JIDC | THE JOURNAL OF INFECTION IN DEVELOPING COUNTRIES

*Coronavirus Pandemic*

# Clinical characteristics and outcomes of critically ill COVID-19 patients with CAUTI: a study in Vietnam

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## Abstract
Introduction: Urethral catheterization is commonly required in coronavirus disease 2019 (COVID-19) patients hospitalized in intensive care units (ICUs). However, this increases their vulnerability to nosocomial infections such as catheter-associated urinary tract infections (CAUTIs). Existing studies on nosocomial infections in COVID-19 patients usually report CAUTI prevalence but neglect the clinical differences between CAUTI and non-CAUTI patients. This study aimed to assess clinical features, microbiological characteristics, and outcomes of COVID-19 patients with CAUTI vs non-CAUTI patients in an ICU.
Methodology: We analyzed the clinical data from a retrospective cohort study of 527 critically ill COVID-19 patients who required urethral catheterization at the ICU of Bach Mai hospital in Ho Chi Minh City, Vietnam, from August to October 2021. A total of 69 patients (n = 37 CAUTI vs n = 32 non-CAUTI) were selected for urine culture, and their clinical features, microbiological characteristics, and outcomes were recorded for analysis.
Results: COVID-19 patients with CAUTI had a higher mortality rate compared to those without CAUTI ($p = 0.02$). The length of stay in the ICU was 1.4 times longer for CAUTI patients compared to the non-CAUTI group ($p = 0.03$). Fungi was the most common microbiological cause of UTI in COVID-19 ICU (91.4%), and Pseudomonas aeruginosa was a significant risk factor of CAUTI. P. aeruginosa, number of antibiotics used, and duration of catheterization had a strong association with the patients' survival time in ICU.
Conclusions: This study provides a better understanding of CAUTI in COVID-19 patients, thus facilitating their future treatment.

**Key words:** CAUTI; COVID-19; ICU.

*J Infect Dev Ctries* 2024; 18(9.1):S153-S162. doi: 10.3855/jidc.18620

(Received 26 May 2023 – Accepted 13 December 2023)



## Introduction

Coronavirus disease 2019 (COVID-19) is an infectious respiratory illness caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus. While the majority of individuals with COVID-19 experienced mild symptoms, approximately 14% developed severe symptoms that necessitated hospitalization, and about 5% became critically ill, requiring intensive care unit (ICU) support [1]. The severe condition has been associated with acute respiratory distress, prolonged mechanical ventilation, and multiple associated infections, including urinary tract infection (UTI) [1].

Superinfection and co-infection were common in severe COVID-19 patients treated in ICUs [2]; these patients had a mortality rate ranging from 50 to 100% [3,4]. As the COVID-19 pandemic has spread worldwide, the prevention of hospital-acquired infections has become increasingly important. There was evidence that a higher risk of co-infection in patients with severe and critically ill COVID-19 was associated with low T-cell levels, suggesting the potential capacity of this virus in suppressing the immune system [3].

Prior to the COVID-19 pandemic, catheter-associated urinary tract infections (CAUTIs) were already recognized as one of the most common nosocomial infections [6]. Urinary catheterization has been a major risk factor for UTI in hospitalized patients, accounting for 67% of UTIs in patients in the hospital, and up to 97% in ICUs [7].

Several studies have investigated the prevalence of CAUTI in individuals with COVID-19 in ICUs. For example, Bardi *et al*. recently reported an 8% prevalence of UTI in a cohort of 140 ICU-admitted patients; most of them were with CAUTI [8]. Chong Hui Ong *et al*. showed a CAUTI rate of 7% in a cohort of n = 71 COVID-19 patients admitted to ICUs [3]. Another study by Soriano *et al*., which included n = 83 cases, reported a CAUTI rate of up to 38.55% [1]. In a retrospective observational study including 87 COVID-19 patients with UTIs admitted at a tertiary hospital in Madrid, Spain, 56 cases (64.4%) were identified with CAUTI [9]. These studies primarily focused on analyzing the clinical characteristics and prevalence of CAUTI in COVID-19, while the comparison between CAUTI and non-CAUTI cases with COVID-19 patients in ICU is still not widely investigated. Therefore, this study aimed to explore the differences between CAUTI vs non-CAUTI groups through characterizing the clinical features, microbiological characteristics, and outcomes of the COVID-19 patients in an ICU in Vietnam.

## Methodology

*Study design and setting*

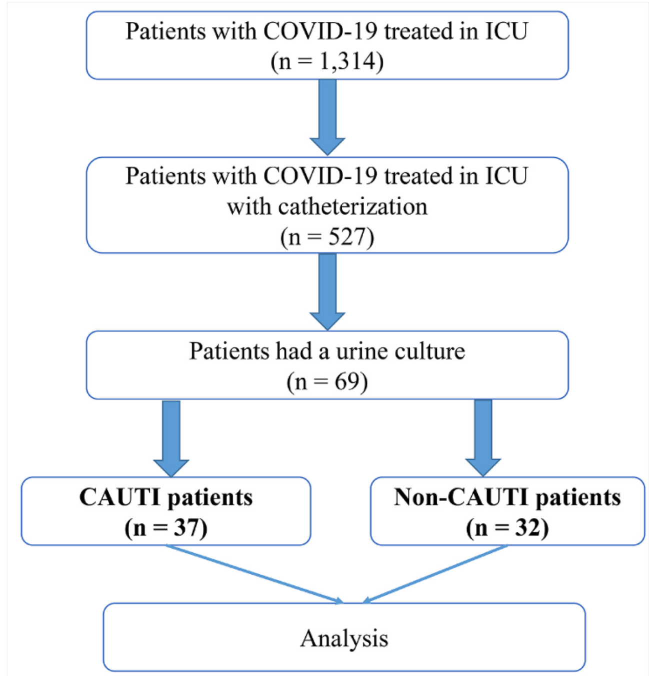
We conducted a cross-sectional study at the Bach Mai Hospital 16th Facility, which has a total of 2,300 beds, including 500 beds for the ICU, from August 1, 2021, to October 30, 2021. The hospital was urgently established in District 7, Ho Chi Minh City, Vietnam, in order to serve COVID-19 patients during the fourth outbreak in the south of Vietnam. The study was approved by the Bach Mai Hospital ethics committee (Ref. 3413).

The cohort consisted of 1,314 COVID-19 patients, as shown in Figure 1. Among 527 patients who required urinary catheters, 69 subjects were selected for urine culture following the Centers for Disease Control and Prevention (CDC) 2009 guidelines [10]. Among these, half were diagnosed with CAUTI (n = 37 cases). Subsequently, we collected the clinical information, microbiological characteristics, mortality, and outcomes of those 69 patients for this study.

