*Retrospective Clinical Research Report*

*Journal of* INTERNATIONAL MEDICAL RESEARCH

Journal of International Medical Research
49(12) 1–7

DOI: 10.1177/03000605211062783
journals.sagepub.com/home/imr
SAGE

# Secondary bloodstream infection in critically ill patients with COVID-19

**Junli Zhang[1,*], Peng Lan[2,*], Jun Yi[3], Changming Yang[4], Xiaoyan Gong[2], Huiqing Ge[5], Xiaoling Xu[6], Limin Liu[7], Jiancang Zhou[2] and Fangfang Lv[1,*]**

## Abstract

**Objective:** Secondary infection, especially bloodstream infection, is an important cause of death in critically ill patients with COVID-19. We aimed to describe secondary bloodstream infection (SBI) in critically ill adults with COVID-19 in the intensive care unit (ICU) and to explore risk factors related to SBI.

**Methods:** We reviewed all SBI cases among critically ill patients with COVID-19 from 12 February 2020 to 24 March 2020 in the COVID-19 ICU of Jingmen First People's Hospital. We compared risk factors associated with bloodstream infection in this study. All SBIs were confirmed by blood culture.

**Results:** We identified five cases of SBI among the 32 patients: three with *Enterococcus faecium*, one mixed septicemia (*E. faecium* and *Candida albicans*), and one *C. parapsilosis*. There were no significant differences between the SBI group and non-SBI group. Significant risk factors for SBI were extracorporeal membrane oxygenation, central venous catheter, indwelling urethral catheter, and nasogastric tube.

[1]Department of Infectious Diseases, Sir Run Run Shaw Hospital, Zhejiang University School of Medicine, Hangzhou, China
[2]Department of Critical Care Medicine, Sir Run Run Shaw Hospital, Zhejiang University School of Medicine, Hangzhou, China
[3]Department of Thoracic Surgery, Jingmen First People's Hospital, Hubei Province, China
[4]Department of Anesthesiology, Jingmen First People's Hospital, Hubei Province, China
[5]Department of Respiratory Therapy, Sir Run Run Shaw Hospital, Zhejiang University School of Medicine, Hangzhou, China
[6]Department of Respiratory and Critical Care Medicine, Sir Run Run Shaw Hospital, Zhejiang University School of Medicine, Hangzhou, China
[7]Dean's Office, Sir Run Run Shaw Hospital, Zhejiang University School of Medicine, Hangzhou, China

*These authors contributed equally to this work.

**Corresponding author:**
Fangfang Lv, Department of Infectious Diseases, Sir Run Run Shaw Hospital, Zhejiang University School of Medicine, No. 3 Qingchun East Road, Hangzhou, Zhejiang 310016, China.
Email: lvfangfang@zju.edu.cn

**Conclusions:** Our findings confirmed that the incidence of secondary infection, particularly SBI, and mortality are high among critically ill patients with COVID-19. We showed that long-term hospitalization and invasive procedures such as tracheotomy, central venous catheter, indwelling urethral catheter, and nasogastric tube are risk factors for SBI and other complications.

**Keywords**
Coronavirus disease 2019, secondary bloodstream infection, critical illness, secondary pneumonia, extracorporeal membrane oxygenation, risk factor

Date received: 17 April 2021; accepted: 8 November 2021

## Introduction

The global COVID-19 pandemic is currently ongoing, with more than 130 million infections and nearly three million deaths worldwide.[1] Mortality in critically ill patients is 22.9% to 61.5%.[2,3] In critically ill patients with COVID-19, the presence of acute respiratory distress syndrome (ARDS) is an important risk factor for secondary bloodstream infection (SBI) because of a prolonged stay in the intensive care unit (ICU), with approximately 13.5% SBI reported.[4] At present, there is no specific treatment for severe COVID-19 infection apart from treatment with antivirals, corticosteroids, and mechanical ventilation. However, the use of corticosteroids (CS) in these patients remains controversial, despite reported benefits of CS treatment in patients with ARDS in the ICU.[2,5–7] There are many types of secondary infection in viral pneumonia, such as pulmonary bacterial infection, pulmonary *Aspergillus* infection, bloodstream infection (sepsis, catheter-related blood stream infection), and urinary tract infection[8–12] The mechanisms are mainly related to physical barriers, immune responses, and flora imbalance. There are many clinical risk factors for clinical secondary infections, such as older age (>60 years) and underlying conditions such as hypertension, diabetes, obesity, and hemodialysis.[5,7] The developments of SBI is closely associated with immunosuppressive therapy (long-term and high-dose glucocorticoid use), invasive procedures (e.g., endotracheal intubation, tracheotomy) and use of broad-spectrum antimicrobial agents. Different types of secondary infection and severe SBI have been observed in the critically ill patients in the COVID-19 ICU of our hospital. In this study, we retrospectively analyzed SBI-related risk factors to provide beneficial evidence for the treatment of critically ill patients with COVID-19 infection.

