OBSERVATIONAL STUDY

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Early Bacterial Coinfections in Patients Admitted to the ICU With COVID-19 or Influenza: A Retrospective Cohort Study

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IMPORTANCE: Previous findings suggest that bacterial coinfections are less common in ICU patients with COVID-19 than with influenza, but evidence is limited.

OBJECTIVES: This study aimed to compare the rate of early bacterial coinfections in ICU patients with COVID-19 or influenza.

DESIGN, SETTING AND PARTICIPANTS: Retrospective propensity score matched cohort study. We included patients admitted to ICUs of a single academic center with COVID-19 or influenza (January 2015 to April 2022).

MAIN OUTCOMES AND MEASURES: The primary outcome was early bacterial coinfection (i.e., positive blood or respiratory culture within 2 d of ICU admission) in the propensity score matched cohort. Key secondary outcomes included frequency of early microbiological testing, antibiotic use, and 30-day all-cause mortality.

RESULTS: Out of 289 patients with COVID-19 and 39 patients with influenza, 117 ($n = 78$ vs 39) were included in the matched analysis. In the matched cohort, the rate of early bacterial coinfections was similar between COVID-19 and influenza (18/78 [23%] vs 8/39 [21%]; odds ratio, 1.16; 95% CI, 0.42–3.45; $p = 0.82$). The frequency of early microbiological testing and antibiotic use was similar between the two groups. Within the overall COVID-19 group, early bacterial coinfections were associated with a statistically significant increase in 30-day all-cause mortality (21/68 [30.9%] vs 40/221 [18.1%]; hazard ratio, 1.84; 95% CI, 1.01–3.32).

CONCLUSIONS AND RELEVANCE: Our data suggest similar rates of early bacterial coinfections in ICU patients with COVID-19 and influenza. In addition, early bacterial coinfections were significantly associated with an increased 30-day mortality in patients with COVID-19.

KEY WORDS: bacterial superinfection; COVID-19; flu; intensive care unit; pneumonia; severe acute respiratory syndrome coronavirus 2

Bacterial coinfections in patients with viral diseases complicate treatment and worsen prognosis (1, 2). In severe influenza cases, bacterial coinfections or secondary infections are identified in 15–30% of patients and are associated with increased morbidity and mortality (3–6). Due to the lack of data on the prevalence of bacterial pathogens in COVID-19 patients, several guidelines rely on the extrapolation of data from other viral pneumonias such as influenza (7).

Previous attempts to determine the frequency of bacterial coinfections in critically ill COVID-19 patients have yielded controversial results (8–12). This may be due, in part, to regional differences and varying microbiologic sampling practices between COVID-19 and influenza patients and between study

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KEY POINTS

Question: How common are early bacterial coinfections (identified within 48 hr of admission) in ICU patients with COVID-19 compared with influenza?

Findings: In this retrospective propensity score matched cohort study, the rate of early bacterial coinfections was similar between COVID-19 (18/78 [23%]) and influenza (8/39 [21%]).

Meaning: In contrast to previous literature, the rate early bacterial coinfections was similar in critically ill COVID-19 and influenza patients.

sites. In these studies, the prevalence of bacterial coinfections in critically ill patients with COVID-19 was found to be lower than in those with influenza (10). However, these results may underestimate the true prevalence of coinfections in COVID-19 due biased testing strategies, as reported by Musher (13).

To date, few studies have examined the microbiologic spectrum of early (≤ 48 hr of ICU admission) bacterial coinfections in patients with severe COVID-19, and only two have compared the spectrum and prevalence in patients with severe COVID-19 versus influenza (10, 12). To address this uncertainty, the present study examined the prevalence of early microbiologically confirmed coinfections in COVID-19 and influenza patients admitted to the ICU. In addition, we compared the 30-day mortality between COVID-19 and influenza with and without early bacterial coinfections.

MATERIALS AND METHODS

Study Design and Setting

This retrospective observational cohort study was conducted at a single European study center (Vienna General Hospital, Vienna, Austria). The study was performed in accordance with the principles embodied by the Declaration of Helsinki. Ethics approval was obtained from the local Ethics Committee (Ethics Committee of the Medical University of Vienna) before the start of the study (EC 2259/2021, project title: "Comparison of Bacterial Co-Infections in Patients Hospitalized with Covid-19 Versus Influenza: A Retrospective Cohort Study," date of approval: February 24, 2022). All data were automatically extracted from electronic medical records. Implausible or missing data were checked manually. Reporting of this observational study was performed according to the Strengthening the Reporting of Observational Studies in Epidemiology recommendations (14).

Study Population

We included all patients, who were hospitalized and admitted to the ICU with either COVID-19 or influenza, both defined by a positive polymerase chain reaction test during hospitalization. COVID-19 cases were included through April 2022. Influenza cases were included in reverse chronological order starting from April 2022 until the predetermined sample size ($n = 39$) was obtained (January 2015). Patients younger than 18 years old were excluded. We also excluded patients who were transferred from other hospitals to our institution to avoid misclassification of early bacterial coinfections.

Microbiological Definitions

The microbiological definitions of early bacterial coinfections were consistent with those of the International Severe Acute Respiratory and Emerging Infections Consortium WHO Clinical Characterisation Protocol UK study (8) and the study by Rouzé et al (10). Early bacterial coinfections related to COVID-19 or influenza were defined by positive cultures from respiratory samples and blood, or a positive urinary antigen test for *Legionella pneumophila* or *Streptococcus pneumoniae*. Respiratory specimens included bronchoalveolar lavage (BAL) samples, endotracheal aspirates, and sputum. Microbiological findings from samples obtained more than 2 days after ICU admission were interpreted as secondary infections and were not included in the analysis. Similar to the two aforementioned studies, we excluded fungal pathogens and *Staphylococci* other than *Staphylococcus aureus* and *Staphylococcus lugdunensis*, which often result from contamination or apathogenic colonization. Furthermore, commensal skin bacteria (i.e., *Cutibacterium* and *Corynebacterium* species) were excluded from blood cultures.

