ORIGINAL RESEARCH

The Impact of Early Antibiotic Use on Clinical Outcomes of Patients Hospitalized with COVID-19: A Propensity Score-Matched Analysis

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Purpose: Early empiric antibiotics were prescribed to numerous patients during the Coronavirus disease 2019 (COVID-19) pandemic. However, the potential impact of empiric antibiotic therapy on the clinical outcomes of patients hospitalized with COVID-19 is yet unknown.

Methods: In this retrospective cohort study, early antibiotics use cohort was defined as control group, which was compared with no antibiotic use and delayed antibiotic use cohorts for all-cause mortality during hospitalization. The 1:2 propensity score matched patient populations were further developed to adjust confounding factors. Survival curves were compared between different cohorts using a Log rank test to assess the early antibiotic effectiveness.

Results: We included a total of 1472 COVID-19 hospitalized patients, of whom 87.4% (1287 patients) received early antibiotic prescriptions. In propensity-score-matched datasets, our analysis comprised 139 patients with non-antibiotic use (with 278 matched controls) and 27 patients with deferred-antibiotic use (with 54 matched controls). Patients with older ages, multiple comorbidities, severe and critical COVID-19 subtypes, higher serum infection indicators, and inflammatory indicators at admission were more likely to receive early antibiotic prescriptions. After adjusting confounding factors likely to influence the prognosis, there is no significant difference in all-cause mortality (HR=1.000(0.246–4.060), p = 1.000) and ICU admission (HR=0.436(0.093–2.04), p = 0.293), need for mechanical ventilation (HR=0.723(0.296–1.763), p = 0.476) and tracheal intubation (HR=1.338(0.221–8.103), p = 0.751) were observed between early antibiotics use cohort and non-antibiotic use cohort.

Conclusion: Early antibiotics were frequently prescribed to patients in more severe disease condition at admission. However, early antibiotic treatment failed to demonstrate better clinical outcomes in hospitalized patients with COVID-19 in the propensity-score-matched cohorts.

Keywords: Coronavirus disease 2019, COVID-19, early antibiotics use, bacterial co-infections, clinical outcomes

Introduction

The Coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has infected over 700 million people and resulted in over 6 million related fatalities worldwide since December 2019.[1] As is known to us all, bacterial co-infection is a common complication of many respiratory viral tract infections and is associated with increased disease severity and mortality.[2,3] Patton's study reported a double 30-day mortality of COVID-19 patients with confirmed bacterial co-infections when compared to influenza virus with bacterial co-infections.[4] In the setting of COVID-19, bacterial co-infections were observed to have a profound impact on an

3425

increased risk of in-hospital mortality, intensive care unit (ICU) admission, and the need for mechanical ventilation.[5,6] During the COVID-19 pandemic, the incidence of gram-positive and gram-negative bacteria co-infections (especially multidrug resistant bacteria) continued to grow.[7] Among the bacterial species found in COVID-19 patients, *Enterobacteria* and carbapenemase-resistant *A. baumanni* showed high rates of colonization and superinfection, which were associated with high mortality especially in ICU super-infection.[8]

Whereas, it is challenging to accurately distinguish between viral infection alone and viral combined with bacterial co-infections based on symptoms, clinical-biological or radiological examinations. In addition, COVID-19 itself could lead to increased inflammatory markers (such as procalcitonin (PCT) and C-reactive protein (CRP)) typically associated with bacterial co-infection, which made it more difficult for physicians to diagnose bacterial co-infection at hospital admission.[9,10] Considering the increased risk of death and disease progression in COVID-19 patients with bacterial co-infection, nearly three-quarters of patients with COVID-19 have received early empiric antibacterial therapy in the first 6 months of the global pandemic.[11,12] Another large, multicenter study also reported that early antibiotics use in patients with COVID-19 accounts for 27% to 84% across different hospitals.[11]

The COVID-19 pandemic had resulted in a sharp rise in antibiotic usage. Overuse or misuse of antibiotics can lead to an increased risk of adverse events, Clostridium difficile infection and global antimicrobial resistance. Adequate antibiotic management is urgently required to reduce the overprescription of antibiotics. As for different countries and different subtypes of COVID-19 viruses, there have not come to a consensus among the various guidelines on the prescription of antibiotics in hospitalized patients with COVID-19. While some guidelines recommended early empiric antibiotic therapy in severe COVID-19 patients, the 2021 UK National Institute for Health and Care Excellence (NICE) rapid guideline on managing COVID-19 demonstrated that the only recommendation for antibiotics use is when there is a strong clinical or paraclinical suspicion of bacterial infection.[13–16] Previous studies have put more emphasis on the rates of antibacterial therapy and microbiologically proven co-infection but ignored the potential impact of early antibiotic therapy on the clinical outcomes of patients hospitalized with COVID-19.[17] It is high time to emphasize the appropriate use of antibiotics among patients with COVID-19, and more studies are urgently needed to assess if early antibiotic therapy work to improve the prognosis and survival rate of hospitalized patients with COVID-19.

We conducted a retrospective analysis aimed to evaluate whether early antibacterial therapy is beneficial to improve the prognosis (including mortality, rate of ICU admission, need for tracheal intubation and mechanical ventilation, and length of hospital stays) of hospitalized COVID-19 patients, which could help clinicians to establish better antimicrobial strategy, reduce unnecessary antibiotic exposure and prevent worsening antimicrobial resistance within global healthcare systems.