## Methods

We retrospectively analyzed the clinical data of all patients in the COVID-19 ICU of Jingmen First People's Hospital from 12 February 2020 to 24 March 2020. Our hospital has established a specialized ICU that is dedicated to the treatment of critically ill patients with COVID-19, with 23 beds. All patient infections were confirmed by SARS-CoV-2 nucleic acid detection, and patients were classified as having critical illness according to guidelines for the diagnosis and treatment of COVID-19.[2] The following kits were used for the detection of SARS-CoV-2 nucleic

acid and antibody detection: 2019-nCoV Ab, Xiamen Wantai Kairui Biotechnology Co., Ltd, Batch number: 20203400198; 2019-nCoV Nucleic acid detection kit (fluorescence PCR method), Huada Biotechnology (Wuhan) Co., Ltd, Batch number: 20203400060. All bacteria were identified using the VITEK 2 system (bioMérieux, Marcy-l'Étoile, France).

This was a retrospective observational study with no special intervention. The study was approved by the institutional review committee of Jingmen First People's Hospital. The requirement for patient informed consent was waived. All treated patients were critically ill. Our team comprised experts from the ICU and the infection disease department, respiratory treatment department, and respiratory department. The professional nursing team comprised senior nurses from the ICU. Supplemental treatment was provided by the rehabilitation and mental health departments. We strictly followed China's continuously improved COVID-19 treatment guidelines and professional work standards. In terms of secondary infection, close attention was paid to the possible sites of secondary infection, etiology, and evaluation of synchronous inflammatory markers.

According to the literature and our COVID-19 treatment experience, secondary infections, especially SBI, are primary complications associated with poor prognosis in critically ill patients with COVID-19. Typical systemic signs of infection with positive blood cultures may indicate bloodstream infection. Patients were divided into two groups according to the presence or absence of SBI (SBI group and non-SBI group). We evaluated differences between the two groups with respect to known and possible risk factors related to SBI, such as the use of CS, endotracheal intubation, indwelling central venous catheter, and length of ICU and hospital stay to identify significant risk factors and provide evidence for the treatment of critically ill patients with COVID-19.

## Statistical analysis

Continuous variables are presented as mean ± standard deviation and categorical variables as number and percentage. Continuous data were compared using the Student *t*-test and categorical data were compared with the chi-square or Fisher's exact test, as appropriate. We set $P < 0.05$ to indicate statistical significance. We used R software version 3.3.3 in the statistical analysis (The R Project for Statistical Computing, Vienna, Austria).

## Results

According to the clinical classification criteria for the diagnosis and treatment of COVID-19, 24 critical patients with COVID-19 and 8 with severe COVID-19 infection were identified. Most treated patients were in the late stage of critical illness. The average patient age was 63.34 ± 12.48 years, with 20/32 (62.5%) male patients. All the results are shown in Table 1. Among the 32 patients, 5 (15.63%) developed SBI; the detected pathogens included three cases of infection with *Enterococcus faecium*, one case with mixed septicemia (*E. faecium* and *Candida albicans*), and one case of C. *parapsilosis* infection.

All patients were treated empirically with antibiotics and Abidol (antiviral drug). In terms of known risk factors, one patient was obese and one had hepatitis B cirrhosis. Of the 32 patients, 21 (65.63%) patients were over 60 years old, 16 (50%) had hypertension, 10 (31.25%) had diabetes, and 3 (9.38%) patients had chronic renal disease (1 patient had undergone kidney transplantation, 2 patients had uremia and were undergoing hemodialysis). There was no significant difference between the two