Outcome Parameters

The primary outcome of this study was confirmed early bacterial coinfection, a composite endpoint that

included either a positive blood or respiratory culture within the first 2 days after ICU admission in the propensity score matched cohort. Secondary outcomes included the frequency of early bacterial coinfections in the unmatched cohort, the distribution and prevalence of pathogens, results from routine antimicrobial susceptibility testing (AST), 30-day all-cause mortality, duration of ventilation, length of ICU stay, and descriptive analysis of the microbiological samples. Results from the AST were only reported for COVID-19 cases, due to a limited number of identified pathogens in the influenza group. The frequency of microbiological sampling was determined for both groups, as higher sampling frequencies may increase the detection of coinfections. We also assessed the use of antibiotics and immunosuppressive medication in the first 2 days of ICU admission (i.e., during the microbiological sampling period). Corticosteroid dosing was converted to dexamethasone equivalents according to Liu et al (15) and classified as high dose (≥ 10 mg/d) and low dose (< 10 mg/d).

Statistical Analysis

Baseline characteristics are reported descriptively with mean ± SD or *n* (%) and were compared using the independent *t* test (age, weight, height, and body mass index [BMI]) or chi-square test (sex and chronic diseases). The frequency of early bacterial coinfections between the two groups (i.e., the primary outcome) was compared with the Fisher exact test. In a time-to-event analysis, hazard ratios (HRs) with 95% CI for the 30-day all-cause mortality from ICU admission were calculated using the Mantel-Haenszel method. Antibiotic use and pathogen distribution and prevalence were reported descriptively. Sensitivity analyses included the comparisons of sampling and coinfection rates between the first and second half of influenza cases, first and second half of COVID-19 cases, and between the COVID-19 variants. We also performed a sensitivity analysis for the primary outcome in the matched cohort within the subgroup of patients admitted to the ICU either via the emergency department or the normal ward, the subgroup of patients who received antibiotics before ICU admission, and the subgroup of patients who received steroids prior to ICU admission. The statistical analysis and visualization were performed using Rstudio interface (Version 2021.09.2, RStudio, Boston, MA) and GraphPad Prism (Version 9.3.1; GraphPad Software, Boston, MA).

Propensity Score Matching

To adjust for confounding, propensity score matching was performed using the R package "MatchIt" (Version 4.4.0) (16). Propensity scores were estimated by logistic regression. COVID-19 cases were matched to influenza cases in a 2:1 ratio with the optimal pair matching method. The included covariates were age, sex, and relevant baseline diseases that may interfere with the study outcomes (i.e., diabetes mellitus, cardiovascular diseases, chronic obstructive pulmonary disease, and chronic kidney disease). Antibiotic use, weight, height, and BMI was adequately balanced after matching, without being explicitly included as covariates. After matching, all baseline diseases had a standardized mean difference below 0.1, indicating a sufficient balance between the two groups (data not shown) (17).

Sample Size

Our sample size calculations were based on the findings of Rouzé et al (10), who found early bacterial coinfections in 9.7% of COVID-19 patients and 33.6% of influenza patients in the ICU setting. We considered this absolute risk difference of approximately 20% to be a clinically important difference and calculated the sample size accordingly. The primary objective was the detection of this difference in the propensity score matched cohort. Because there were more COVID-19 cases than influenza cases, we performed matching at a ratio of 2:1 to obtain greater statistical power without including influenza cases whose observation period was too far in the past. Based on these assumptions, a total sample size of 117 cases matched at a 2:1 ratio (n = 78 vs 39) provided an 80% power to detect a statistically significant group difference with the Fisher exact test at a two-sided alpha of 0.05. We included all available influenza cases in reverse chronological order starting from April 2022 until we reached 39 cases. These 39 influenza cases were then matched at a 2:1 ratio to the total sample of available COVID-19 cases (n = 289).

RESULTS

Study Population

To obtain the prespecified number of influenza cases (n = 39), we included patients in reverse chronological order from the most recent influenza case until January 2015

(**Fig. 1**). Between January 2015 and April 2022, 263 influenza cases were identified, of which 39 were admitted to the ICU and eligible for analysis. We included all available COVID-19 patients at our study site between January 2020 and April 2022 (n = 1,378). We excluded transferred patients and patients younger than 18 years old. The final analysis set consisted of 289 COVID-19 and 39 influenza cases.

Table S1 (http://links.lww.com/CCX/B171) shows the baseline characteristics of the total study population before and after propensity score matching. The COVID-19 group was younger (55.8 ± 15.5 vs 58.6 ± 17.5 yr) and had higher proportion of male patients than the influenza group (66.8% vs 53.8%). Overall, the influenza group had more comorbidities than the COVID-19 group, with significantly higher rates of diabetes mellitus, cardiovascular diseases, digestive disorders, chronic kidney diseases, and neurologic disorders (Table S1, http://links.lww.com/CCX/B171).