*Patient selection*

The selected patients were aged ≥ 18 years with a confirmed diagnosis of COVID-19, admitted to the ICU of Bach Mai Hospital 16th Facility due to severe acute lung injury/acute respiratory distress syndrome (ARDS), and met the indication for bladder catheterization (Supplementary Table 1). We used two criteria for catheterization and urine culture in accordance with the CDC 2009 guidelines [10], which were selected to be appropriate for the ICU area (Supplementary Table 1). SARS-CoV-2 was confirmed using reverse transcriptase-polymerase chain reaction (RT-PCR) from a nasopharyngeal swab specimen of the respiratory tract, performed at standard testing facilities which were validated by the Vietnam Ministry of Health. Exclusion criteria included COVID-19 patients who died within the first 48 hours of admission to the ICU.

**Figure 1.** Overview of the patients in the COVID-19 cohort at the ICU of Bach Mai hospital.




CAUTI: catheter-associated urinary tract infection; COVID-19: coronavirus disease 2019; ICU: intensive care unit.

*Data collection and definition*

For all participants, we recorded demographic data including age, gender, and co-morbidities. We also recorded the time of catheterization, identified antibiotic resistance, information about the ICU admission including length of stay, results of paraclinical tests including serum and urine laboratory tests, antibiotics received, and microbiology tests results. Furthermore, the data on mortality and outcomes of patients were collected during their stay in the ICU. CAUTIs were diagnosed based on clinical practice recommendations of the European Urological Association (EUA) 2021 [11]; which includes UTIs that occur in a person whose urinary tract is currently catheterized or has had a catheter in place within the last 48 hours. UTIs were diagnosed according to the guidelines provided by the CDC [10]. Nosocomial CAUTI is defined as new bacteriuria or funguria and is identified with a count of more than $10^3$ CFUs/mL [12]. In this study, CAUTI was not checked at the time of ICU admission since all 69 cases did not undergo endotracheal intubation and urinary catheterization before they were admitted to the ICU.

Foley bladder catheters were used for all patients for whom catheterization was indicated. Patients requiring cystectomy were excluded from the study. The patients included in this study were the ones being treated in the ICU and had an indication for urinary catheterization. They were performed by ICU nurses and treated according to a unified procedure. The treatment procedure included fixing the catheter in the inner thigh for female patient, fixing urinary catheter in the pubic region for male patients, connecting to a standard collection bag, cleaning daily, and changing catheter after seven days. In this study, co-infections included pneumonia (following the 2016 Clinical Practice Guidelines of the Infectious Diseases Society of America and the American Thoracic Society [13]), blood infection (following the Third International Consensus Definitions for Sepsis and Septic Shock in 2016 [16]), and dengue fever.

*Sample collection and identification of microbial strains*

The urine specimens were collected, stored, and cultured according to the procedures of the Microbiology Department at Bach Mai Hospital. Particularly, urine samples were collected prior to administering antibiotic therapy. The drainage catheter was disinfected using 70% alcohol. Subsequently, approximately 10 mL of urine was aspirated using a needle, transferred to a sterile bottle, and the lid was tightly secured. The collected sample was promptly transported to the Microbiology Department. If immediate transfer to the laboratory was not possible, the samples were stored at temperatures between 2-8 ºC for up to 24 hours.

The urine specimens were then inoculated on Oxoid™ blood agar and Oxoid™ UTI agar. A loop filled with 10 µL of the urine sample was streaked onto both Blood agar and UTI agar plates. The plates were subsequently incubated at 37 ºC for a period of 24-48 hours.

On the following day, individual colonies with a quantity of at least $\geq 10^3$ CFU (for fungi) or $\geq 10^4$ CFU (for bacteria) were selected for identification [12]. Then, the isolates were identified using the VITEK 2 Compact system (BioMerieux, Marcy-l'Étoile, France).

*Statistical analysis*

The collected data were analyzed using SPSS version 16.0 [17]. Demographics and disease characteristics were described through appropriate descriptive statistics for (i) those with CAUTI, and (ii) those without CAUTI. Quanlitative variables were represented as a count (n) and a ratio (%). Quantitative variables were expressed as mean ± standard deviation. The comparison between CAUTI and non-CAUTI groups was conducted using Mann Whitney's non-parametric test for quantitative variables and Chi square or Fisher's test for qualitative variables. For qualitative variables, the Fisher's test was used if the number of cases less than five accounted for more than 20% of the cells; otherwise, the Chi square test was used. The results were statistically significant with $p < 0.05$. CAUTI rates (%) were defined at three levels: per 100 COVID-19 patients in the ICU with urinary catheters, per 100 COVID-19 patients in ICU (including both with and without urinary catheters), and per 1000 device-days. Survival analysis and Kaplan-Meier estimate was performed using R version 4.1.2 [18].

*Ethics considerations*

This study was approved by the ethics committee of Bach Mai Hospital (Ref. 3413). Patient consent was waived by the ethics committee for this study due to the utilization of retrospective data obtained from the hospital, which was established during the peak of the COVID-19 outbreak in Vietnam. Given the urgency of the situation, it was impractical to collect written informed consent from patients. This was because the personnel for administrative procedures in the ICU supporting this task were very limited due to the COVID-19 outbreak. In addition, it was almost impossible to get access to the patients for obtaining the consent because they were admitted in emergency situations. Furthermore, due to the very strict isolation policy in Vietnam at that time, no relatives were allowed to accompany the patients, and thus, the document could not be requested on their behalf. The identities of all patients were anonymized before any analysis to protect their personal information.

## Results

*Clinical characteristics of CAUTI in COVID-19 ICU*

The clinical characteristics of 69 subjects who underwent urine culture, out of 527 catheterized COVID-19 patients in the ICU, are shown in Table 1.

