linlin Liu*
Influenza Reference Laboratory, Institute of Health Inspection and Testing, Hubei Provincial Center for Disease Control and Prevention, Wuhan 430079, China

**Corresponding author. Department of Dermatology, Peking University First Hospital, Beijing, 100034, China.
E-mail address: mycolab@126.com (R. Li)

*Corresponding author.
E-mail address: flu87740787@163.com (L. Liu)

6 May 2020
Available online ■ ■ ■

Please cite this article as: Lei Y et al., Fungal antigenemia in patients with severe Coronavirus disease 2019 (COVID-19): The facts and challenges, Journal of Microbiology, Immunology and Infection, https://doi.org/10.1016/j.jmii.2020.05.010