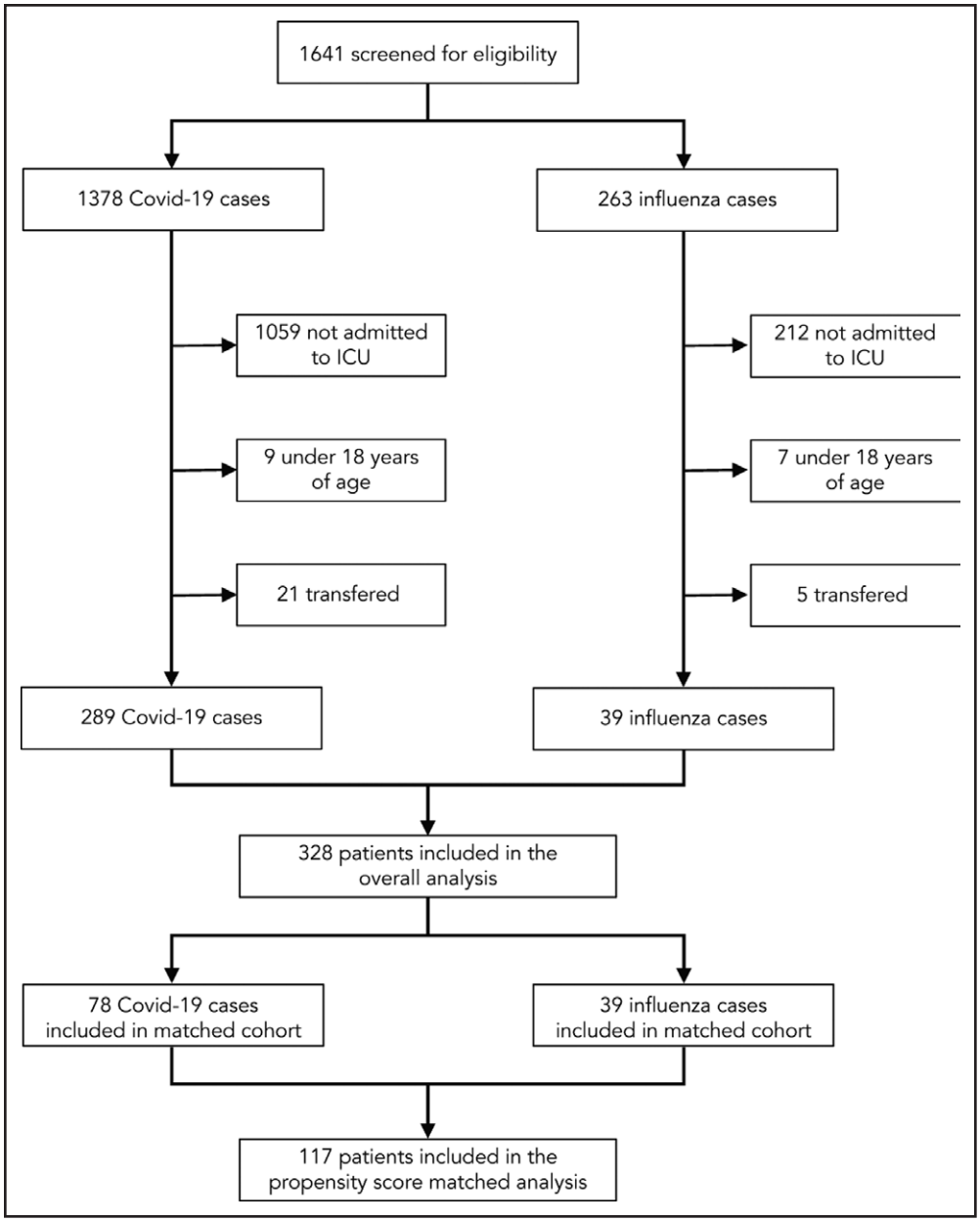

Figure 1. Flow chart of study population.

Of the 39 influenza cases, 33 (84.6%) were caused by influenza virus A and 6 (15.4%) were caused by influenza virus B. Of the 289 COVID-19 cases, 57 (19.7%) were caused by the wild-type virus, 128 (44.3%) by the alpha variant, and 68 (23.5%) by the delta variant. Thirty-six cases (12.5%) were not sequenced.

Propensity Score Matching

Propensity score matching was performed in a 2:1 ratio (n = 78 vs 39) using age, sex, and diagnoses of cardiovascular disease, diabetes mellitus, chronic obstructive pulmonary disease, and chronic kidney disease as covariates. Table S1 (http://links.lww.com/CCX/B171) shows the baseline characteristics after matching. All included covariates were well balanced between the two groups after propensity score matching.

Early Bacterial Coinfections

Figure 2 compares the frequency of early (within 2 d of ICU admission) microbiological testing and coinfections between the two groups. In the matched cohort, the frequency of early microbiological testing and

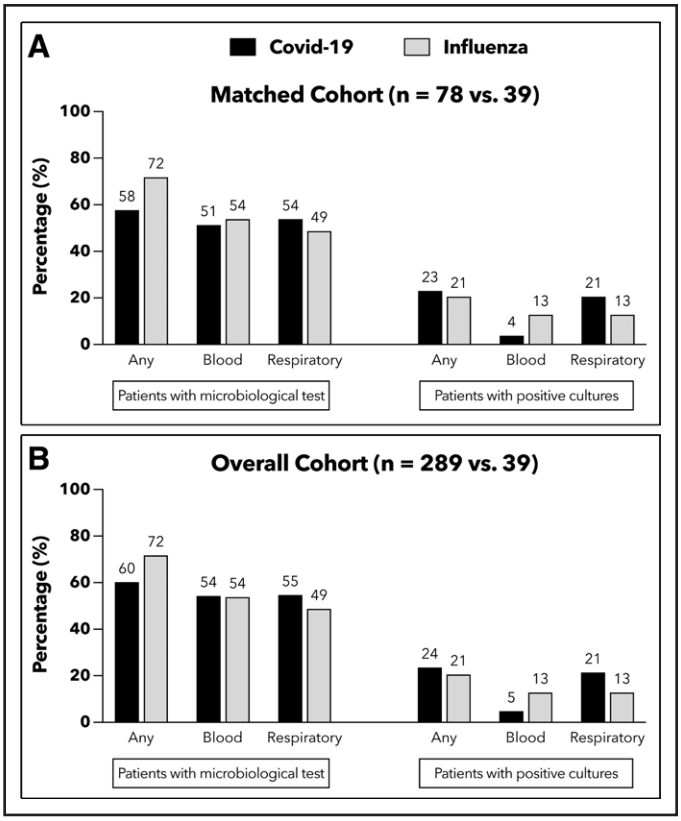

Figure 2. Frequency of early microbiological testing and identification of bacterial pathogens. **A**, Propensity score matched cohort **B**, Unmatched cohort.

frequency of bacterial coinfections were similar between the groups. Early microbiological testing (blood and/or respiratory) was performed in 45 of 78 patients (58%) with COVID-19 and in 28 of 39 patients (72%) with influenza (odds ratio [OR], 0.54; 95% CI, 0.21–1.31; $p = 0.16$) (**Fig. 2*A***). Furthermore, the relative frequency of any early coinfection was similar between the COVID-19 and influenza group (18/78 [23%] vs 8/39 [21%]; OR, 1.16; 95% CI, 0.42–3.45; $p = 0.82$) (**Fig. 2*B***). Of the patients with at least one microbiological sample, 18 of 45 COVID 19 patients (40%) and seven of 28 influenza patients (25%) had at least one positive culture (OR, 1.98; 95% CI, 0.64–6.71; $p = 0.215$).

In the unmatched cohort, the frequency of early microbiological testing was similar, with numerically fewer samples (blood and/or respiratory) in the COVID-19 group than in the influenza group (174/289 [60%] vs 28/39 [72%]; OR, 0.6; 95% CI, 0.26–1.3; $p = 0.22$) (Fig. 2*A*). There were numerically more early coinfections in the COVID-19 group than in the influenza group (68/289 [24%] vs 8/39 [21%]; OR, 1.19; 95% CI, 0.51–3.15; $p = 0.84$). Of the patients with at least one microbiological sample, 68 of 174 COVID-19 patients (39.1%) and seven of 28 influenza patients (25%) had at least one positive culture in the unmatched cohort (OR, 1.92; 95% CI, 0.74–5.6; $p = 0.21$).