**Table 1.** Distribution of characteristics among CAUTI patients and non-CAUTI patients in the ICU for urine- cultured COVID-19 patients. *p* values with (*) indicates statistical significance ($p < 0.05$).

| Variables | All (n = 69) | CAUTI (n = 37) | Non-CAUTI (n = 32) | *p* |
|---|---|---|---|---|
| | N (%) | N (%) | N (%) | |
| **Clinical characteristics** | | | | |
| Age (Mean ± SD) | 61.3 ± 15.6 | 63.1 ± 15.4 | 59.2 ± 15.7 | 0.28 |
| **Gender** | | | | |
| Female | 41 (59.4) | 22 (59.5) | 19 (59.4) | 0.99 |
| Male | 28 (40.6) | 15 (40.5) | 13 (40.6) | |
| **Underlying diseases** | | | | |
| Diabetes Mellitus | 46 (66.7) | 28 (75.7) | 18 (56.2) | 0.09 |
| Hypertension | 44 (63.8) | 26 (70.3) | 18 (56.2) | 0.23 |
| Cardiovascular disease | 1 (1.4) | 1 (2.7) | 0 (0.0) | 1.00 |
| Chronic lung disease | 4 (5.8) | 1 (2.7) | 3 (9.4) | 0.33 |
| Chronic liver disease | 1 (1.4) | 1 (2.7) | 0 (0.0) | 1.00 |
| Chronic kidney disease | 2 (2.9) | 1 (2.7) | 1 (3.1) | 1.00 |
| Malignant disease Immunodeficiency | 0 (0.0) | 0 (0.0) | 0 (0.0) | X |
| Long-term corticosteroids | 0 (0.0) | 0 (0.0) | 0 (0.0) | X |
| Others | 29 (42.0) | 17 (45.9) | 12 (37.5) | 0.45 |
| Time of catheterization (Mean days ± SD) | 11.7 ± 10.4 | 13.2 ± 11.7 | 9.8 ± 8.4 | 0.21 |
| **Laboratory values on the first day of ICU** | | | | |
| **Serum laboratory test** | | | | |
| WBC, G/l | 13.3 ± 6.9 | 11.7 ± 5.3 | 15.2 ± 8.1 | 0.07 |
| NEU, % | 88.6 ± 7.2 | 86.9 ± 8.2 | 89.4 ± 5.8 | 0.25 |
| LYM, % | 6.6 ± 5.3 | 7.3 ± 6.2 | 5.7 ± 4.1 | 0.37 |
| PLT, G/l | 262.9 ± 148.9 | 246.5 ± 123.6 | 282.5 ± 174.6 | 0.51 |
| CRP, mg/dL | 9.4 ± 5.8 | 8.5 ± 5.4 | 10.3 ± 6.1 | 0.20 |
| PCT, ng/ml | 5.9 ± 17.2 | 7.7 ± 20.6 | 3.9 ± 12.4 | 0.18 |
| **Urine laboratory test** | | | | |
| uLEU, cell/ml | 32.8 ± 118.5 | 25.8 ± 99.9 | 39.6 ± 135.6 | 0.33 |
| Positive NIT | 2 (3.9) | 0 (0.0) | 2 (7.7) | 0.49 |
| uERY, cell/ml | 68.5 ± 82.8 | 69.9 ± 86.7 | 67.5 ± 80.5 | 0.96 |
| **Intervention in the ICU** | | | | |
| Hemodialysis | 32 (46.4) | 20 (54.1) | 12 (37.5) | 0.17 |
| Corticosteroids | 66 (95.7) | 36 (97.3) | 30 (93.8) | 0.59 |
| Mononuclear antibody | 1 (1.4) | 1 (2.7) | 0 (0.0) | 1.00 |
| Number of used antibiotics (Means ± SD) | 3.9 ± 1.5 | 3.9 ± 1.4 | 3.9 ± 1.6 | 0.89 |
| Combined anti-fungal | 15 (21.7) | 10 (27.0) | 5 (15.6) | 0.25 |
| Combined anti-virus | 25 (36.2) | 17 (45.9) | 8 (25.0) | 0.07 |
| **Co-infection** | | | | |
| Co-infection disease | 57 (82.6) | 32 (86.5) | 25 (78.1) | 0.36 |
| Superinfections pneumonia | 43 (62.3) | 27 (73.0) | 16 (50.0) | 0.05 |
| *Pseudomonas aeruginosa* | 18 (26.1) | 14 (37.8) | 4 (12.5) | 0.03 (*) |
| *Acinetobacter baumannii* | 18 (26.1) | 12 (32.4) | 6 (18.8) | 0.20 |
| *Klebsiella pneumoniae* | 16 (23.2) | 8 (21.6) | 8 (25.0) | 0.74 |
| *Staphylococcus aureus* | 1 (1.4) | 0 (0.0) | 1 (3.1) | 0.46 |
| *Stenotrophomonas maltophilia* | 1 (1.4) | 0 (0.0) | 1 (3.1) | 0.46 |
| *Escherichia coli* (*E. coli*) | 1 (1.4) | 1 (2.7) | 0 (0.0) | 1.00 |
| Sepsis | 32 (46.4) | 17 (45.9) | 15 (46.9) | 0.94 |
| *Klebsiella pneumoniae* | 12 (17.4) | 7 (18.9) | 3 (15.6) | 0.72 |
| *Acinetobacter baumannii* | 8 (11.6) | 6 (16.2) | 2 (6.2) | 0.27 |
| *Stenotrophomonas maltophilia* | 4 (5.8) | 1 (2.7) | 3 (9.4) | 0.33 |
| *Acinetobacter ursingii* | 3 (4.3) | 1 (2.7) | 2 (6.2) | 0.59 |
| *E. coli* | 2 (2.9) | 0 (0.0) | 2 (6.2) | 0.21 |
| *Enterococcus faecalis* | 2 (2.9) | 1 (2.7) | 1 (3.1) | 1.00 |
| *Enterococcus casseliflavus* | 1 (1.4) | 1 (2.7) | 0 (0.0) | 1.00 |
| *Staphylocccus hominis* | 1 (1.4) | 1 (2.7) | 0 (0.0) | 1.00 |
| *Salmonella sp.* | 1 (1.4) | 0 (0.0) | 1 (3.1) | 0.46 |
| *Pseudomonas aeruginosa* | 1 (1.4) | 0 (0.0) | 1 (3.1) | 0.46 |
| Dengue Fever | 14 (20.3) | 6 (16.2) | 8 (25.0) | 0.37 |
| **Outcome** | | | | |
| Non-survival | 52 (75.4) | 32 (86.5) | 20 (62.5) | **0.02** |
| ARDS | 44 (63.8) | 26 (70.3) | 18 (56.2) | 0.23 |
| Septic shock | 6 (8.7) | 3 (8.1) | 3 (9.4) | 1.00 |
| Cardiac arrest | 27 (39.1) | 16 (43.2) | 11 (34.4) | 0.45 |
| Multi-organ failure | 0 (0.0) | 0 (0.0) | 0 (0.0) | X |
| Others | 0 (0.0) | 0 (0.0) | 0 (0.0) | X |
| Being treated | 17 (24.6) | 5 (13.5) | 12 (37.5) | **0.02** |
| Length of stay in ICU (Mean days ± SD) | 14.6 ± 9.0 | 16.8 ± 7.2 | 11.8 ± 9.8 | **0.02** |

ARDS: acute respiratory distress syndrome; CAUTI: catheter-associated urinary tract infection; COVID-19: coronavirus disease 2019; CRP: C-reactive protein; ICU: intensive care unit; LYM: lymphocytes; NIT: nitrites; NEU: neutrophils; *p*: *p* value of the comparison between CAUTI and non-CAUTI groups; PCT: procalcitonin; PLT: platelets; uLEU: urine leukocytes; uERY: urine erythrocytes; WBC: white blood cell counts; X: not surveyed.