Methods
Study Design and Patients

We conducted a retrospective cohort study in West China Hospital of Sichuan University, which comprised hospitalized patients with positive real-time reverse transcription polymerase chain reaction (RT-PCR) or rapid antigen test results from an oronasopharyngeal swab for SARS-CoV-2 infection at admission during the period from Dec 2nd, 2022 to Mar 15th, 2023.

This is a retrospective study for follow-up observation of clinical features and prognosis of COVID-19 cohort. All data in this study was extracted from the Electronic Medical Record. The West China Hospital of Sichuan University Ethics Review Committee, in accordance with the principles of the Helsinki Declaration II, approved this research. The authors only had access to anonymized data and had no interaction with patients or patient samples, so The West China Hospital of Sichuan University Ethics Review Committee has approved the waiver for individual patient-informed consent. All analysis was performed in accordance with relevant guidelines and regulations.

We included patients aged ≥16 years old in both the ICU and non-ICU settings. Patients were eligible for inclusion if their positive oronasopharyngeal swab was identified before hospitalization. Exclusion criteria include: (1) patients discharged within 24 h of admission and patients who were still in hospitalization as of March 15, 2023; (2) positive tests for COVID-19 during hospitalization; (3) patients whose antibiotics course was < 48h; (4) patients who were incidentally admitted during this period (eg, for surgery), and were found to be asymptomatic cases of COVID-19; (5) patients with

confirmed positive bacterial culture before admission; and (6) antibiotics were prescribed by confirmed proof of a non-pulmonary microbiological infection (eg, for bacterial skin infections).

Data Collection

Electronic medical records for each patient were collected, including demographic characteristics, body mass index (BMI), former or current smoker, comorbidity (including diabetes, hypertension, chronic kidney disease, chronic hepatic disease, chronic lung diseases, cardiovascular disease, immune system disease, and malignancy), antibiotics prescription records, and disease severity for COVID-19. Laboratory parameters on admission included serum lymphocyte count, PCT, CRP, interleukin-6 (IL-6), D-dimer level, CD4+ T cells, and CD8+ T cells count.

Patients with antibiotic exposure (this study included antibiotics intended for systemic use, which does not include topical antibiotics; and antibiotics in our study pertains to antibacterials drug used to inhibit bacterial growth and kill bacteria) were classified as non-early antibiotic use cohort and early antibiotic use cohort based on whether or not to commence antibiotics within 48 h of hospital admission. Non-early antibiotic use cohort was further categorized as non-antibiotic use cohort and Delayed-antibiotic use according to antibiotics prescription record. Delayed-antibiotic use refers to antibiotic Initial used more than 48 h of hospital admission, yet non-antibiotic use refers to cases that never received antibiotics during their hospital stay.

According to World Health Organization (WHO) definitions of disease severity, COVID-19 has been classified as critical COVID-19, severe COVID-19, and non-severe COVID-19.[15] All patients were followed until death in hospital or hospital discharge. The primary outcome was all-cause mortality during hospitalization. Secondary outcomes included initiating mechanical ventilation (including tracheal intubation and non-invasive ventilator), the need for tracheal intubation, ICU admission, and the length of hospital stays.

Propensity Score Matching

Propensity score matching (PSM) refers to the screening of experimental and control groups by certain statistical methods, so that the selected subjects are comparable in terms of potential confounders (applicable to both continuous variables and categorical variables).[18] In our study, PSM was used to balance the differences in baseline variables that might confound the impact of early antibiotic use on clinical outcomes of hospitalized COVID-19 patients.[18] The following baseline variables were included for propensity score matching: demographic characteristics (age and gender), BMI, current or former smoker, comorbidities, and disease severity for COVID-19. We excluded patients with missing data on any of these baseline variables. Considering great higher number of early-antibiotic treated patients, matched study groups were created using nearest-neighbor 1:2 matching without replacement (each patient with non-antibiotic use and delayed-antibiotic use were matched exactly with two patients with early-antibiotic use).[19]

Statistical Analyses

All statistical learning methods in our research were chosen based on statistical learning theory. Categorical data were expressed as counts and frequencies (%) and analyzed using Fisher's exact test or chi-squared test depending on the data. Quantitative variables were expressed as means ± standard deviations (SD) and analyzed by independent-samples *T*-test or Mann–Whitney *U*-test when appropriate. Wilcoxon rank-sum tests or Spearman correlation test was selected by ranked data.

The 1:2 propensity score matched patient populations were established based on the Greedy algorithm using the package MatchIt (Nonparametric Preprocessing for Parametric Causal Inference) in R 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria). Balance was assessed within the matched cohorts using the standardized mean difference, with a standardized mean difference <0.100 indicating sufficient balance. Hazard ratios (HRs) with a 95% confidence interval (CI) for each outcome parameter used were estimated using univariate binary logistic regression. Survival curves were generated by the group using the Kaplan–Meier estimator and compared using a Log rank test.

SPSS Statistics Version 26.0 (Armonk, NY) was used for statistical analysis before and after matching. For all comparisons, differences were tested using two-tailed tests, and P < 0.05 was considered to indicate statistical significance.