**Table 1.** Clinical characteristics and risk factors of critically ill patients with COVID-19, with and without SBI.

| | All patients (N = 32) | SBI (N = 5) | Non-SBI (N = 27) | P value |
|---|---|---|---|---|
| All patients | | 5 (15.63%) | 27 (84.37%) | |
| Baseline factors | | | | |
| Age (years), mean ± SD | 63.34 ± 12.48 | 66.20 ± 8.23 | 62.81 ± 13.04 | 0.506 |
| Sex (male), n (%) | 20 (62.5) | 3 (60) | 17 (62.96) | 0.338 |
| Known risk factors | | | | |
| BMI >30 kg/m$^2$, n (%) | 1 (3.13) | 0 | 1 (3.70) | 1 |
| Advanced age (>60 years), n (%) | 21 (65.63) | 4 (80) | 17 (62.96) | 0.637 |
| Hypertension, n (%) | 16 (50) | 3 (60) | 13 (48.15) | 1 |
| Diabetes, n (%) | 10 (31.25) | 2 (40) | 8 (29.63) | 0.637 |
| Chronic renal disease | | | | |
| Renal transplant | 1 (3.13) | 0 | 1 (3.70) | 1 |
| Uremia/hemodialysis | 2 (6.25) | 0 | 2 (7.41) | 1 |
| Hepatitis B cirrhosis, n (%) | 1 (3.13) | 0 | 1 (3.70) | 1 |
| Critical illness, n (%) | 24 (75) | 5 (100) | 19 (70.37) | 0.296 |
| Risk factors | | | | |
| Corticosteroids | 21 (65.63) | 3 (60) | 15 (55.56) | 1 |
| CS>7 days, n (%) | 16 (50) | 3 (60) | 13 (48.15) | 1 |
| Cumulative dose of CS (mg), average (range) | 512 (80–1136) | 640 (560–720) | 462 (80–1136) | 0.593 |
| Duration of corticosteroids (days), average (range) | 14 (1–26) | 10 (10–16) | 14.5 (1–26) | |
| CRRT, n (%) | 7 (21.86) | 3 (60) | 4 (14.81) | 0.057 |
| Vasopressors, n (%) | 10 (31.25) | 3 (60) | 7 (25.93) | 0.087 |
| Mechanical ventilation, n (%) | | | | |
| Endotracheal intubation | 14 (43.75) | 4 (80) | 10 (37.04) | 0.142 |
| Tracheotomy | 2 (6.25) | 2 (40) | 0 (0) | 0.02* |
| Non-invasive ventilation | 18 (56.25) | 1 (20) | 17 (62.96) | 0.142 |
| ECMO, n (%) | 4 (12.5) | 3 (60) | 1 (3.7) | 0.008* |
| Central venous catheterization | 14 (43.75) | 5 (100) | 9 (33.33) | 0.01* |
| Indwelling urethral catheter | 14 (43.75) | 5 (100) | 9 (33.33) | 0.01* |
| Indwelling nasogastric tube | 14 (43.75) | 5 (100) | 9 (33.33) | 0.01* |
| Pneumonia (bacterial or fungal), n (%) | 9 (28.13) | 4 (80) | 5 (18.52) | 0.015* |
| Alive at hospital discharge, n (%) | 23 (71.88) | 3 (60) | 20 (74.07) | 0.121 |
| Duration of disease (days), mean ± SD | 44.03 ± 16.56 | 31.60 ± 13.20 | 41.96 ± 17.93 | 0.121 |
| Duration before admission to ICU, mean ± SD | 19.43 ± 9.71 | 19.2 ± 6.04 | 19.48 ± 10.29 | 0.932 |
| Length of ICU stay (days), mean ± SD | 18.53 ± 13.09 | 31.60 ± 9.22 | 16.11 ± 12.24 | 0.023* |
| Length of hospital stay (days), mean ± SD | 37.56 ± 13.62 | 49.80 ± 10.13 | 35.29 ± 12.97 | 0.042* |

*$P < 0.05$.

SBI, secondary bloodstream infection; ICU, intensive care unit; ECMO, extracorporeal membrane oxygenation; CRRT, continuous renal replacement therapy; CS, corticosteroids; SD, standard deviation; BMI body mass index.

groups (SBI group and non-SBI group) for these known risk factors.