The CAUTI group had mean age of 63.1 ± 15.4 years and it was predominantly composed of females (59.5%). In the CAUTI group, diabetes was observed in 75.7% of cases, followed by hypertension with 70.5% of patients. In addition, the mean duration of catheterization in the CAUTI group was 13.2 ± 11.7 days, which was higher than that in the non-CAUTI group, but the difference was not statistically significant ($p = 0.21$).

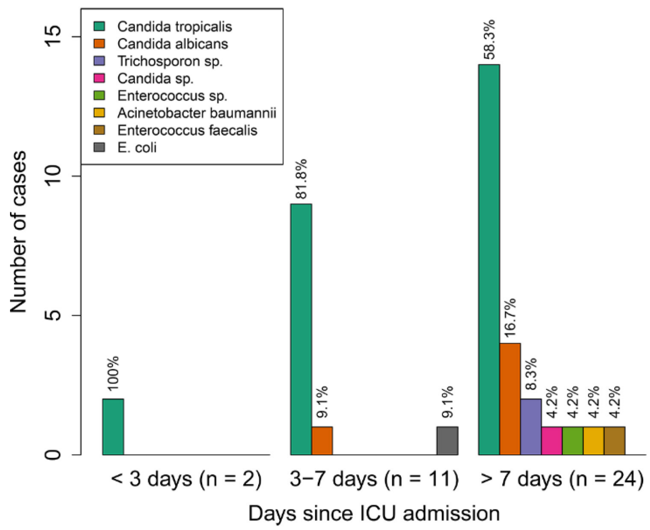
When investigating the laboratory values on the first day of ICU admission, we observed that the inflammation tests results for all 69 patients in the group showed mean values higher than the reference threshold used in the laboratory system at Bach Mai Hospital. These laboratory values included white blood cell count (WBC), C-reactive protein (CRP), procalcitonin (PCT), and urinalysis. However, no statistically significant differences were observed between CAUTI and non-CAUTI groups for any of these laboratory values ($p > 0.05$).

The study subjects were treated for COVID-19 with a variety of interventions (Table 1). We observed that all patients required mechanical ventilation, and most of them (95.7%) received corticosteroids. In the CAUTI group, 54.1% of subjects required hemodialysis support, and only one patient received a monoclonal antibody called Tocilizumab (Actemra®, U.S.). The *p* values for all comparisons were greater than 0.05, indicating that there were no significant differences between the CAUTI and non-CAUTI patients.

*Prevalence of CAUTI in COVID-19 ICU*

Overview of the patients included in the COVID-19 cohort of this study is presented in Figure 1. From August 2021 to October 2021, there were a total of 527 (40.1%) bladder catheterized participants out of 1,314 COVID-19 patients admitted in the ICU. Among these catheterized cases, 69 patients (13.1%) underwent a urine culture, which was the main focus of this study. Among these cases, CAUTI was detectable in 37 patients (7.0%), as shown in Table 2. During the 1,000-day catheterization service, the CAUTI incidence was 11.6%. Further details can be found in Table 2.

**Figure 2.** Distribution of catheter-associated urinary tract infections by time of detection after admission to the ICU.




The x-axis presents the distributions of microorganisms in three groups categorized by the time of detected CAUTI since ICU admission: < 3 days, 3-7 days, and > 7days. The y-axis of the bar plot presents the number of patients in each (group; microorganism) on the x-axis. The color of the bar indicates a microorganism in the top-left legend. The percentage on top of each bar is the proportion of the microorganism in its group. CAUTI: catheter-associated urinary tract infection; ICU: intensive care unit.

*Timing of CAUTI diagnosis*

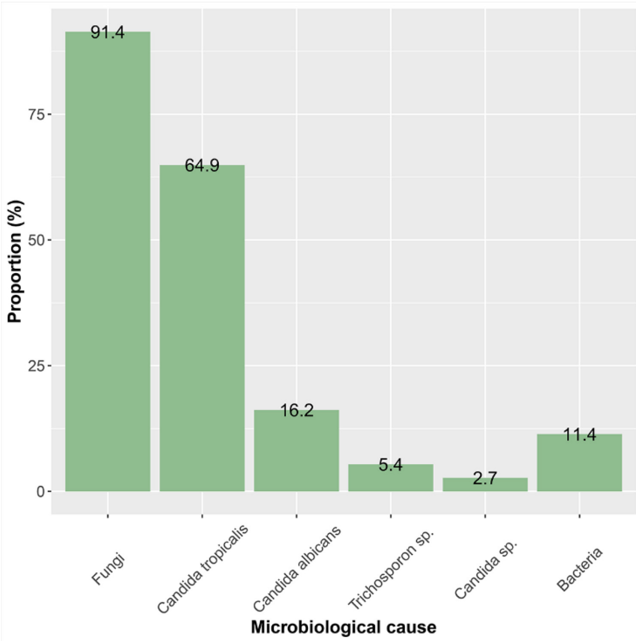
We categorized the time of detection of CAUTI since ICU admission into three groups: < 3 days, 3-7 days, and > 7 days (Figure 2). The figure shows that the majority of CAUTI cases were detected and diagnosed after seven days since ICU admission (64.9%, 24 out of 37 cases). Only two and 11 cases were detected very early (< 3 days and 2-7 days), respectively. Furthermore, the time of CAUTI diagnosis was also associated with the diversity of microorganisms of patients (Figure 2). In the group < 3 days, only *Candida tropicalis* was isolated in urine culture. The number of microorganisms (fungi and bacteria) increased to three

**Table 2.** Distribution of catheter-associated urinary tract infection (CAUTI) in ICU among COVID-19 patients. A total of 527 (40.1%) out of 1,314 COVID-19 patients required urethral catheterization.

| Patients with COVID-19 in ICU with catheterization | Number of patients (n = 527) |
|---|---|
| Cases had a urine culture | 69 (13.1%) |
| Cases had CAUTI | 37 (7.0%) |
| CAUTI/1000 days of catheterization | 11.6‰ |
| CAUTI/1000 days of stay | 8.7‰ |
| Total days of catheterization | 603 |
| Total number of days of treatment | 808 |
| Device utilization ratio | 74.6% |

COVID-19: coronavirus disease 2019; ICU: intensive care unit.