Results

We identified 4999 patients with a confirmed diagnosis of SARS-CoV-2 infection who were admitted to West China Hospital between Dec 2nd, 2022, and Mar 15th, 2023. A total of 1472 patients were eligible for inclusion and 1287 patients (87.4%) received early antibiotic treatments (Figure 1). Besides, the delayed-antibiotic use cohort and non-antibiotic use cohort include 36 patients and 149 patients, respectively, (The detailed baseline characteristics and laboratory parameters of three cohorts after propensity score matching were listed in Table S1). Beta-lactam antibiotic was the most commonly used antibiotics in our study population. Patients with early antibiotic use were defined as controls.

The Early Antibiotic Consumption Trending in Patients Hospitalized with COVID-19 Before Propensity Score Matching

Baseline characteristics of three cohorts before 1:2 propensity-score matching are presented in Table 1. Before matching, the non-antibiotic use cohort had a significantly lower age (61.42 ± 19.00 vs 71.24 ± 16.95, $p < 0.001$) than the controls. More than 50% of the patients were male in all three cohorts. In comparison with the control cohort, the non-antibiotic use cohort had lower prevalence rates of diabetes, chronic kidney disease, chronic lung disease, and cardiovascular disease. Fewer patients with more than 2 types of comorbidities were found in patients with non-antibiotic use (28.2% vs 55.7%, $p < 0.001$) and delayed-antibiotic use cohort (38.9% vs 55.7%, $p = 0.045$) than controls. The proportion of patients belonged to severe COVID-19 and critical COVID-19 was identified to be 39.4% and 23.5%, respectively, in the early antibiotic use cohort, which was much higher than that of both delayed-antibiotic use cohort ($p<0.001$) and non-antibiotic use cohort ($p<0.001$).

Among patients with non-antibiotic use, several infectious indicators and inflammatory indicators (including serum PCT (0.17 ± 0.44 VS 1.20 ± 4.36, $p < 0.001$), CRP (40.49 ± 49.76 VS 75.91 ± 70.77, $p < 0.001$), IL-6 (22.35 ± 42.51 VS 60.50 ± 105.44, $p < 0.001$), D-dimer (1.22 ± 1.70 VS 3.85 ± 5.81, $p < 0.001$)) at admission were much lower than that of
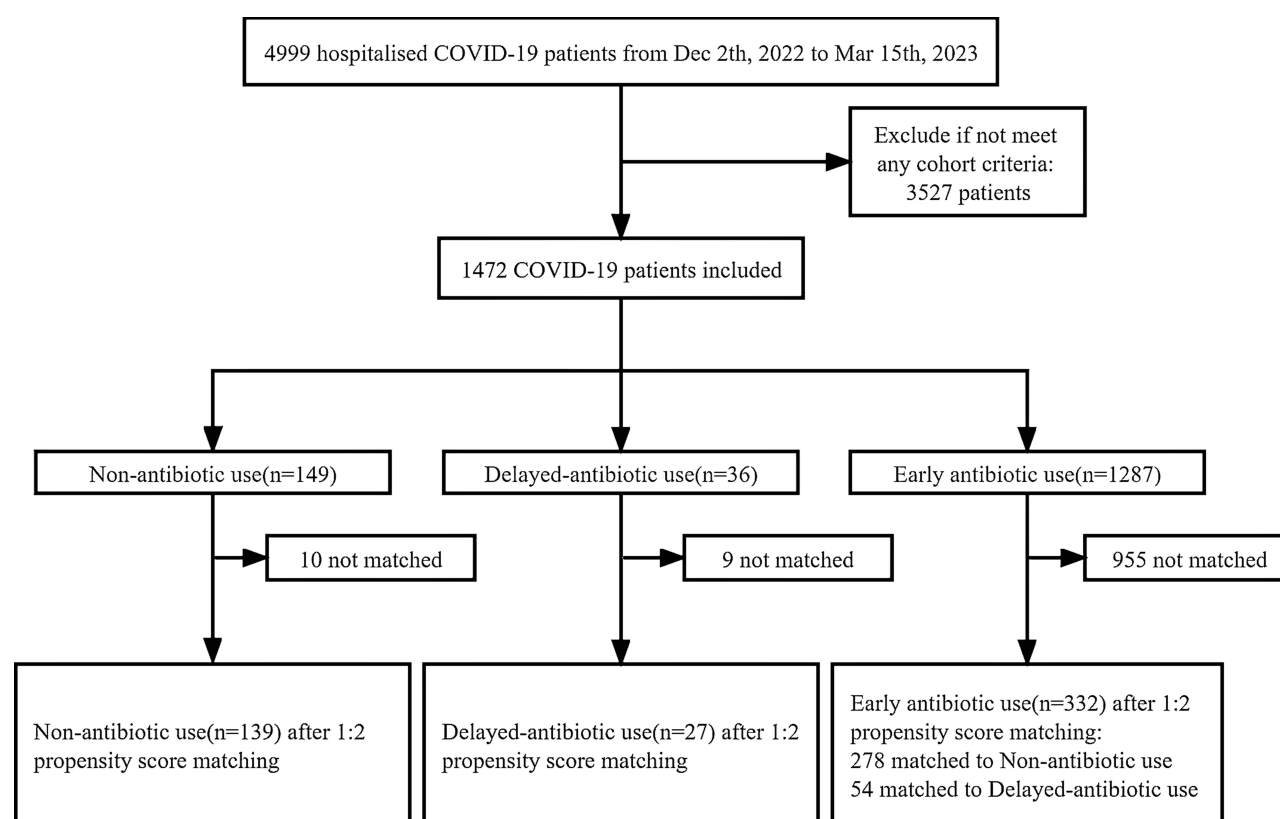
Figure 1 Identification of delayed-antibiotic use, non-antibiotic use and their matched controls (early-antibiotic use) among patients hospitalized with COVID-19 during the study period.

