

# Risk Factors of Secondary Infections in Severe and Critical Patients Hospitalized with COVID-19: A Case-Control Study

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## Research article

**Keywords:** COVID-19, Risk factor, Secondary infection, Severe

**DOI:** <https://doi.org/10.21203/rs.3.rs-55958/v1>

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## Abstract

**Background:** Severe patients hospitalized with COVID-19 suffered secondary infections which greatly increased the length of hospital stay and the mortality. We aimed to explore risk factors of secondary infections that can help clinicians early implement preventive measures to dispose of severe and critical inpatients with COVID-19.

**Methods:** A case-control study enrolled 238 severe and critical patients with COVID-19. Characteristics of cases and controls were compared.

**Results:** Severity of illness on admission, ICU admission, ventilator, central venous catheterization were common in the cases, however almost none of these factors was observed in the controls. Multivariable regression showed risk factors of secondary infections included male (OR 4.08; 95% CI 1.58-10.50), age 65 or older (OR 3.11; 95% CI 1.25-7.76), heart diseases (OR 3.96; 95% CI 1.40-11.27), hypoproteinemia on admission (OR 6.41; 95% CI 1.65-24.92) and corticosteroids (OR 19.83; 95% CI 7.3-53.55) and proton-pump inhibitors (OR 3.96; 95% CI 1.51-10.37).

**Conclusions:** male, older age, heart diseases, hypoproteinemia, corticosteroid and proton-pump inhibitors were independent risk factors of secondary infections. Inpatients needing ICU admission and invasive devices still need to be given optimal cares and to be minimized the duration.

## Background

In December 2019, a new coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged and rapidly spread throughout Wuhan, which was later designated coronavirus disease 2019 (COVID-19) [1, 2]. More than 50,000 people were infected and over 3,000 people died of COVID-19. In July 20, 2020, World Health Organization (WHO) reported 14,043,176 confirmed cases and 597,583 deaths from 216 countries, areas or territories [3]. An ongoing worldwide outbreak of COVID-19 severely affected international health and economy.

About 20% of patients with COVID-19 would develop into severe and critical illness (14% and 6%), some of whom occurring serious complications such as dyspnea, acute respiratory distress syndrome, and septic shock, required hospitalization. At present, there were no specific medicines for COVID-19. Supportive therapies and preventions of secondary infections were available treatments for inpatients with COVID-19 [4, 5].

Severe and critical patients with COVID-19 usually required the use of invasive devices during hospitalization. Dai-Shi Tian et al. reported that COVID-19 might also attack the patients' immune system and disrupt immune response [6], which would facilitate pathogens invasion and body susceptibility to infection. Bin Cao et al. reported that about 15% of severe and critical inpatients with COVID-19 developed into secondary infections during hospitalization, half of dead inpatients experienced secondary infections [7].

Obviously, secondary infection is an important factor that affects the treatment and outcome of inpatients with COVID-19. The sooner prevention and intervention could reduce the incidence of secondary infections. Hospital-acquired pneumonia (HAP) was the second most common nosocomial infection and the leading cause of death in critical illness patients. About 1/3 of nosocomial pneumonias occurred in ICU, and most of them were ventilator-associated pneumonia [8]. The occurrence of bloodstream infections (BSI) was dangerous for inpatients, because it would prolong length of hospitalization and even might threaten their lives. Especially for critical illness patients who needed to be admitted to the intensive care unit (ICU), once occurred BSI, 40–60% of them lost their lives [9].

This case-control study aimed to compare demographic, treatment, and laboratory data between cases and controls, to explore risk factors of secondary pneumonia and bloodstream infections caused by bacteria or fungal in severe and critical patients hospitalized with COVID-19.

## Methods

### Study design and participants

The case-control study included adult inpatients ( $\geq 18$  years old) with COVID-19. 1102 severe and critical patients were admitted to West Campus of Wuhan Union Hospital from February 5, 2020 to March 10, 2020. We reviewed electronic medical records of the 1102 inpatients with COVID-19, and excluded inpatients with incomplete records on admission, or co-infection before admission, or nosocomial infections less than 48 hours after admission, or secondary urinary tract infections.