**Figure 3.** Microbiology of catheter-related urinary tract infections.




The x-axis presents the microorganism, and the y-axis indicates the proportion of the microorganism in the CAUTI patients. The number on top of each bar is the actual percentage value. CAUTI: catheter-associated urinary tract infection.

and seven for the groups of 3-7 days and > 7 days, respectively. Across all groups, *C. tropicalis* remained the most dominant microorganism.

*Microorganisms causing CAUTI and treatment in COVID-19 ICU*

The primary cause of CAUTI was fungi infections, (91.4%) (Figure 3). The most prevalent fungal species was *C. tropicalis*, accounting for 64.9% of cases; followed by *Candida albicans* (16.2% cases). *Trichosporon* sp. and *Candida* sp. were found in only a few cases, accounting for 5.4% and 2.7%, respectively. Among 37 CAUTI cases, only 27% (n = 10 patients) received combined antifungal drugs as a treatment for co-infection (Table 1). It is worth noting that these combined antifungal drugs were generally applied to COVID-19 patients. For this CAUTI group, an extra antifungal therapy was utilized for 68.8% of cases with fungal urine cultures. Bacterial causes were presented in only 11.4% of the culture cases.

Bacterial infections in CAUTI patients were found in only n = 4 culture cases (11.4%); one each of *Acinetobacter baumannii*, *Enterococcus* sp., *Enterococcus faecalis*, and *Escherichia coli*. All the bacterial CAUTI patients were treated with antibiotics (Supplementary Table 2). Among those, only one patient infected with *A. baumannii* showed multi-drug resistance. The remaining strains of bacteria were resistant to one or two groups of antibiotics but still sensitive to other antibiotic types. All four urinary isolates were found to be resistant to quinolone classes of antibiotics, including ciprofloxacin and levofloxacin. On the other hand, two culture cases showed sensitivity to colistin, linezolid, and tigecycline (Supplementary Table 2). Besides other treatments for COVID-19, each CAUTI patient received an average of 3.9 ± 1.4 antibiotics during their time in the ICU, the same as non-CAUTI group (see Table 1).

*Co-infection in CAUTI patients in the COVID-19 ICU*

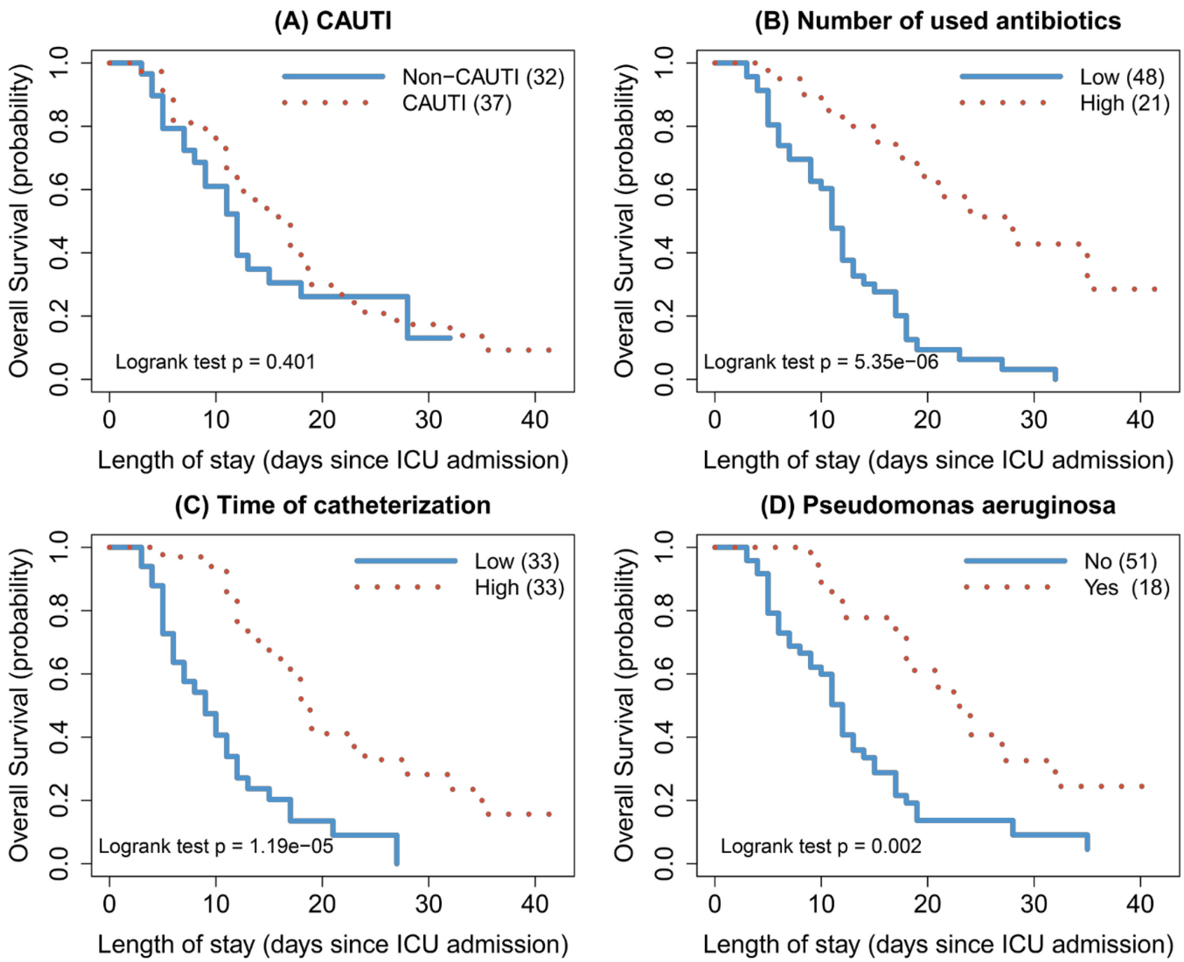
Co-infections, such as superinfections pneumonia and sepsis, were observed in the majority of COVID-19 cases in the ICU, as well as the CAUTI group (Table 1). Out of the 37 CAUTI cases, we recorded 32 cases of co-infection (85.6%), including 27 cases of superinfection pneumonia, 17 cases of sepsis, and 6 cases of dengue. Among the subtypes of co-infection, only *Pseudomonas aeruginosa* in superinfection pneumonia showed a statistically significant difference between the groups of CAUTI and non-CAUTI patients ($p = 0.03$).