Table 1 Baseline Characteristics and Laboratory Parameters of Patients Hospitalized with COVID-19 Before and After Propensity Score Matching

	Before 1:2 Propensity-Score Matching					After 1:2 Propensity-Score Matching	
	Non-Antibiotic use (n=149)	Delayed-Antibiotic use (n=36)	Early Antibiotic use (Controls(n=1287))	p* Value	p$^\Delta$ Value	p* Value	p$^\Delta$ Value
Baseline covariates							
Age(years)	61.42±19.00	69.11±21.34	71.24±16.95	<0.001	0.557	0.388	0.944
Sex:				0.512	0.199	0.499	0.813
Female	33.6%(50/149)	41.7%(15/36)	30.6%(394/1287)				
Male	66.4%(99/149)	58.3%(21/36)	69.4%(893/1287)				
BMI	23.82±3.60	25.66±3.11	23.39±3.87	0.220	0.003	0.942	0.913
Current or former smoker	16.8%(25/149)	13.9%(5/36)	22.5% (290/1287)	0.117	0.235	0.512	0.744
Comorbidity:							
Diabetes	18.8%(28/149)	25.0%(9/36)	27.8%(358/1287)	0.019	0.851	1.000	0.613
Hypertension	40.9%(61/149)	47.2%(17/36)	46.1%(593/1287)	0.259	1.000	0.334	0.816
Chronic kidney disease	16.1%(24/149)	13.9%(5/36)	26.4%(340/1287)	0.007	0.122	0.586	0.681
Chronic hepatic disease	5.4%(8/149)	0.0%(0/36)	7.2%(93/1287)	0.499	0.106	1.000	NA
Chronic lung diseases	8.1%(12/149)	8.3%(3/36)	21.5%(277/1287)	<0.001	0.062	1.000	0.742
Cardiovascular disease	11.4%(17/149)	19.4%(7/36)	27.7%(356/1287)	<0.001	0.345	0.585	0.765
Immune system disease	3.4%(5/149)	0.0%(0/36)	4.1%(53/1287)	0.678	0.397	0.767	NA
Malignancy	8.7%(13/149)	13.9%(5/36)	13.8%(177/1287)	0.097	1.000	0.726	0.681
≥ 2 types of Comorbidity	28.2%(42/149)	38.9%(14/36)	55.7%(717/1287)	<0.001	0.045	0.723	0.803
Disease severity for COVID-19:				<0.001	0.001	0.296	0.296
Non-severe COVID-19	73.2%(109/149)	63.9%(23/36)	37.1%(478/1287)				
Severe COVID-19	24.2%(36/149)	33.3%(12/36)	39.4%(507/1287)				
Critical COVID-19	2.6%(4/149)	2.8%(1/36)	23.5%(302/1287)				
Laboratory parameters at admission							
Lymphocytes, 10^9 /L	0.96±0.46	0.93±0.44	0.83±0.92	0.090	0.508	0.807	0.782
PCT, ng/mL	0.17±0.44	0.10±0.09	1.20±4.36	<0.001	<0.001	0.069	0.077
CRP, mg/L	40.49±49.76	40.35±50.56	75.91±70.77	<0.001	0.013	0.034	0.311
IL-6, μg/L	22.35±42.51	28.51±45.17	60.50±105.44	<0.001	0.001	0.066	0.987
D-Dimer, mg/L	1.22±1.70	2.65±5.09	3.85±5.81	<0.001	0.229	0.079	0.849
CD4+ T cells, cell/μL	389.50±279.86	267±227.84	213.19±199.26	0.005	0.450	0.076	0.460
CD8+ T cells, cell/μL	251.54±183.97	161.38±116.58	152.06±124.93	0.015	0.834	0.052	0.493

Notes: p* Value: comparison between non-antibiotic use cohort and controls; p$^\Delta$ Value: comparison between delayed-antibiotic use and controls.
Abbreviations: COVID-19, Coronavirus disease 2019; BMI, Body mass index; PCT, procalcitonin, CRP, C-reactive protein, IL-6, interleukin 6, NA, not applicable.

control cohort. Furthermore, immune indicators (CD4+T cells (389.50 ± 279.86 VS 213.19 ± 199.26, p = 0.005) and CD8 + T cells count (251.54 ± 183.97 VS 152.06 ± 124.93, p = 0.015)) of patients with non-antibiotic use were observed to be greatly higher than controls. Compared with patients with early antibiotic use, similar lower serum PCT (p < 0.001), CRP (p = 0.013), and IL-6 (p = 0.001) levels were also seen in the delayed-antibiotic use cohort.