In terms of the studied risk factors, 21/32 (65.63%) patients were treated with CS and 16/32 (50%) received CS for more than 7 days; the average cumulative dose of CS was 512 (80–1136) mg. There were no significant differences between the two groups

in these factors. In total, 7/32 (21.86%) were treated with continuous renal replacement therapy and 10/32 (31.25%) patients received vasopressors, with no significant differences between groups. Among the total, 14/32 (43.75%) patients were intubated, 2/32 (6.25%) patients underwent tracheotomy (all in the SBI group, 2/5 [40%]), and 18/32 (56.25%) patients were treated with non-invasive ventilation. Tracheotomy had a strong influence on the occurrence of SBI ($P = 0.02$). Four (12.5%) patients were treated with extracorporeal membrane oxygenation (ECMO) (3/5 [60%] in the SBI group; $P = 0.008$). Fourteen (43.75%) patients had a central venous catheter, indwelling urethral catheter, and a nasogastric tube. All patients (100%) in the SBI group had an indwelling catheter; thus, an invasive indwelling catheter was identified as a significant risk factor for SBI ($P = 0.01$).

Nine of the 32 (28.13%) patients were complicated with secondary pneumonia (bacterial or fungal) confirmed by sputum culture, lung imaging, and clinical manifestations; each patient tested positive multiple times. In the SBI group, 4/5 (80%) patients had secondary pneumonia; the detected pathogens were as follows: 1 patient with *Escherichia coli* (extended-spectrum beta-lactamase +), sensitive *Acinetobacter baumannii*, *C. parapsilosis*, *C. albicans*, sensitive *Stenotrophomonas maltophilia*, and *C. lusitaniae*. There was a significant difference between the two groups ($P = 0.015$).

We also analyzed effects of the course of disease and length of hospital stay on SBI. The average duration of disease was $44.03 \pm 16.56$ days, and the average duration before admission to the ICU was $19.43 \pm 9.71$ days; there were no significant differences between the two groups. The total average length of ICU stay was $18.53 \pm 13.09$ days ($31.60 \pm 9.22$ days in the SBI group; $P = 0.023$). The total average length of hospital stay was $37.56 \pm 13.62$ days ($49.80 \pm 10.13$ days in the SBI group, $P = 0.042$). Thus, both ICU stay and hospital stay had an impact on the occurrence of SBI. A total of 23/32 (71.88%) patients were cured and discharged (3/5 [60%] in the SBI group), with no significant difference between groups.

## Discussion

We treated 32 critically ill patients in the COVID-19 ICU. Among them, 15.63% of patients developed SBI; 60% of patients in the SBI group survived. Among patients in a traditional ICU ward, SBI has a high mortality rate of 40% to 60%.[2] In total, 28.13% of patients were complicated with secondary pneumonia in the COVID-19 ICU. In the SBI group, 80% of patients had secondary pneumonia, making this a significant risk factor for death and secondary infection in critically ill patients with COVID-19. The distribution characteristics and drug resistance among pathogens differed from those involved in SBI among patients in a traditional ICU, *E. faecium* and *Candida* were the main pathogens detected. No multidrug-resistant bacteria were detected, perhaps because our ICU was newly established for patients with COVID-19 and our team included experts in nosocomial infection control, which were very favorable factors for our patients. These characteristics not only reduce mortality related to multidrug resistance but also reduce the cost of treatment.[8,13]

The average age among our patients was 63.34 years, with 65.63% over age 60 years. Although we found no significant difference in the incidence of SBI between patients younger than 60 years of age and those with advanced age, older age has been reported to be associated with high mortality in critically ill patients.[2,5,7] Among our patients, 62.5% were male. Many studies also report a higher proportion of

male patients with serious COVID-19 infection, although the specific mechanism is unclear. [2,5,7]

Having underlying diseases has also been associated with high mortality and greater likelihood of developing severe illness in patients with COVID-19.[2,5,7,14] In our study, only one patient was obese and one had hepatitis B cirrhosis; 50% of patients had hypertension, 31.25% had diabetes (seven cases were complicated with hypertension), three patients had chronic renal disease (one patient had undergone kidney transplantation and was complicated with hypertension, two patients had uremia complicated with hypertension and were undergoing hemodialysis). However, we found no significant difference between the SBI and non-SBI groups with respect to these known risk factors,

Although the use of CS in COVID-19 is controversial, low doses in patients with mild disease and high doses in critically ill patients have been reported to be beneficial.[6,15,16] In this study, 65.63% of patients were treated with CS and 50% were treated for more than 7 days, with an average cumulative dose of 512 mg. CS treatment was not identified as a risk factor for SBI in this study. From our clinical observation, clinical symptoms and lung imaging among patients were improved after treatment with CS.