The details of microbiological co-infections are described in Table 1. The most frequent bacterium among CAUTI patients with superinfection pneumonia was *P. aeruginosa* (37.8% of cases), followed by *A. baumannii* (32.4%), and *Klebsiella pneumoniae* (21.6%). Regarding sepsis, *K. pneumonia* was the most common cause, accounting for 18.9% of cases, followed by *A. baumannii* (16.2%). However, no significant differences in microbiological co-infections were found between CAUTI and non-CAUTI patients ($p > 0.05$).

*Mortality and survival time of CAUTI group in COVID-19 ICU*

The mortality rate was very high among COVID-19 patients with catheterization in the ICU, accounting for 52 patients (75.4%) (Table 1). The mortality in the CAUTI group (n = 32, 86.5%) was significantly higher than that in the non-CAUTI group (n = 20, 62.5%) ($p = 0.02$). In both groups, the main cause of death was ARDS, followed by cardiac arrest, and septic shock. However, there were no significant differences in the causes of death between the two groups ($p > 0.05$). Furthermore, the length of stay in the ICU was 1.4 times longer in the CAUTI group (16.8 ± 7.2 days) compared to the non-CAUTI group (11.8 ± 9.8 days), with *p* value of 0.02. The survival analysis (Figure 4A) showed a trend of longer survival time for the CAUTI group in the first 20 days. However, overall, CAUTI was not

**Figure 4.** Kaplan-Meier survival curves for association with the survival time in the ICU.




A: CAUTI groups; B: Number of used antibiotics; C: Time of catheterization; and D: *Pseudomonas aeruginosa*.
In each panel, the x-axis presents the length of stay since ICU admission (days), while y-axis indicates the overall survival. The number in the parentheses after each group name refers to the number of patients in the group. CAUTI: catheter-associated urinary tract infection; ICU: intensive care unit.

strongly associated with survival time in the ICU ($p$ = 0.4).

We further investigated survival time in the ICU by using individual variables in Table 1. For the quantitative variables, we separated patients into two groups by the median: high (> median) and low (≤ median). $p$ values were used to compute false discovery rate (FDR) using the Benjamini-Hochberg procedure. As a result, we identified three features with FDR < 0.05, including number of used antibiotics (FDR = 0.0018), time of catheterization (FDR = 0.0020), and *P. aeruginosa* (FDR = 0.0219). Figure 4B showed that patients using more antibiotics were strongly associated with the long survival time in the ICU ($p$ = 5.35e-06). A similar result was observed for time of catheterization ($p$ = 1.19e-05) (Figure 4C). Finally, patients with *P. aeruginosa* exhibited better survival time in the ICU ($p$ = 0.002), especially within the first 20 days (Figure 4D).

## Discussion

We analyzed CAUTI in critically ill COVID-19 patients in the ICU during the fourth outbreak in South Vietnam in the middle of 2021. We described the clinical characteristics of CAUTI in COVID-19 ICU patients in Vietnam. We also performed a comparative analysis between CAUTI and non-CAUTI groups of COVID-19 patients which collectively considered multiple aspects, including clinical characteristics, laboratory test values on the first day of ICU, intervention in the ICU, co-infection with microbiological characteristics, and outcome. In addition, the study explored the association of those characteristics with the survival time of the COVID-19 patients in ICU.

In this study, there were 37 CAUTI cases, which included 7% of catheterized COVID-19 individuals or 2.8% of the entire cohort, with a CAUTI rate of 8.7‰ per 1,000 days of stay. Different rates of CAUTI have been reported in different studies on co-infections in COVID-19 ICU. For example, in the single-center prospective descriptive study of 83 COVID-19 patients in a Spanish ICU, Soriano *et al.* reported a CAUTI rate of 38.55% and a rate of 17.18‰ per 1000 device-days [1]. However, in another study [3], Ong *et al.* recorded a lower incidence with 4 out of 71 cases (5.6%) of CAUTI-related COVID-19 in the ICU, with 7.24‰ per 1000 device-days. The differences in the incidence of CAUTI between studies may be due to several factors. It can be that the catheterization rate and catheterization device utilization ratio were different between studies. For example, these rates and ratios in the study by Ong *et al.* (59% and 76.3%) [3] were higher compared to the values in Table 1 (40.1% and 74.6%). Furthermore, regional differences in the incidence of infectious diseases were related to the empirical use of antibiotics for patients with COVID-19 in each region [4,15]. In our study, the rate of combined antibiotic usage was 100%, but in the study by Ong *et al*., only 90% reported antibiotic use [3]. Soriano *et al.* also reported similar explanations for the differences in their results compared to previous studies [1].

The average age of CAUTI cases in this study was similar to the studies on co-morbid infections in ICU units, which were reported to be between 60 and 70 years [3,4]. In contrast to the results from some studies in western countries [1,3,4], the CAUTI cases in this study were dominated by females. However, this observation was consistent with the gender distribution of COVID-19 patients from other epidemiological reports from Vietnam [16,19].

The urine-cultured COVID-19 patients in this study had most common underlying medical conditions, including diabetes and hypertension, which were similar to the results of some recent studies [1,3,4]. At Bach Mai ICU, the rate of using high-tech interventions such as hemodialysis (46.4%), antinuclear antibodies like Tocilizumab (1.4%), and antiviral therapy (36.2%) was lower compared to the rates reported in Europe. For example, in the study of Soriano *et al*., Tocilizumab and antiviral therapy were used up to 60.2% and 85.5%, respectively [1].

We observed that the most common cause of CAUTI in this cohort was fungi, dominated by *C. tropicalis*. We reasoned that the use of corticosteroids and mononuclear antibodies for treatment in the majority of patients (> 95%) allows suppressing the immune system, consequently increasing the risk of fungal infection. ICU is the last unit to provide treatment for critically ill patients and we recorded COVID-19 patients entering the ICU with bacterial infections. As a result, most patients with CAUTI who had fungal infections were treated with antibiotics and corticosteroids. Similar results were found in the report of most fungal superinfections in COVID-19 patients in the study by Chen *et al.* [20]. During the pandemic, there was evidence of the proliferation of fungal superinfections in various organs. Indeed, the use of broad-spectrum antibiotics, steroids, prolonged ICU stay, and multiple invasive devices, as well as the high prevalence of diabetes, played a significant role in the development trend of fungal superinfections [20,21]. However, the number of cases from which bacteria were isolated in this study was only four, and all of them were Gram negative. This result was opposite to the statistics prior to the COVID-19 pandemic, in which several reports demonstrated a higher prevalence of bacterial infections compared to fungi infections for CAUTIs in the ICU. For example, the study by Dan Peng *et al.* highlighted that Gram-negative bacteria accounted for 47.46% of the causes of CAUTI in the ICU, which was higher than the prevalence of fungi (27.81%) [22].