During the study period, 190 of the 1287 patients (14.8%) with early antibiotic use died, which was greatly higher than 3.1% of the non-antibiotic use cohort (0.194(95% CI: 0.085–0.443), p < 0.001) (Table 2). What's more, patients with non-antibiotic use were found to stay in the hospital for a significantly shorter time than controls (10.56 ± 5.89 VS 15.74 ± 10.15, p < 0.001). Among patients with non-antibiotic use, the risk of ICU admission (0.091(95% CI: 0.022–0.369), p = 0.001), need for mechanical ventilation (0.149(95% CI: 0.077–0.285), p < 0.001) and tracheal intubation (0.132(95% CI: 0.032–0.541), p = 0.005) were identified to be much lower than controls. However, there was no significant difference in all-cause mortality, length of hospital stays, and the risk of tracheal intubation between the

Table 2 Comparison of Outcomes Parameters Between Patients with Non-Antibiotic Use and Early Antibiotic Use Before and After Propensity Score Matching

	Before 1:2 Propensity-Score Matching						After 1:2 Propensity-Score Matching					
	Non-Antibiotic use (n=149)	Early Antibiotic use (n=1287)	Crude HR	95% CI		p value	Non-Antibiotic use (n=139)	Early Antibiotic use (n=278)	Crude HR	95% CI		p value
Mechanical ventilation	6.7%(10/149)	32.6%(420/1287)	0.149	0.077	0.285	<0.001	5.0%(7/139)	6.8%(19/278)	0.723	0.296	1.763	0.476
Tracheal intubation	1.3%(2/149)	9.3%(120/1287)	0.132	0.032	0.541	0.005	1.4%(2/139)	1.1%(3/278)	1.338	0.221	8.103	0.751
ICU admission	1.3%(2/149)	13.1%(168/1287)	0.091	0.022	0.369	0.001	1.4%(2/139)	3.2%(9/278)	0.436	0.093	2.047	0.293
Length of hospital stay(days)	10.56±5.89	15.74±10.15	NA	NA	NA	<0.001	10.55±5.81	13.88±7.38	NA	NA	NA	<0.001
Mortality	2.7%(4/149)	14.8%(190/1287)	0.159	0.058	0.435	<0.001	2.2%(3/139)	2.2%(6/278)	1.000	0.246	4.06	1.000

Abbreviations: NA, not applicable; ICU, Intensive Care Unit; HR, Hazard ratios; CI, Confidence interval.

delayed-antibiotic use cohort and the early antibiotic use cohort. In comparison with the control cohort, a lower risk of ICU admission (p = 0.018) and mechanical ventilation (p = 0.006) were shown in the delayed-antibiotic use cohort.

Early Antibiotic Effectiveness in Patients Hospitalized with COVID-19 After Propensity Score Matching

After propensity score matching, our analysis included 139 patients with non-antibiotic use (with 278 matched controls) and 27 patients with delayed-antibiotic use (with 54 matched controls). The baseline characteristics of the case cohorts and matched control cohort were balanced with no significant difference (Table 1). The standard mean differences were greater than 0.1, indicating good balance. With the above methods, 332 patients with early antibiotic use (Figure S1 and Table S2) and 278 patients with antibiotic use (Figure S2 and Table S3) were successfully matched to 166 patients with non-early antibiotic use and 139 patients with non-antibiotic use, respectively. After matching for baseline characteristics, laboratory parameters at admission in the delayed-antibiotic use cohort and non-antibiotic use cohort were found to be not significantly different from corresponding matched controls (except for lower serum CRP level in patients with non-antibiotic use).

Comparison of Outcome Parameters Between Patients with Non-Antibiotic Use, Delayed-Antibiotic Use, and Matched Controls

Further analysis was conducted in propensity-score-matched datasets and observed no evidence of improved outcome parameters in patients who received early antibiotics treatment. Compared with the non-antibiotic use cohort, matched controls did not have lower all-cause mortality (HR = 1.000(0.246–4.060), P = 1.000), lower risk of ICU admission (HR = 0.436(0.093–2.047), P = 0.293), mechanical ventilation (HR = 0.723(0.296–1.763), P = 0.476) and tracheal intubation (HR = 1.338(0.221–8.103), P = 0.751) (Table 2). Similar results were observed in the comparison of outcome parameters between patients with deferred-antibiotic use and matched controls (Table 3). However, patients with non-early antibiotic use, who had a less serious disease condition, tend to stay in the hospital for a significantly shorter time period than matched controls (10.55 ± 5.81 VS 13.88 ± 7.38, P < 0.001).

In propensity score matching cohorts analysis, Log rank test for comparison of survival curves in the non-antibiotic use cohort versus matched controls (HR = 1.522(95% CI: 0.339–7.109, p = 0.522), delayed-antibiotic use cohort versus matched controls (HR=1.014(95% CI: 0.169–6.086), p = 0.988) had no statistical difference (Figure 2).

Comparison of Outcome Parameters Between Patients with and without Early Antibiotic Use, and Patients with and without Antibiotic Use

The above comparison of outcome parameters was conducted between patients with and without early antibiotic use and patients with and without antibiotic use in propensity-score-matched cohorts. Similarly, both the non-early antibiotic use cohort (Table 4) and the non-antibiotic use cohort (Table 5) showed no statistical difference in all-cause mortality, the risk for ICU admission, mechanical ventilation, and tracheal intubation from that of their respective matched controls.