This study was approved by the ethics committee of Union Hospital, Huazhong University of Science and Technology ([2020]0104).

## Inclusion criteria

Inclusion criteria for case group: inpatients with COVID-19 who were conformed as secondary bacterial and fungal pneumonia or bloodstream infections 48 hours after admission. Inclusion criteria of control group: inpatients with COVID-19 who had no bacterial or fungal infections from admission to discharge.

Case group included 56 inpatients with secondary infections (pneumonia and bloodstream infections caused by bacteria or fungal); control group included 182 inpatients (no bacterial or fungal infections).

## Data collection

The demographic, laboratory findings and treatments of cases and controls were extracted from electronic medical records. Data of case group were recorded from hospital admission to secondary infections. Data of control group were recorded from hospital admission to discharge or death. To ensure the accuracy of data, two independent researchers were arranged to review and check the data form.

## Definitions

Disease severity status on admission was defined according to the diagnostic and treatment guideline for COVID-19 (version 7) [5]. Comorbidities was identified according to the International Classification of Diseases and Injuries-10 diagnostic codes. In our study secondary infections referred to secondary pneumonia and bloodstream infections caused by bacteria or fungal. Secondary infections were confirmed when inpatients showed clinical symptoms or signs of pneumonia or bloodstream infections, as well as positive culture of a new pathogen obtained from lower respiratory tract specimens or blood samples 48 h after admission [10, 11]. Ventilator-associated pneumonia was diagnosed according to the guidelines for treatment of hospital-acquired and ventilator-associated pneumonia [12]. Anemia was defined as blood hemoglobin of less than 90 g/L. Hypoproteinemia was defined as blood albumin of less than 25 g/L. Electrolyte disturbance was confirmed when at least one of sodium, potassium, calcium and magnesium of human plasma was lower or higher than the normal range.

## Statistical analysis

Continuous variables were presented as median (IQR); categorical variables were present as frequencies. Differences between cases and controls were compared with Mann-Whitney U test,  $\chi^2$  test, or Fisher's exact test. Subgroup analysis was presented as percentage. Multivariable binary logistic regression models were used to explore the risk factors associated with secondary infections.

Severity of illness on admission, ICU admission, mechanical ventilator, central venous catheterization, gastric catheterization, catheter catheterization, and sedatives were common in the cases, while almost none of these factors was observed in the controls. Therefore, regression analysis was not performed on these factors.

Considering the total number of case patients (n = 56) in our study, we chose six variables based on previous findings of pneumonia, bloodstream infections and clinical importance.<sup>7, 13-16</sup> The six variables included sex, age 65 or older, comorbidity (heart diseases), laboratory findings (hypoproteinemia) on admission and drug therapy (corticosteroids and PPI) during hospitalization.

P value less than 0.05 was regarded as statistically significant. All statistical analyses were performed by IBM SPSS Statistics 26.0.

## Results

### Demographic

A total of 238 inpatients with COVID-19 were enrolled, the median age of 238 inpatients was 59.0 years old (IQR 50.0–68.0), ranging from 21 to 91-year-old. The median age of case group was higher than that of the control group (IQR 66.0 vs 57.0).

The proportion of males in the cases was significantly higher than that of the control group (67.9% vs 41.8%). Similarly, the proportion of patients (age,  $\geq$  65 years) in the cases was nearly one times that of the control group (55.4% vs 29.1%) (Table 1). 62.2% of patients suffered from at least one comorbidity, and this proportion was as high as 91.1% in the cases, which was significantly higher than 53.3% in the controls. Several diseases recorded were common in cases, such as hypertension (64.3%), heart diseases (33.9%), cerebrovascular disease (19.6%) and history of malignancy (12.5%) (Table 1).

### Laboratory findings and treatment

Over half of the cases appeared electrolyte disturbance, while the proportion was 34.6% in controls. Odds of hypoproteinemia (albumin of less than 25 g/L) was higher in case group. 75.0% of patients used PPI in cases, while the proportion was only 29.1% in controls. 69.6% of cases

used corticosteroids, which was only 8.8% in the controls (Table 1).