The respiratory samples included were predominantly BAL samples. In the unmatched cohort, of the 62 COVID-19 patients with positive respiratory specimens, 58 (94%) were detected in BAL specimens, 3 (4.8%) were detected in endotracheal aspirates, and 1 (1.6%) was detected in sputum. All positive respiratory specimens in influenza patients were BAL specimens. In the matched cohort, all respiratory samples were BAL samples. The positive respiratory samples in this study were analyzed using qualitative (35.8%), semiquantitative (19.4%), and quantitative (44.7%) microbiological culture techniques.

Identified Pathogens

Figure 3 shows the relative frequency of the identified pathogens in the overall cohort. In the COVID-19 group, *S. aureus* (36/120 [30.0%]), *Klebsiella* species (17/120 [14.2%]), and *Streptococcus* species (16/120 [13.3%]) were the most common pathogens. In the influenza group, *Escherichia coli* (3/10 [30.0%]) and *S. aureus* (2/10 [20.0%]) were the predominant pathogens. Of the overall 130 identified pathogens, 68 (52.3%) were Gram-positive and 62 (47.7%) were Gram-negative bacteria. Of the 38 *S. aureus* isolates, four were classified as methicillin-resistant *S. aureus*. The relative frequency of identified pathogens was similar in the matched cohort (**Fig. S2**, http://links.lww.com/CCX/B171).

Antibiotic Use and Antimicrobial Susceptibility

Antibiotic use was high during the microbiological sampling period and similar between the COVID-19 and influenza group before (225/289 [77.9%] vs 31/39 [79.5%]) and after matching (60/79 [76.9%] vs 31/39 [79.5%]). Antimicrobial agents used in both groups in the overall cohort and matched cohort are listed in **Table 1** and **Table S2** (http://links.lww.com/CCX/B171), respectively. Overall, the most prescribed antibiotics were piperacillin/tazobactam (24.5%), meropenem (16.8%), and linezolid (10.2%). Noticeable differences between the two groups were higher use of meropenem and linezolid but lower use of fluoroquinolones in the COVID-19 group than in the influenza group. **Figure**

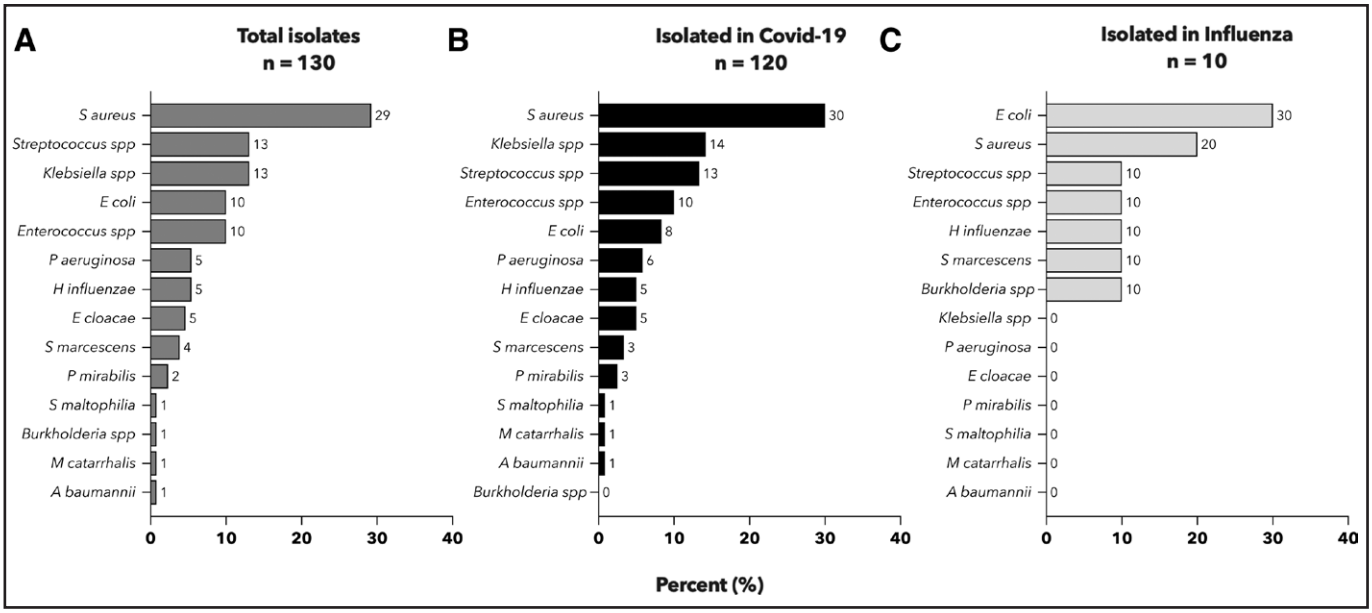

Figure 3. Relative frequencies (%) of strains identified in isolates in the overall cohort. **A**, Total isolates **B**, Isolates in COVID-19 group **C**, Isolates in the influenza group.

4 depicts overall antimicrobial susceptibility according to the routine AST from each sample. Shown are the most frequently isolated Gram-negative (**Fig. 4*A***) and Gram-positive (**Fig. 4*B***) bacterial pathogens and their resistance against selected antibiotics. Two of six isolates (33.3%) of *Enterobacter cloacae*, two of nine isolates (22.2%) of *Pseudomonas aeruginosa*, and four of 14 isolates (28.6%) of *Klebsiella* species showed resistance to piperacillin/tazobactam. Of the six *P. aeruginosa* isolates tested against carbapenems in antibiotic susceptibility testing, 4 (66.7%) were carbapenem-resistant.

In the matched cohort, 58 of 68 COVID-19 patients (85.3%) and eight of eight influenza patients (100%) with early bacterial coinfections received adequate empiric antibiotic coverage according to the results of the antibiogram ($p = 0.54$). In the overall cohort, 15 of 18 COVID-19 patients (83.3%) and eight of eight influenza patients (100%) with early bacterial coinfections received adequate empiric antibiotic coverage according to the results of the antibiogram ($p = 0.57$).