The high co-infection rate of CAUTI cases in this study was also consistent with the results of a recent study [3]. We found that *P. aeruginosa* was the main cause of pneumonia superinfections; which was similar to the research conducted by Tommaso *et al.* on hospital-acquired and ventilator-acquired pneumonia in Spain [8]. *A. baumannii* was also commonly found in pneumonia superinfections in this cohort; however, it was found in less than 5% of cases in the retrospective cohort study on pulmonary superinfection by Baskaran *et al.* from a multicenter ICU in UK [4]. The study also reported *K. pneumonia* as the main cause for sepsis, as we observed here.

The overall mortality rate in this cohort of COVID-19 subjects with ICU catheterization was high at 75.4%, which was consistent with the study on co-infection in COVID-19 patients by Soriano *et al*. [1]. When investigating the survival time of COVID-19 patients in the ICU, we identified a strong association between the number of used antibiotics and the survival time in the ICU. Similarly, significant results (FDR < 0.05) were discovered for lengths of catheterization and *P. aeruginosa*. There was a close association between these factors. A longer time in ICU possibly increased the risk of co-infections; herein *P. aeruginosa* was the most prevalent in this study. Thus, this in turn led to the increased use of antibiotics for treatment. On the other hand, using more antibiotics was also able to prolong the time in ICU. When considering the duration of catheterization, the patients with the longer survival time in the ICU would require catheters for a longer time. We also did not observe a significant association between CAUTI and the patients' survival time in the ICU.

## Conclusions

This study had several limitations. First, the sample sizes of both the CAUTI and non-CAUTI groups were small, which limited the power of the statistical tests. As a result, we only identified a few significant factors for differentiating the CAUTI group from the non-CAUTI group. However, increasing the number of patients with indicated urine culture was not practical in this ICU. Second, since this study focused on the CAUTI and non-CAUTI groups, the analysis did not utilize the available data from all 1,314 patients treated in the ICU. Extending this study to utilize more data from the cohort would be a future work. Third, in microbiology diagnostics, we observed one *Candida* isolate for which the VITEK 2 compact system suggested three possible species of *Candida*, but none with high confidence. Unfortunately, no additional experiments such as next-generation-sequencing were performed for further investigation. This was due to the limited access of the field hospital during the COVID-19 outbreak in Vietnam. Therefore, we used genus instead of species information for this case. Similar observation was made in one isolate each of *Trichosporon* and *Enterococcus*. However, the overall results of this study were not significantly affected by the issue. Finally, the study was based on a single ICU, which may not be representative for all ICU systems in Vietnam. However, this was beyond the scope of this study.

## Acknowledgements

The authors acknowledge all participating patients and the Bach Mai Hospital 16th Facility for supporting this study. We also acknowledge all staff in the COVID-19 unit for help with data collection.

## References

1. Soriano MC, Vaquero C, Ortiz-Fernández A, Caballero A, Blandino-Ortiz A, de Pablo R (2021) Low incidence of co-infection, but high incidence of ICU-acquired infections in critically ill patients with COVID-19. J Infect 82: e20–e21. doi: 10.1016/j.jinf.2020.09.010.
2. Garcia-Vidal C, Sanjuan G, Moreno-García E, Puerta-Alcalde P, Garcia-Pouton N, Chumbita M, Fernandez-Pittol M, Pitart C, Inciarte A, Bodro M, Morata L, Ambrosioni J, Grafia I, Meira F, Macaya I, Cardozo C, Casals C, Tellez A, Castro P, Marco F, García F, Mensa J, Martínez JA, Soriano A (2021) Incidence of co-infections and superinfections in hospitalized patients with COVID-19: a retrospective cohort study. Clin Microbiol Infect 27: 83–88. doi: 10.1016/j.cmi.2020.07.041.
3. Ong CCH, Farhanah S, Linn KZ, Tang YW, Poon CY Lim AY, Tan HR, Binte Hamed NH, Huan X, Puah SH, Ho BCH, Soon MML, Ang BSP, Vasoo S, Chan M, Leo YS, Ng OT, Marimuthu K (2021) Nosocomial infections among COVID-19 patients: an analysis of intensive care unit surveillance data. Antimicrob Resist Infect Control 10: 119. doi: 10.1186/s13756-021-00988-7.
4. Baskaran V, Lawrence H, Lansbury LE, Webb K, Safavi S, Lim AY, Tan HR, Binte Hamed NH, Huan X, Puah SH, Ho BCH, Soon MML, Ang BSP, Vasoo S, Chan M, Leo YS, Ng OT, Marimuthu K Zainuddin NI, Huq T, Eggleston C, Ellis J, Thakker C, Charles B, Boyd S, Williams T, Phillips C, Redmore E, Platt S, Hamilton E, Barr A, Venyo L, Wilson P, Bewick T, Daniel P, Dark P, Jeans AR, McCanny J, Edgeworth JD, Llewelyn MJ, Schmid ML, McKeever TM, Beed M, Lim WS (2021) Co-infection in critically ill patients with COVID-19: an observational cohort study from England. J Med Microbiol 70: 001350. doi: 10.1099/jmm.0.001350.
5. Xu B, Fan C-Y, Wang A-L, Zou Y-L, Yu Y-H, He C, Xia W-G, Zhang J-X, Miao Q (2020) Suppressed T cell-mediated immunity in patients with COVID-19: a clinical retrospective study in Wuhan, China. J Infect 81: e51–e60. doi: 10.1016/j.jinf.2020.04.012.
6. Tedja R, Wentink J, O'Horo JC, Thompson R, Sampathkumar P (2015) Catheter-associated urinary tract infections in intensive care unit patients. Infect Control Hosp Epidemiol 36: 1330–1334. doi: 10.1017/ice.2015.172.
7. Parker V, Giles M, Graham L, Suthers B, Watts W, O'Brien T, Searles A (2017) Avoiding inappropriate urinary catheter use and catheter-associated urinary tract infection (CAUTI): a pre-post control intervention study. BMC Health Serv Res 17: 314. doi: 10.1186/s12913-017-2268-2.
8. Bardi T, Pintado V, Gomez-Rojo M, Escudero-Sanchez R, Azzam Lopez A, Diez-Remesal Y, Martinez Castro N, Ruiz-Garbajosa P, Pestaña D (2021) Nosocomial infections associated to COVID-19 in the intensive care unit: clinical characteristics and outcome. Eur J Clin Microbiol Infect Dis 40: 495–502. doi: 10.1007/s10096-020-04142-w.
9. Díaz Pollán B, Guedez López GV, García Clemente PM, Jiménez González M, García Bujalance S, Gómez-Gil Mirá MR (2022) Urinary tract infections in hospitalized COVID-19 patients, what's up, doc? J Clin Med 11: 1815. doi: 10.3390/jcm11071815.
10. Gould CV, Umscheid CA, Agarwal RK, Kuntz G, Pegues DA, Healthcare Infection Control Practices Advisory Committee (2010) Guideline for prevention of catheter-associated urinary tract infections 2009. Infect Control Hosp Epidemiol 31: 319–326. doi: 10.1086/651091.