Severity of illness on admission, ICU admission, ventilator, central venous catheterization, gastric catheterization, catheter catheterization, and sedatives were common in the cases, however almost none of them was observed in the controls (Table 1).

## Subgroup analysis

Among 56 patients of the case group, the number of severe and critical patients were 20 (35.7%) and 36 (64.3%), respectively. Severity of illness on admission, ICU admission, ventilator, central venous catheterization, gastric catheterization, catheter catheterization, and sedatives were more common in critical patients (Table 2).

Of the 56 cases with secondary infections, 50 had pneumonia and 6 had bloodstream infections, respectively. 11 of pneumonia patients subsequently developed bloodstream infections; half of 6 bloodstream infections patients occurred pneumonia. 4 of the 14 inpatients with both pneumonia and bloodstream infections were infected by the same pathogens (Carbapenem-Resistant *Klebsiella pneumoniae*) (Table 2).

## Risk factors for secondary infections

Multivariable regression showed significant risk factors associated with secondary infections including male (OR 4.08; 95% CI 1.58–10.50), age 65 or older (OR 3.11; 95% CI 1.25–7.76), heart diseases (OR 3.96 ; 95% CI 1.40-11.27), hypoproteinemia (OR 6.41 ; 95% CI 1.65–24.92) and corticosteroids (OR 19.83; 95% CI 7.3-53.55) and PPI (OR 3.96; 95% CI 1.51–10.37) (Table 3).

## Discussion

In this case-control study, we identified several risk factors of secondary infections in severe and critical patients hospitalized with COVID-19. Significant risk factors were male, age 65 or older, heart diseases, hypoproteinemia, corticosteroids and PPI.

As previously covered risk factors for hospital acquired pneumonia (HAP), male, age 65 or older were risk factors of secondary infection [13, 17]. Recent studies related to COVID-19 reported that male was a risk factor associated with disease severity status, and age 65 or older was a risk factor related to death [7, 15, 18, 19].

In multivariate regression model, heart disease was the only underlying comorbidity associated with secondary infections. It had been uncovered that, acute cardiac events and poor prognosis appeared on patients with coronary heart disease were related to influenza and lower respiratory tract virus infection [20]. Previous report indicated that MERS-CoV would damage the heart muscle, when COVID-19 appeared, some researchers also confirmed its heart damage effect [21]. So what was the relationships between heart diseases and secondary infections in patients with COVID-19? We speculated that patients with heart disease once infected with COVID-19 were more likely to develop into severe illness, thus exposing inpatients to invasive devices such as mechanical ventilation and central venous catheterization.

Diabetes was generally considered as a risk factor for infections [22], but in our study, there was no statistically significant difference between cases and controls. Previous risk factors of pneumonia reported chronic obstructive pulmonary disease (COPD) to be one risk factor associated with secondary infection [23]. We also found the proportion of COPD in the cases was more than three times that in the controls. Unfortunately, we did not record enough patients with COPD in the two groups. Despite the incidence of anemia between cases and controls were notable difference, there were only 3 patients in each group. Therefore anemia couldn't be included in univariable regression.

In a sepsis study, albumin could be used as a predictor of disease severity [24]. Hypoproteinemia was a risk factor of carbapenem-resistant *Klebsiella pneumoniae* bacteremia in non-transplant patients [14]. In our study, we found that hypoproteinemia was also a key risk factor of secondary infections. Report showed COVID-19 attacked the body's immune and disrupted immune response [6]. Besides, hypoproteinemia would weaken immunity to be susceptible to infections, and systemic edema, ascites and pleural effusion caused by hypoproteinemia might cause infections.

Among factors identified by multivariate regression, corticosteroids' risk ratio was notable. Corticosteroids could suppress the immune system if taken for long time or large doses. A research of BSI in ICU reported immunosuppressants were associated with BSI [9]. One possible cause of hospital-acquired pneumonia (HAP) was that diseases on admission destroyed patients' immune system, thus making patients be susceptible to infections [25]. In addition, COVID-19 attacked the human immune system and made corticosteroids' influences more prominent [6]. Therefore, the use of corticosteroids to treat inflammation was a double-edged sword. It was necessary to comprehensively evaluate the patient's condition before rationally using corticosteroids in the short term.