According to the findings of this study, multiple invasive procedures are important risk factors of SBI, such as tracheotomy, ECMO, and having various indwelling catheters. Among the associated infections, candidemia was most common, and 60% of cases were non-*C. albicans* infections.[9–12] It is very important to follow extra preventive measures in patients who undergo multiple invasive operations, extubate as soon as possible, evaluate secondary infection regularly, and treat infections early.

The average length of ICU stay and length of hospital stay were longer in the SBI group than in the non-SBI group, which were also factors associated with SBI and poor prognosis.

## Conclusion

Our findings confirmed that mortality is high in critically ill patients with COVID-19. According to published reports, these patients can benefit from antiviral therapy, early appropriate mechanical ventilation, treatment with CS, and early admission to the ICU. However, owing to rapid disease progression, older patients and those with underlying diseases are at increased risk of critical illness. Long-term hospitalization and invasive procedures such as tracheotomy or the use of a central venous catheter, indwelling urethral catheter, and nasogastric tube are strong risk factors for SBI and other complications in critically ill patients with COVID-19 infection.

### Declaration of conflicting interest

The authors declare that there is no conflict of interest.

### Funding

The authors disclosed receipt of the following financial support for the research, authorship, and publication of this article: This work was supported by the Major Science and Technology Project of Zhejiang Province Health Commission (WKJ-ZJ-2112) and the Clinical Research Project of Zhejiang Provincial Department of Health (2018ZD030).

### ORCID iD

Fangfang Lv https://orcid.org/0000-0001-8573-350X

### References

1. Centers for Disease Control and Prevention. COVID-19. https://www.coronavirus.gov.
2. WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group; Sterne JAC, Murthy S, Diaz JV, et al. Association between administration

of systemic corticosteroids and mortality among critically ill patients with COVID-19: A meta-analysis. *JAMA*. 2020; 324: 1330–1341.
3. Yang X, Yu Y, Xu J, et al. *Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan*, China: a single-centered, retrospective, observational study. *Lancet Respir Med*. 2020; 8: 475–481. doi: 10.1016/S2213-2600(20)30079-5.
4. Zhang Z, Navarese EP, Zheng B, et al. Analytics with artificial intelligence to advance the treatment of acute respiratory distress syndrome. *J Evid Based Med*. 2020; 13: 301–312.
5. Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA Intern Med*. 2020; 180: 934–943.
6. Mahmoodpoor A, Shadvar K, Ghamari AA, et al. Management of critically ill patients with COVID-19: What we learned and what we do. *Anesth Pain Med*. 2020; 10: e104900.
7. Asselah T, Durantel D, Pasmant E, et al. COVID-19: Discovery, diagnostics and drug development. *J Hepatol*. 2021; 74: 168–184.
8. Timsit JF, Ruppé E, Barbier F, et al. Bloodstream infections in critically ill patients: An expert statement. *Intensive Care Med*. 2020; 46: 266–284.
9. Buetti N and Timsit JF. Management and prevention of central venous catheter-related infections in the ICU. *Semin Respir Crit Care Med*. 2019; 40: 508–523.
10. Lee JH, Kim MU, Kim ET, et al. Prevalence and predictors of peripherally inserted central venous catheter associated bloodstream infections in cancer patients: A multicentre cohort study. *Medicine (Baltimore)*. 2020; 99: e19056.
11. Feneley RC, Hopley IB, Wells PN. Urinary catheters: History, current status, adverse events and research agenda. *J Med Eng Technol*. 2015; 39: 459–470.
12. da Silva RB, Neves RP, Hinrichsen SL, et al. Candidemia in a public hospital in northeastern brazil: Epidemiological features and risk factors in critically ill patients. *Rev Iberoam Micol*. 2019; 36: 181–185.
13. Ge H, Pan Q, Zhou Y, et al. Lung mechanics of mechanically ventilated patients with COVID-19: Analytics with high-granularity ventilator waveform data. *Front Med (Lausanne)*. 2020; 7: 541.
14. Bassetti M, Righi E, Carnelutti A. Bloodstream infections in the intensive care unit. *Virulence*. 2016; 7: 267–279.
15. Alhazzani W, Møller MH, Arabi YM, et al. Surviving Sepsis Campaign: Guidelines on the management of critically ill adults with coronavirus disease 2019 (COVID-19). *Crit Care Med*. 2020; 48: e440–e469.
16. Li Y, Meng Q, Rao X, et al. Corticosteroid therapy in critically ill patients with COVID-19: A multicenter, retrospective study. *Crit Care*. 2020; 24: 698.