Immunosuppressive Medication

In the matched cohort, corticosteroid use was higher in COVID-19 patients than influenza patients (Table S1, http://links.lww.com/CCX/B171). High-dose glucocorticoids were used in 14 of 78 COVID-19 patients (17.9%) and five of 39 influenza patients (12.8%). Low-dose glucocorticoids were administered in 35 of 78 COVID-19 patients (44.9%) and 10 of 39 influenza patients (25.6%).

Similarly, glucocorticoid use was also higher in COVID-19 patients than influenza patients in the unmatched cohort. High-dose glucocorticoids were used in 46 of 289 COVID-19 patients (15.9%) and in five of 39 influenza patients (12.8%). Low-dose glucocorticoids were administered in 131 of 289 COVID-19 patients (45.3%) and in 10 of 39 influenza patients (25.6%).

Overall, the rate of bacterial coinfections was higher in patients receiving corticosteroids (53/195 [27.2%]) than in patients without corticosteroids (23/133 [17.3%]) (OR, 1.78; 95% CI, 1.0–3.24; $p = 0.045$).

Prescribed corticosteroids included dexamethasone, prednisolone, methylprednisolone, and hydrocortisone. A total of eight cases, all of which were COVID-19 patients, received other immunosuppressive medication including tacrolimus, anakinra, and mycophenolic acid.

Clinical Outcomes

Mortality. In the matched cohort, the 30-day mortality was similar between COVID-19 and influenza patients (19/78 [24%] vs 9/39 [23%]; HR, 1.26; 95% CI, 0.57–2.79; $p = 0.33$) (**Fig. 5*A***). In the overall cohort, death at 30 days occurred in 61 of 289 COVID-19 patients (19%) and nine of 39 influenza cases (23%) (HR, 1.07; 95% CI, 0.54–2.13; $p = 0.84$) (**Fig. 5*B***). Within the COVID-19 group, early bacterial

TABLE 1.
Overview of Antimicrobial Agents Used During the Microbiological Sampling Period

Antibiotic Agents	Total Antibiotics Used (*n* = 322)	Antibiotics Used in COVID-19 Group (*n* = 286)	Antibiotics Used in Influenza Group (*n* = 36)
Penicillins	120 (37.3)	105 (36.7)	15 (41.7)
Piperacillin/tazobactam	79 (24.5)	70 (24.5)	9 (25.0)
Ampicillin/sulbactam	36 (11.2)	33 (11.5)	3 (8.3)
Amoxicillin/clavulanic acid	4 (1.2)	1 (0.3)	3 (8.3)
Flucloxacillin	1 (0.3)	1 (0.3)	0 (0)
Cephalosporins	63 (19.6)	59 (20.6)	4 (11.1)
Cefuroxime	26 (8.1)	26 (9.1)	0 (0.0)
Ceftriaxone	10 (3.1)	9 (3.1)	1 (2.8)
Cefotaxime	9 (2.8)	8 (2.8)	1 (2.8)
Cefepime	9 (2.8)	7 (2.4)	2 (5.6)
Cefazoline	6 (1.9)	6 (2.1)	0 (0.0)
Ceftolozane/tazobactam	2 (0.6)	2 (0.7)	0 (0.0)
Ceftaroline	1 (0.3)	1 (0.3)	0 (0.0)
Carbapenems	55 (17.1)	53. (18.5)	2 (5.6)
Meropenem	54 (16.8)	52 (18.2)	2 (5.6)
Ertapenem	1 (0.3)	1 (0.3)	0 (0)
Macrolides	12 (3.7)	9 (3.1)	3 (8.3)
Erythromycin	5 (1.6)	4 (1.4)	1 (2.8)
Azithromycin	5 (1.6)	3 (1.0)	2 (5.6)
Clarithromycin	2 (0.6)	2 (0.7)	0 (0)
Fluoroquinolones	9 (2.8)	3 (1.0)	6 (16.7)
Levofloxacin	5 (1.6)	3 (1.0)	2 (5.6)
Ciprofloxacin	2 (0.6)	0 (0.0)	2 (5.6)
Moxifloxacin	2 (0.6)	0 (0.0)	2 (5.6)
Trimethoprim/sulphonamides	9 (2.8)	7 (2.4)	2 (5.6)
Trimethoprim/salmeterol	8 (2.5)	6 (2.1)	2 (5.6)
Trimethoprim/sulfamethoxazole	1 (0.3)	1 (0.3)	0 (0)
Aminoglycosides	6 (1.9)	5 (1.7)	1 (2.8)
Gentamicin	5 (1.6)	4 (1.4)	1 (2.8)
Tobramycin	1 (0.3)	1 (0.3)	0 (0)
Glycopeptides	3 (0.9)	3 (1.0)	0 (0)
Teicoplanin	2 (0.6)	2 (0.7)	0 (0)
Vancomycin	1 (0.3)	1 (0.3)	0 (0)
Others	45 (14.0)	42 (14.7)	3 (8.3)
Linezolid	33 (10.2)	32 (11.2)	1 (2.8)
Fosfomycin	4 (1.2)	4 (1.4)	0 (0.0)
Clindamycin	4 (1.2)	2 (0.7)	2 (5.6)
Aztreonam	2 (0.6)	2 (0.7)	0 (0.0)
Metronidazole	2 (0.6)	2 (0.7)	0 (0.0)

Data are shown as *n* (%).