Survival curves in Figure 2 did not find any significant difference between patients with and without early antibiotic use (HR = 1.143(95% CI: 0.386–3.386), p = 0.387), patients with and without antibiotic use (HR = 1.281(95% CI: 0.393–4.171), p = 0.804).

Discussion

In conclusion, early-antibiotic use was associated with older age, multiple comorbidities, severe and critical COVID-19 subtype, higher serum infectious indicators, and inflammatory indicators at admission. Compared to patients with delayed-antibiotic use and non-antibiotic use cohorts, early antibiotics use in patients hospitalized with COVID-19 had no beneficial effect on all-cause mortality, risk of ICU admission, need for tracheal intubation, and mechanical ventilation after adjusting for baseline characteristics.

The morbidity of bacterial co-infection was highly variable between different respiratory viruses. Other respiratory viral pathogens, such as influenza virus and rhinovirus, may be susceptible to bacterial invasion due to impaired physical barrier, dysregulation of an inflammatory response, and immune response.[20] The impact of SARS-CoV-2 on bacterial co-infection remains unclear now. In a meta-analysis of hospitalized ICU and non-ICU COVID-19 patients, only 7% of the

Table 3 Comparison of Outcomes Parameters Between Patients with Delayed-Antibiotic Use and Early Antibiotic Use Before and After Propensity Score Matching

	Before 1:2 Propensity-Score Matching						After 1:2 Propensity-Score Matching					
	Delayed-Antibiotic use (n=36)	Early Antibiotic use (n=1287)	Crude HR	95% CI		p value	Delayed-Antibiotic use (n=27)	Early Antibiotic use (n=54)	Crude HR	95% CI		p value
Mechanical ventilation	8.3%(3/36)	32.6%(420/1287)	0.188	0.057	0.615	0.006	3.7%(1/27)	13.0%(7/54)	3.872	0.451	33.222	0.217
Tracheal intubation	0.0%(0/36)	9.3%(120/1287)	NA	NA	NA	0.069	0.0%(0/27)	1.9%(1/54)	NA	NA	NA	1.000
ICU admission	0.0%(0/36)	13.1%(168/1287)	NA	NA	NA	0.018	0.0%(0/27)	1.9%(1/54)	NA	NA	NA	1.000
Length of hospital stay(days)	18.08±8.10	15.74±10.15	NA	NA	NA	0.170	18.07±8.26	15.69±11.73	NA	NA	NA	0.347
Mortality	5.6%(2/36)	14.8%(190/1287)	0.340	0.081	1.425	0.140	7.4%(2/27)	5.6%(3/54)	0.735	0.115	4.686	0.745

Abbreviations: NA, not applicable, ICU, Intensive Care Unit, HR, Hazard ratios, CI, Confidence interval.
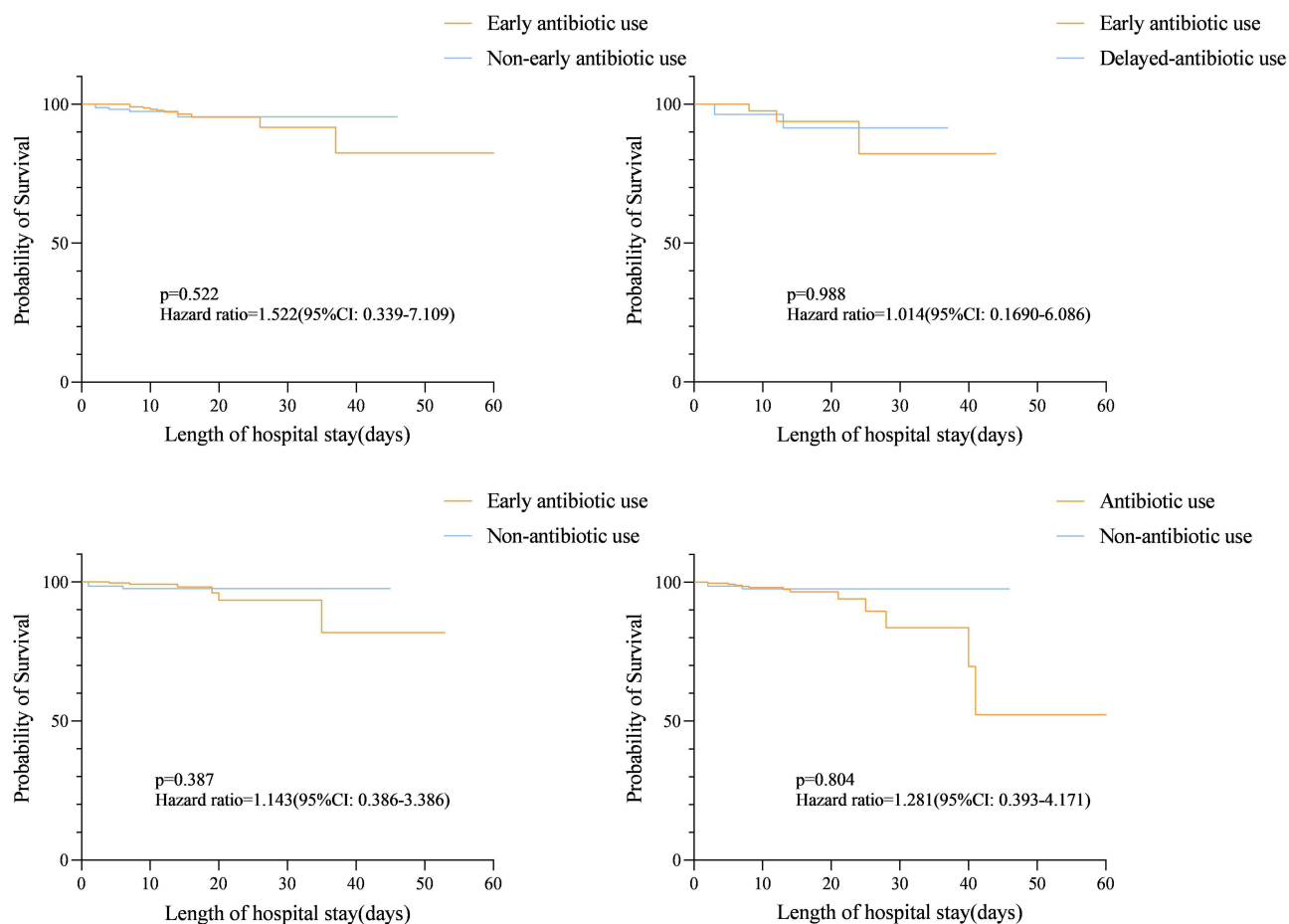
Figure 2 Survival curves of patients with the early antibiotic use cohort versus non-antibiotic use cohort, delayed-antibiotic use cohort, non-early antibiotic use cohort, and antibiotic use cohort versus non-antibiotic use cohort.