Taking proton pump inhibitors (PPI) increased the risk of secondary infections in patients hospitalized with COVID-19. Herzig SJ et al. reported acid-suppressive medication use was associated with 30% increased odds of hospital-acquired pneumonia. Statistically significant risk was demonstrated only for use of PPI [16].

Undoubtedly, risk factors associated with secondary infections were severity of illness on admission, ICU admission, ventilator, central venous catheterization. Disease severity status on admission was a leading cause for secondary infections. Critical illness of patients usually had decreased level of consciousness and needed to be admitted to the ICU. Once it happened, invasive devices such as ventilator and central venous catheterization were required. These were the major risk factors of secondary infections confirmed in many previous studies [26–30].

Unfortunately, of the same pathogens from sputum and blood culture 4 inpatients all died. We speculated prolonged pneumonia or bloodstream infections could cause another infection.

In recent years, scholars reported gastric catheterization and urinary catheterization were risk factors of nosocomial infections [14, 19, 31]. Intravenous sedatives were typically used to enhance inpatients comfort and patient-ventilator synchrony. A systematic review about the relationship between sedatives and healthcare-associated infection reported that, the three most common sedatives (benzodiazepines, propofol, and dexmedetomidine) for mechanically ventilation patients had different pharmacologic and immunomodulatory effects, which might impact infection risk.<sup>32</sup>Further observations were demanded to confirm the relationship between gastric catheterization, urinary catheterization, and sedatives with secondary infections.

However, our study has several limitations. Firstly, control group could not include enough critical inpatients due to the characteristics of pneumonia caused by COVID-19. Almost none of these phenomena were observed in the controls (severity of illness on admission, ICU admission, ventilator, central venous catheterization, gastric catheterization, urinary catheterization, and sedatives). More prospective studies were needed to quantify the odds of secondary infections increased by these factors. Secondly, due to the lack of certain records on admission, some factors that might be related to secondary infections could not be explored, e.g. smoking history and BMI (body mass index). Finally, limited by the number of inpatients enrolled in case group, some variables could not be included in the multivariate regression model simultaneously.

To the best of our knowledge, this is the first report of risk factors for secondary infections in severe and critical patients hospitalized with COVID-19. Severe and critical inpatients with male, age ( $\geq 65$  years), heart diseases, hypoproteinemia, treated with corticosteroids, and PPI need to be observed carefully and to be intervened with drugs to prevent the occurrence of secondary infections as early as possible. In particular, inpatients needing ICU admission and invasive devices also need to be given optimal cares and to be minimized the duration.

## Abbreviations

COVID-19	Coronavirus disease 2019
ICU	Intensive Care Unit
IQR	Interquartile range
OR	Odds ratio
CI	Confidence interval
PPI	Proton Pump Inhibitor

## Declarations

## Acknowledgements

Not applicable.

## Funding

None.

## Conflicts of interest

All authors report no conflicts of interest relevant to this article.

## Ethics approval

This study was approved by the ethics committee of Union Hospital, Huazhong University of Science and Technology ([2020]0104). Individual informed consent was waived by the ethics committee listed above because this study did not pose any additional risks to the patients. Informed consent about study participation was officially announced by mail. All patient data were anonymized prior to the analysis.

## Consent for publication

Not applicable.

## Availability of data and material

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

## Authors' contributions

Jie Li (Writing - original draft), Jingchao Cao (Writing - review and editing), Peishan Cai (Acquisition of data) (Investigation), Baoxia Shi (Acquisition of data) (Investigation), Jie Cao (Analysis and interpretation of data), Yu Zhang (Supervision), Junwei Wang (Validation) (Conceptualization).