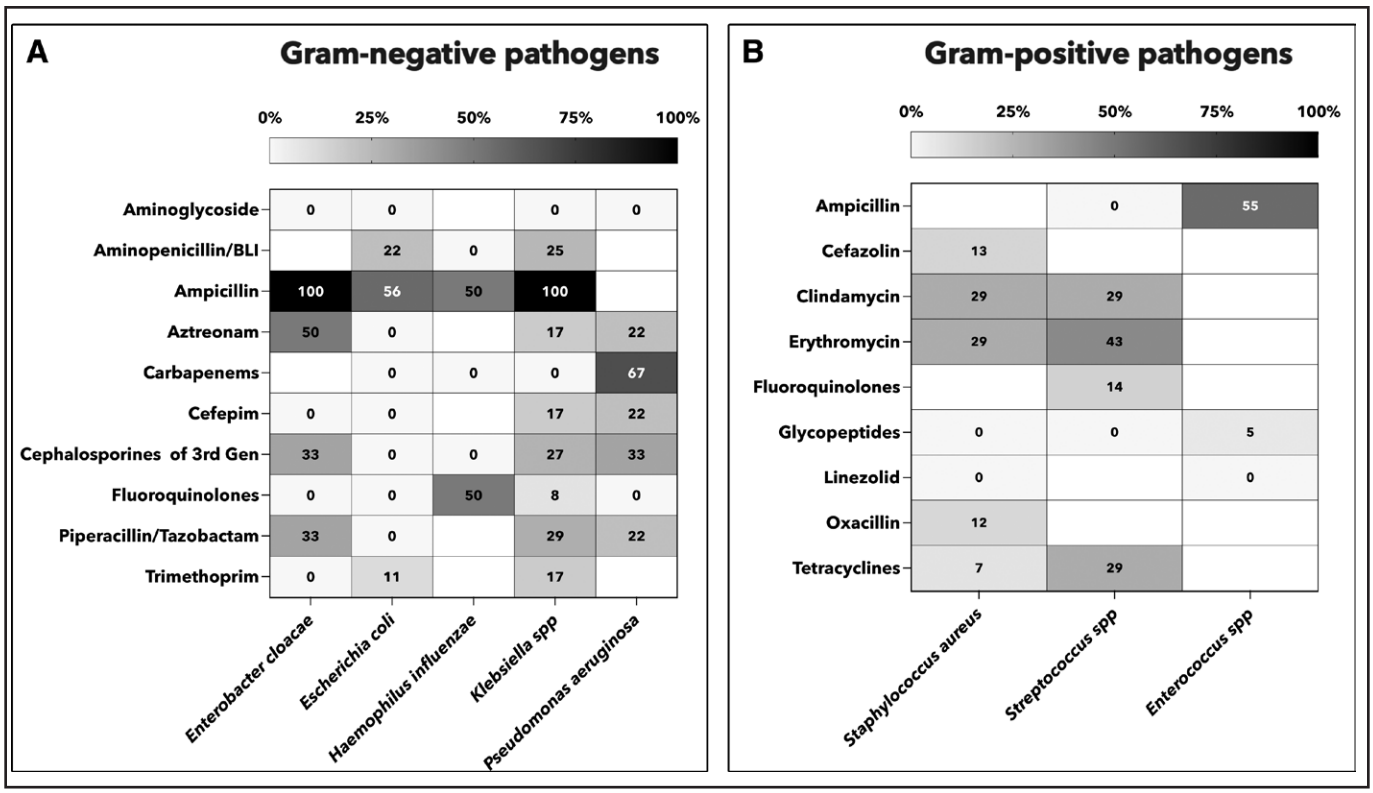

Figure 4. Relative frequency (%) of antimicrobial resistance as assessed by routine susceptibility testing of pathogens isolated from the COVID-19 group. Selected isolated Gram-negative bacterial pathogens (**A**) and Gram-positive bacterial pathogens (**B**) and their resistance to tested antibiotics. Since not all isolates were tested against all antibiotics, denominators resulting in the presented percentages may differ. *Blank fields* indicate that the corresponding pairs were not tested. Aminopenicillin/beta-lactamase inhibitors (BLIs) included the combinations amoxicillin/clavulanic acid and ampicillin/sulbactam. Cephalosporins of the third generation included cefixime, ceftriaxone, cefotaxime, and ceftazidime.

coinfections were significantly associated with an increased 30-day mortality rate (21/68 [30.9%] vs 40/221 [18.1%]; HR, 1.84; 95% CI, 1.01–3.32; p = 0.045) (**Fig. 5*C***). This association was not observed in the influenza group (**Fig. 5*D***).

Ventilation. In the matched cohort, the mean days of ventilation in COVID-19 patients were 16.2 ± 10.8 with early bacterial coinfections and 10.1 ± 14.7 days without early bacterial coinfections (mean difference, 6; 95% CI, –0.76 to 13.1; p = 0.08). The mean days of ventilation in influenza patients were 7.3 ± 6.0 days with early bacterial coinfections and 7.3 ± 7.4 days without early bacterial coinfections (mean difference, 0; 95% CI, –11.8 to 11.8; p = 1).

Overall, patients with bacterial infections were at greater risk of ventilation within 28 days after ICU admission (HR, 1.54; 95% CI, 1.17–2.03; p = 0.002) (**Fig. S1**, http://links.lww.com/CCX/B171).

Length of ICU Stay. In the matched cohort, the mean length of stay in COVID-19 patients was 30.8 ± 19.5 days with early bacterial coinfections and 17.1 ± 20.3 days without early bacterial coinfections (mean difference, 13.8; 95% CI, 3–24.6; p = 0.014). The mean length of stay in influenza patients was 26.7 ± 25.6 days with early bacterial coinfections and 19.5 ± 18.5 days without early bacterial coinfections (mean difference, 7.2; 95% CI, –16.7 to 31; p = 0.5).

Overall, patients with early bacterial coinfections had a longer length of stay (29.5 ± 23.3 d) than patients without coinfections (19.2 ± 23.7 d) (mean difference, 10.4; 95% CI, 4.3–16.5; p = 0.001).

Sensitivity Analyses

Comparing the first half of influenza cases (January 2015 to February 2017) with the second half of influenza cases (March 2017 to December 2020), we found almost identical frequencies of early microbiological testing (14/20 [70%] vs 14/19 [73.7%]) and rates of early coinfections (4/20 [20%] vs 4/19 [21.1%]). Comparing the first (January 2020 to February 2021) with the second (March 2021 to April 2022) half of COVID-19