patients combined with bacterial co-infection, which was significantly lower than the influenza co-infection rate.[21] Consistent with other research, most reported epidemiological investigations from China and Spain also showed similarly low bacterial co-infection rates.[22–24] However, it's worth noting that the proportion of hospitalized COVID-19 patients who received antibiotics far exceeds the reported prevalence of microbiologically proven co-infection.[11,25]

As high as 87.4% of hospitalized patients with COVID-19 in our study received early-antibiotic treatments, with an all-cause mortality of 14.8%. The higher reported rate of antibiotic use may be due to that our study excluded asymptomatic COVID-19 patients and mild COVID-19 patients who did not require hospitalization, so that severe and critical COVID-19 accounted for a high proportion of our study population. Our data showed that antibiotics were frequently prescribed in patients with older age, multiple comorbidities, severe and critical COVID-19 subtype, higher serum infectious indicators, and inflammatory indicators at admission. Especially the severity of COVID infection was reported as an important factor related with mortality regardless of antibiotic use and bacteria co-infection.[8] Both hyperinflammation and immune dysfunction are reported to play a necessary role in COVID-19-related pathogenesis and clinical outcomes.[26] Abnormally increased inflammation markers (such as CRP\IL-6\PCT) and decreased immune associated markers (such as Lymphocytes \CD4+ T cell\CD8+ T cell count) were observed in all groups, especially in patients with early antibiotic use. Patients with the above characteristics were regarded as population with high risk for death, and antibiotics prescribing in these patients was believed to be conducive for preventing secondary bacterial super-infection and improving prognosis initially.[3,16] However, simple COVID-19 infection also could cause abnormalities of immune and inflammation markers, our another research found that only critical COVID-19 subtype was an independent risk factor for both co-infection and secondary infection.[27]

Table 4 Comparison of Outcomes Parameters Between Patients with and without Early Antibiotic Use Before and After Propensity Score Matching

	Before 1:2 Propensity-Score Matching						After 1:2 Propensity-Score Matching					
	Non-early Antibiotic use (n=185)	Early Antibiotic use (n=1287)	Crude HR	95% CI		P value	Non-early Antibiotic use (n=166)	Early Antibiotic use (n=332)	Crude HR	95% CI		P value
Mechanical ventilation	7.0%(13/185)	32.6%(420/1287)	0.156	0.088	0.277	<0.001	4.8%(8/166)	9.3%(31/332)	0.492	0.221	1.095	0.082
Tracheal intubation	1.1%(2/185)	9.3%(120/1287)	0.106	0.026	0.434	0.002	1.2%(2/166)	0.9%(3/332)	1.337	0.221	8.083	0.751
ICU admission	1.1%(2/185)	13.1%(168/1287)	0.073	0.018	0.296	<0.001	1.2%(2/166)	1.8%(6/332)	0.663	0.132	3.319	0.617
Length of hospital stay(days)	12.02±7.02	15.74±10.15	NA	NA	NA	<0.001	11.77±6.83	13.94±8.12	NA	NA	NA	0.003
Mortality	3.1%(6/185)	14.8%(190/1287)	0.194	0.085	0.443	<0.001	3.0%(5/166)	3.3%(11/332)	0.906	0.310	2.653	0.857

Abbreviations: NA, not applicable; ICU, Intensive Care Unit; HR, Hazard ratios; CI, Confidence interval.