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## Tables

Table 1.  
Demographic, treatment and laboratory findings of inpatients with COVID-19

	Controls (n%)	Cases (n%)	$\chi^2$	p value
N	182	56		
Male	76(41.8%)	38(67.9%)	11.688	0.010
Age <sup>a</sup> ,years	57(49–67)	66(58–72)		0.000
Age, $\geq$ 65 year	53(29.1%)	31(55.4%)	12.907	0.000
Disease severity status			132.499	0.000
Severe	181(99.5%)	20(35.7%)		
Critical	1(0.5%)	36(64.3%)		
Time from illness onset to Hospital admission <sup>a</sup> , days	15.5(11–20)	10(7–14)		0.000
Time from hospital admission to Secondary infections <sup>a</sup> , days	18(14–22)	10(5–15)		0.000
Comorbidity	97(53.3%)	51(91.1%)	25.986	0.000
Hypertension	59(32.4%)	36(64.3%)	18.134	0.000
Diabetes	27(14.8%)	11(19.6%)	0.738	0.390
COPD	3(1.6%)	3(5.4%)	2.397	0.144
Heart diseases	22(12.1%)	19(33.9%)	14.326	0.000
Cerebrovascular diseases	6(3.3%)	11(19.6%)	17.251	0.000
History of malignant tumor	5(2.7%)	7(12.5%)	8.507	0.010
ICU admission	0	33(58.9%)	124.515	0.000
Ventilator	0	40(71.4%)	156.263	0.000
Gastric catheterization	1(0.5%)	27(48.2%)	93.725	0.000
Catheter catheterization	1(0.5%)	33(58.9%)	119.191	0.000
Central venous catheterization	0	24(42.9%)	86.748	0.000
Sedatives	0	24(42.9%)	86.748	0.000
Corticosteroids	16(8.8%)	39(69.6%)	89.242	0.000
PPI	53(29.1%)	42(75.0%)	37.584	0.000
Electrolyte disturbance	63(34.6%)	36(64.3%)	15.518	0.000
Anaemia	3(1.6%)	3(5.4%)	2.379	0.144
Hypoproteinemia	9(4.9%)	11(19.6%)	12.019	0.001
Non-Survivor	0	29(51.8%)	107.328	0.000

<sup>a</sup> Median(IQR).P values were from Mann-Whitney U test,  $\chi^2$  test, or Fisher's exact test .  
COPD = Chronic Obstructive Pulmonary Disease. PPI = Proton Pump Inhibitors.



Table 2.  
Subgroup analysis

	Severe	n%	Critical	n%
N	20		36	
ICU admission	5	25.0%	28	77.8%
Ventilator	11	55.0%	30	83.3%
Gastric catheterization	9	45.0%	18	50.0%
Catheter catheterization	9	45.0%	24	66.7%
Central venous catheterization	6	30.0%	18	50.0%
Sedatives	7	35.0%	17	47.2%
Pneumonia	18	90.0%	32	88.9%
Bloodstream infection	2	10.0%	4	11.1%
Death of pneumonia	5	25.0%	21	58.3%
Death of bloodstream infections	0	0.0%	3	8.3%
Pneumonia and bloodstream infections	2	10.0%	12	33.3%
Pneumonia appeared bloodstream infections	2	10.0%	9	25.0%
Bloodstream infections appeared pneumonia	0	0.0%	3	8.3%
Same pathogen of sputum and bloodstream culture	1	5.0%	3	8.3%
Non-survivor	5	25.0%	24	66.7%
Categorical variables were present as n or n/N (%).				

Table 3.  
Risk factors associated with secondary infections

	Univariable	95% CI	p value	Multivariable	95% CI	p value
	OR			OR		
Male	2.94	1.56-5.55	0.001	4.08	1.58-10.50	0.004
Age, ≥65 year	3.02	1.63-5.59	0.000	3.11	1.25-7.76	0.015
Comorbidity	8.94	3.41-23.43	0.000			
Hypertension	3.75	2.00-7.04	0.000			
Heart diseases	3.73	1.84-7.60	0.000	3.96	1.40-11.27	0.010
Cerebrovascular Diseases	7.17	2.52-20.43	0.000			
History of malignant tumor	5.06	1.54-16.63	0.008			
Corticosteroids	23.80	11.06-51.23	0.000	19.83	7.34-53.55	0.000
PPI	7.30	3.68-14.47	0.000	3.96	1.51-10.37	0.005
Electrolyte disturbance	3.40	1.82-6.36	0.000			
Hypoproteinemia	4.70	1.84-12.03	0.001	6.41	1.65-24.92	0.007
P values are from univariable or multivariable regression model. CI=confidence interval. OR= odds ratio.						