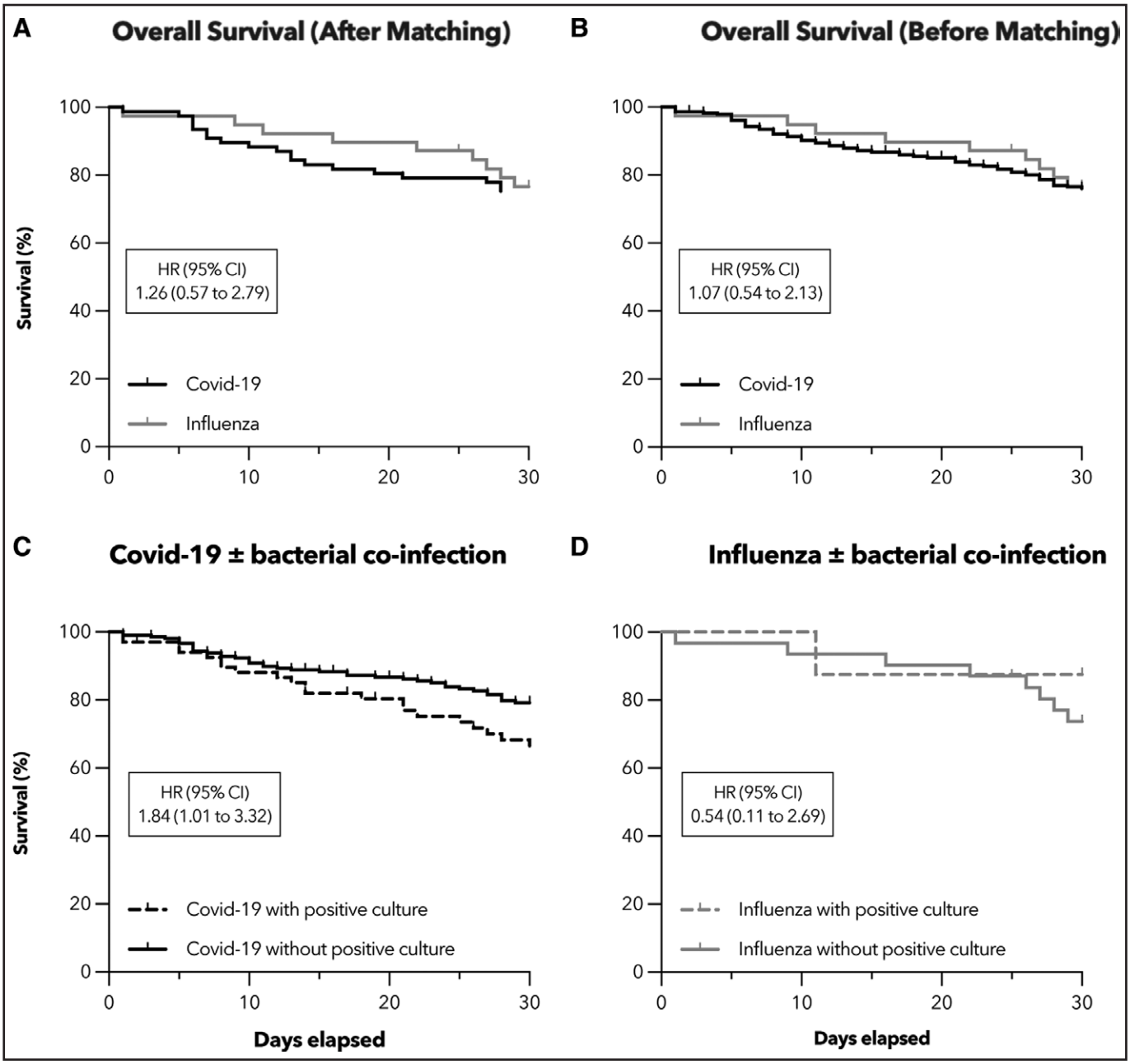

Figure 5. Survival probabilities of selected subgroups in days after ICU admission. **A**, Comparison of survival between the COVID-19 and influenza groups before matching. **B**, Comparison of survival between the COVID-19 and influenza groups after matching. **C**, Comparison of survival between COVID-19 cases with and without positive microbiological cultures. **D**, Comparison of survival between Influenza cases with and without positive microbiological cultures. HR = hazard ratio.

cases, we also found no relevant differences in the frequency of testing (90/144 [62.5%] vs 84/145 [57.9%]) and coinfections (30/144 [20.8%] vs 38/145 [26.2%]). With respect to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants, there was a similar frequency of microbiological sampling (wildtype vs alpha vs delta, 36/57 [63.2%] vs 79/128 [61.7%] vs 41/68 [60.3%]; $p = 0.94$), but a slightly increased rate of coinfections in the delta variant subgroup (wildtype vs alpha vs delta, 11/57 [19.3%] vs 30/128 [23.4%] vs 21/68 [30.9%]; $p = 0.32$).

In the subgroup of patients within the matched cohort who were admitted to the ICU via the emergency departments, any bacterial coinfection was identified in 10 of 33 COVID-19 patients (30.3%) and in three of 18 influenza patients (16.7%) (OR, 2.14; 95% CI, 0.45–14.1; $p = 0.34$). In the subgroup of patients within the matched cohort who were admitted to the ICU via

the normal ward, any bacterial coinfection was identified in eight of 45 COVID-19 patients (17.8%) and in five of 21 influenza patients (23.8%) (OR, 0.7; 95% CI, 0.17–3.14; $p = 0.74$).

In the subgroup of patients within the matched cohort who received antibiotics before ICU admission, any bacterial coinfection was identified in four of 10 COVID-19 patients (40%) and in two of seven influenza patients (28%) (OR, 1.62; 95% CI, 0.15–25.3; $p = 1$). In the subgroup of patients within the matched cohort who did not receive antibiotics before ICU admission, any bacterial coinfection was identified in 14 of 68 COVID-19 patients (20.6%) and in six of 32 influenza patients (18.8%) (OR, 1.12; 95% CI, 0.35–4; $p = 1$).

In the subgroup of patients within the matched cohort who received steroids prior to ICU admission, any bacterial coinfection was identified in four of nine COVID-19 patients (44.4%) and in one of four influenza patients (25%) (OR, 2.25; 95% CI, 0.12–156; $p = 1$). In the subgroup of patients within the matched cohort who received no steroids prior to ICU admission, any bacterial coinfection was identified in 14 of 69 COVID-19 patients (20.3%) and in seven of 35 influenza patients (20%) (OR, 1.01; 95% CI, 0.34–3.34; $p = 1$).

DISCUSSION

The present study compared the prevalence of early (within 2 d of ICU admission) bacterial coinfections between patients admitted to the ICU with COVID-19 and influenza by early identification of bacterial pathogens in blood or respiratory samples. In the propensity score matched cohort, we found a similar prevalence of coinfections in COVID-19 (23%) and influenza patients (21%), although the frequency of microbiologic testing was slightly lower in the COVID-19 group (58% vs 72%), possibly due to additional safety precautions when treating patients with COVID-19. However, 40% of COVID-19 patients and 28.6% of influenza patients with at least one microbiological sample yielded a positive culture in the matched cohort. This discrepancy may suggest that microbiological sampling was performed more often in cases of strong clinical suspicion of bacterial coinfection in COVID-19 patients. Similar results were observed in the overall, unmatched cohort.