Table 5 Comparison of Outcomes Parameters Between Patients with and without Antibiotic Use Before and After Propensity Score Matching

	Before 1:2 Propensity-Score Matching						After 1:2 Propensity-Score Matching					
	Non-Antibiotic use(n=149)	Antibiotic use (n=1287)	Crude HR	95% CI		P value	Non-Antibiotic use (n=139)	Antibiotic use (n=278)	Crude HR	95% CI		P value
Mechanical ventilation	6.7%(10/149)	32.0%(423/1287)	0.153	0.08	0.294	<0.001	5.0%(7/139)	9.0%(25/278)	0.537	0.226	1.273	0.158
Tracheal intubation	1.3%(2/149)	9.1%(120/1287)	0.136	0.033	0.557	0.006	1.4%(2/139)	3.6%(10/278)	0.391	0.085	1.811	0.230
ICU admission	1.3%(2/149)	12.7%(168/1287)	0.094	0.023	0.381	0.001	1.4%(2/139)	3.6%(10/278)	0.391	0.085	1.811	0.230
Length of hospital stay(days)	10.56±5.89	15.80±10.11	NA	NA	NA	<0.001	10.55±5.81	14.10±8.27	NA	NA	NA	<0.001
Mortality	2.7%(4/149)	14.5% (192/1287)	0.163	0.059	0.444	<0.001	2.2%(3/139)	4.3%(12/278)	0.489	0.136	1.762	0.274

Abbreviations: NA, not applicable; ICU, Intensive Care Unit; HR, Hazard ratios; CI, Confidence interval.

Current clinical trials on the efficacy of antibiotics in patients with COVID-19 are mainly limited to azithromycin for its supposed immunomodulatory and pro-inflammatory cytokines downregulation action. Nevertheless, subsequent research failed to demonstrate a significant clinical benefit of azithromycin against SARS-CoV-2.[28,29] Our study raises questions about the effectiveness of early antibiotic therapy on improving clinical outcomes, and we found that patients with early antibiotic use had worse outcomes, including increased all-cause mortality, prolonged length of hospital stay, higher risk of ICU admission, mechanical ventilation, and tracheal intubation before adjusting to patients' baseline characteristics. However, this apparent deterioration in outcomes should not be crudely attributed to early antibiotic treatment.[30] We concluded that the poor prognosis was due to the fact that early antibiotic therapy was more common in patients with older age and multiple comorbidities (including diabetes, chronic lung, and kidney diseases, and cardio-vascular disease), those with more severe disease conditions of COVID-19 (a large proportion of patients belonged to severe or critical subtype (62.9%)) and higher inflammatory markers level, rather than due to the effect of the antibiotic therapy itself. Considering that patients with the above characteristics were reported to have a higher risk of disease progression and death,[31,32] empiric antibiotic therapy was initiated at hospital admission.

Whereas, after carefully adjusting to these confounding factors likely to influence the prognosis, no significant correlation between early antimicrobial use and outcomes parameters was seen. Early antibiotic treatment failed to demonstrate a clear positive effect on all-cause mortality, the risk for ICU admission, mechanical ventilation, and tracheal intubation. These conclusions could apply to all subtypes of COVID-19 and all age groups. Furthermore, additional subgroup analyses in our supplement came to the same results. Buetti's research conducted in critically ill patients with COVID-19 also came to a similar conclusion that early administered antibiotics do not impact neither mortality or delayed hospital-acquired infections.[33] In the LEOSS cohort, compared with patients without antibiotic therapy, antibiotics therapy in SARS-CoV-2-infected patients did not illustrate a significant benefit for all-cause mortality or disease progression.[34] Compared with the first wave of COVID-19 (spring of 2020), less antimicrobial use was observed in the second wave (winter of 2020), which did not significantly affect mortality in critically ill patients.[35] With deeper knowledge of COVID-19, more and more data were reported to support our point that early antibiotic prescription does not appear to worsen nor improve the prognosis in the context of COVID-19.[36,37]

There are several limitations to our study. Firstly, this is a monocentric, retrospective study, and the number of patients without early antibiotic use was small. Secondly, viral in this study mainly included the COVID-19-Omicron variant for the study period limited from Dec 2022 to Mar 2023. Thirdly, COVID-19 patients without early antibiotic use (including delayed antibiotic use and non-antibiotics use) majorly belonged to non-severe COVID-19 patients, which needs more data to strengthen the credibility of this conclusion in severe and critical COVID-19 patients. In addition, inactivated vaccine and recombinant protein vaccine were the main types of vaccines for Chinese population. However, we ignored to make a detailed record of every patient's vaccination to explore the impact of vaccination on antibiotic prescription. And lack of comparison of antiviral drugs for COVID-19 between groups was another limitation of our study. Lastly, we need to further supplement the data on bacteria distribution and risk factors associated with bacterial co-infection during hospitalization in these patients to better understand the association between COVID-19 and bacterial co-infection.

Conclusion

Antibiotic consumption trending in our data indicated that early antibiotics were frequently prescribed in patients with more severe disease conditions (including older age, multiple comorbidities, severe and critical COVID-19 subtype, higher serum infectious indicators, and inflammatory indicators) at admission. However, compared with delayed antibiotics therapy or non-antibiotics therapy, early antibiotics therapy in hospitalized patients with COVID-19 does not successfully demonstrate better clinical outcomes in the propensity-score-matched cohorts. Therefore, our study did not recommend early antibiotic therapy for COVID-19 patients at hospital admission to prevent worsening worldwide antimicrobial resistance. The prescription of early empiric antimicrobial treatment should be restricted and carefully evaluated at hospital admission to reduce unnecessary antibiotic use and guide proper antibiotic management.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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