11. Bonkat G, Bartoletti R, Bruyère F, Cai T, Geerlings SE, Köves B, Schubert S, Wagenlehner F (nd) EAU guidelines: urological infections. Available: https://uroweb.org/guideline/urological-infections/. Accessed: 3 March 2022.
12. Tambyah PA, Maki DG (2000) Catheter-associated urinary tract infection is rarely symptomatic: a prospective study of 1497 catheterized patients. Arch Intern Med 160: 678–682. doi: 10.1001/archinte.160.5.678.
13. Kalil AC, Metersky ML, Klompas M, Muscedere J, Sweeney DA, Palmer LB, Napolitano LM, O'Grady NP, Bartlett JG, Carratalà J, El Solh AA, Ewig S, Fey PD, File TM, Restrepo MI, Roberts JA, Waterer GW, Cruse P, Knight SL, Brozek JL (2016) Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 clinical practice guidelines by the Infectious Diseases Society of America and the American Thoracic Society. Clin Infect Dis 63: e61–e111. doi: 10.1093/cid/ciw353.
14. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, Bellomo R, Bernard GR, Chiche J-D, Coopersmith CM, Hotchkiss RS, Levy MM, Marshall JC, Martin GS, Opal SM, Rubenfeld GD, van der Poll T, Vincent J-L, Angus DC (2016) The third international consensus definitions for sepsis and septic shock (sepsis-3). JAMA 315: 801–810. doi: 10.1001/jama.2016.0287.
15. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, Qiu Y, Wang J, Liu Y, Wei Y, Xia J, Yu T, Zhang X, Zhang L (2020) Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 395: 507–513. doi: 10.1016/S0140-6736(20)30211-7.
16. Hoang VM, Hoang HH, Khuong QL, La NQ, Tran TTH (2020) Describing the pattern of the COVID-19 epidemic in Vietnam. Glob Health Action 13: 1776526. doi: 10.1080/16549716.2020.1776526.
17. SPSS Inc. Released 2007. SPSS for Windows, Version 16.0. Chicago, SPSS Inc.
18. R Core Team (2023) R: a language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. Available: https://www.R-project.org/.
19. Van Nguyen Q, Cao DA, Nghiem SH (2021) Spread of COVID-19 and policy responses in Vietnam: an overview. Int J Infect Dis 103: 157–161. doi: 10.1016/j.ijid.2020.11.154.
20. Chen X, Liao B, Cheng L, Peng X, Xu X, Li Y, Hu T, Li J, Zhou X, Ren B (2020) The microbial coinfection in COVID-19. Appl Microbiol Biotechnol 104: 7777–7785. doi: 10.1007/s00253-020-10814-6.
21. Roudbary M, Kumar S, Kumar A, Černáková L, Nikoomanesh F, Rodrigues CF (2021) Overview on the prevalence of fungal infections, immune response, and microbiome role in COVID-19 Patients. J Fungi (Basel) 7: 720. doi: 10.3390/jof7090720.
22. Peng D, Li X, Liu P, Luo M, Chen S, Su K, Zhang Z, He Q, Qiu J, Li Y (2018) Epidemiology of pathogens and antimicrobial resistance of catheter-associated urinary tract infections in intensive care units: a systematic review and meta-analysis. Am J Infect Control 46: e81–e90. doi: 10.1016/j.ajic.2018.07.012.

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**Conflict of interests:** No conflict of interests is declared.

## Annex – Supplementary Items

**Supplementary Table 1.** The standards for catheterization and urine culture criteria.

| Standards for catheterization | Urine culture criteria |
|---|---|
| – Acute urinary retention or bladder outlet obstruction<br>– Accurate measurement of urine output is required in critically ill patients<br>– Preoperative use for selected surgical procedures<br>– Urinary incontinence when there is an open wound on the perineum or sacrum<br>– Patient needs immobilization for any reason<br>– Improved comfort for hospice | – Evaluate new fever<br>– Pregnant women<br>– Decrease in neutrophils<br>– After urological procedure/surgery<br>– Kidney transplant patients<br>– In patients with known urinary tract obstruction or stents in the urinary system<br>– Unexplained lower quadrant or lower back pain<br>– Spinal cord injury patient with new or worsening spasticity, autonomic hyperreflexia, irritability, coma, or malaise. |

**Supplementary Table 2**. Antibiotic resistance of CAUTI microorganism in COVID-19 ICU.

| | ***Acinetobacter baumannii*** | ***Enterococcus sp*** | ***Enterococcus faecalis*** | ***E. coli*** |
|---|---|---|---|---|
| **Multi-drugs resistance** | Yes | No | No | No |
| **Antibiotics** | | | | |
| Amikacin | | | | S |
| Amoxicillin + Clavulanic acid | | | | |
| Ceftazidime | R | | | S |
| Ciprofloxacin | R | R | R | R |
| Gentamycin | R | | | S |
| Colistin | S | | | S |
| Linezolid | | S | S | |
| Vancomycin | | S | R | |
| Tigercycline | | S | S | |
| Ertapenem | | | | |
| Cefepime | R | | | S |
| Fosfomycin | | | | |
| Imipenem | R | | | S |
| Levofloxaxin | R | R | R | I |
| Meropenem | R | | | S |
| Trimethoprim-sulfamethoxazole | R | | | R |
| Piperacillin + Tazobactam | R | | | |

R: resistant; S: susceptible; I: intermediate; CAUTI: catheter-associated urinary tract infection; COVID-19: coronavirus disease 2019; ICU: intensive care unit.