Previous studies examining the prevalence of bacterial coinfections in COVID-19 patients have yielded controversial results. As a result, the use of empiric antimicrobials in severe COVID-19 cases remains questionable and relies on extrapolation of data from other viral pneumonias such as influenza (7). The current Surviving Sepsis Campaign guidelines recommend the use of empiric broad-spectrum antimicrobials in mechanically ventilated patients with COVID-19 and respiratory failure (18). In contrast, the National Institute of Health (NIH) argues that there is insufficient evidence to support either for or against the use of broad-spectrum antimicrobials in the absence of further evidence (19).

Previously, a large multicenter study including 1,050 patients, a meta-analysis including 568 subjects reported a low prevalence of positive bacterial cultures in 10% and 8% of COVID-19 patients admitted to the ICU, respectively (9, 10, 12). However, the former study did not provide information on the frequency of microbiological sampling in either group, and both were performed at multiple, multiregional study sites, making them susceptible to different sampling and treatment practices. A recent retrospective study by Pandey et al (12) evaluated the rate of early bacterial coinfections in critically ill patients with COVID-19 and influenza and found that 8.7% and 25% of patients had positive blood or respiratory cultures, respectively. Although the coinfection rates in influenza patients are comparable to our results, the rate in COVID-19 patients is notably lower. This discrepancy may be attributed to higher frequency of testing among the influenza patient population compared with the COVID-19 patient population. Our results are well in line with those of Contou et al (20), who found early bacterial coinfections in 28% of COVID-19 patients admitted to the ICU with a similar study design to ours. The results of a large multicenter study including 48,902 patients reported a very high rate of positive bacterial cultures in 31% of COVID-19 patients admitted to the ICU (8). However, these cultures were not limited to the first 2 days of hospitalization, so they represent a combination of early (≤ 48 hr) and late (> 48 hr) coinfections.

The most common bacterial pathogens isolated in patients with COVID-19 were *S. aureus*, *Klebsiella* species, and *Streptococcus* species, whereas most common pathogens in the influenza group were *E. coli* and *S. aureus*. These are common pathogens isolated in critical care settings and are consistent with previous literature (8, 10, 20). Some identified pathogens such as *E.*

coli or *Enterococcus* species may be atypical pathogenic causes of pneumonia. However, we opted to include them in our analysis since they were either isolated from the lower respiratory tract at multiple occasions, isolated from blood, or were abundant in semi-quantitative analyses and thus deemed clinically relevant. Furthermore, our definitions were in line with those of larger multicenter trials such as those of Russell et al (8) and Rouzé et al (10), which also included these pathogens in their analyses.

Early use of antimicrobial agents in critically ill COVID-19 patients remains high (11). In line with these findings, 78% of COVID-19 and 80% of influenza patients received any antimicrobial therapy at the time of ICU admission, that is, the microbiological sampling period. It is noted that inadequate exposure to antimicrobials may promote the emergence of bacterial resistance, which is associated with increased mortality (21–23). Although piperacillin/tazobactam was the most frequently prescribed antibiotic in our cohort, antibiotic resistance against the drug was present in about 20–30% of *E. cloacae*, *P. aeruginosa*, and *Klebsiella* species isolates. In addition, 67% of tested *P. aeruginosa* isolates were carbapenem-resistant. However, consistent with previous literature, no Gram-negative pathogens displayed resistance against aminoglycosides (24).

No significant difference in 30-day mortality was observed between the matched COVID-19 and influenza cohort (24% vs 23%). Notably, early bacterial coinfections in COVID-19 patients were associated with a statistically significant increase in 30-day mortality (31% vs 18%).

Our study presents findings obtained from the pre-Omicron period. At present, the Omicron strain of SARS-CoV-2 is widely prevalent and characterized by a less severe clinical presentation compared with the variants analyzed in our sample. To date, no direct comparison has been made regarding the frequency of bacterial coinfections in critically ill patients with the omicron variant versus other variants. Our results indicate similar rates of bacterial coinfections among the various variants. Thus, while there may be distinctions in the average clinical course between variants, critically ill patients, regardless of the variant they are infected with, may be susceptible to similar risks of developing bacterial infections.

We acknowledge several limitations of this study. First, the sample size of the influenza group was small and only powered for the detection of substantial group differences in early bacterial coinfections (i.e., absolute risk difference of approximately 20%). Therefore, subtle differences may have remained undetected and cannot be ruled out based on our findings. However, the frequency of early bacterial coinfections in influenza patients admitted to the ICU was similar to that observed in previous literature (4–6). In addition, our study revealed an absolute difference of 14% in the frequency of testing between COVID-19 and influenza patients. Although this difference was not found to be statistically significant, a larger sample size may have demonstrated greater significance (4–6). Second, the patients in the two groups were not hospitalized contemporaneously because the admission of most influenza patients occurred further back in time than the onset of the COVID-19 pandemic. However, matching at a 2:1 instead of a 1:1 ratio reduced the necessary number of influenza patients required for the desired statistical power. Therefore, reverse chronological inclusion of influenza patients did not need to extend beyond 2015, thus limiting the temporal gap between the inclusion periods of the two groups. Furthermore, our sensitivity analyses revealed no significant differences in testing frequencies or occurence of bacterial coinfections over time. Finally, our study was limited to a single study center. However, the nature of a single center may have created more comparable sampling and treatment practices and microbial environment across all patients.

In conclusion, our results show a similar prevalence of early bacterial coinfections in critically ill patients hospitalized with COVID-19 and influenza. The prevalence of early bacterial coinfections in critically ill patients with COVID-19 was higher than previously reported and was associated with significantly higher mortality compared with patients without coinfections. Therefore, previous studies reporting a low prevalence of bacterial coinfections in critically ill COVID-19 patients must be interpreted with caution. Although larger randomized controlled trials would be necessary to challenge current recommendations outlined in the Surviving Sepsis guidelines, we believe that our results warrant close monitoring of patients for possible bacterial coinfections and prompt initiation of appropriate antimicrobial therapy in accordance with culture antibiograms.

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