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## Evaluation of early antibiotic use in patients with non-severe COVID-19 without bacterial infection



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### ABSTRACT

**Objectives:** The use of antibiotics was common in some countries during the early phase of the coronavirus disease 2019 (COVID-19) pandemic, but adequate evaluation remains lacking. This study aimed to evaluate the effect of early antibiotic use in patients with non-severe COVID-19 admitted without bacterial infection.

**Methods:** This multi-centre retrospective cohort study included 1,373 inpatients with non-severe COVID-19 admitted without bacterial infection. Patients were divided into two groups according to their exposure to antibiotics within 48 h of admission. The outcomes were progression to severe COVID-19, length of stay >15 days and mortality rate. A mixed-effect Cox model and random effect logistic regression were used to explore the association between early antibiotic use and outcomes.

**Results:** During the 30-day follow-up period, the proportion of patients who progressed to severe COVID-19 in the early antibiotic use group was almost 1.4 times that of the comparison group. In the mixed-effect model, the early use of antibiotics was associated with higher probability of developing severe COVID-19 and staying in hospital for >15 days. However, there was no significant association between early use of antibiotics and mortality. Analysis with propensity-score-matched cohorts displayed similar results. In subgroup analysis, patients receiving any class of antibiotic were at increased risk of adverse health outcomes. Azithromycin did not improve disease progression and length of stay in patients with COVID-19.

**Conclusions:** It is suggested that antibiotic use should be avoided unless absolutely necessary in patients with non-severe COVID-19, particularly in the early stages.

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COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; ID, identification; EAU, early antibiotic use; NEAU, non-early antibiotic use; IQR, interquartile range; COPD, chronic obstructive pulmonary disease; NSAIDs, non-steroidal anti-inflammatory drugs; DID, difference-in-difference; SD, standard deviation; HR, hazard ratio; CI, confidence interval; OR, odds ratio; FEU, fibrinogen equivalent units.

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### 1. Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has spread rapidly worldwide since December 2019 [1]. This pandemic has brought a major challenge to global health systems [2]. However, as for severe acute respiratory syndrome and Middle East respiratory syndrome, there are no specific medications for COVID-19 other than supportive and adjunctive therapies [3].

Although antibiotic therapy is not recommended for patients with virus infections [4], the use of antibiotics was common in some countries during the early phase of the COVID-19 pandemic. A recent meta-analysis showed that the prevalence of antibiotic prescribing for patients with COVID-19 was 74.6% in the first 6 months of the pandemic [5]. A possible explanation for this is that the clinical symptoms of COVID-19 are similar to those of bacterial pneumonia, such as coughing, fever and fatigue [6]. When these

disease diagnoses cannot be identified effectively, clinicians usually treat patients with empirical or prophylactic antibiotics. In addition, most patients with COVID-19 have mild clinical symptoms in the early stages. A report of 72,314 cases by the Chinese Centre for Disease Control and Prevention showed that 81% of patients with COVID-19 were classified as non-severe cases [7]. When non-severe patients were admitted to hospital, their specific symptoms for COVID-19 were not obvious, and laboratory confirmation could not be obtained quickly due to the limited ability of nucleic acid testing. Moreover, antigen and antibody detection reagents based on immunochromatographic techniques were still in the development stage during the early phase of the COVID-19 pandemic [8,9]. It is anticipated that an increased number of non-severe patients will be prescribed with antibiotics for empirical or prophylactic therapy during the COVID-19 pandemic. Therefore, it is necessary to evaluate the effect of early antibiotic use in patients with COVID-19.

Few studies have been conducted to evaluate the efficacy of antibiotics in patients with COVID-19 [10]. Existing research has mainly focused on specific drugs, particularly azithromycin [11–14]. However, the effectiveness of azithromycin remains uncertain. Gautret et al. reported that the virological cure rate at day 5–6 post-inclusion among patients treated with a combination of hydroxychloroquine and azithromycin was significantly higher compared with patients treated with hydroxychloroquine alone and other control groups [15,16]. However, in some studies, azithromycin did not reduce in-hospital mortality [11] and was even associated with increased risk of lethal arrhythmias [17]. In these studies, azithromycin was evaluated for therapeutic efficacy as a potential drug to treat SARS-CoV-2 infection [12,13]. Few studies have evaluated the impact of empirical antibiotic use on clinical outcomes in patients with COVID-19 without bacterial infection. Thus, proper evaluation of the effect of the use of antibiotics among patients with COVID-19 is still needed.

Based on the data of patients admitted with non-severe COVID-19, this study used a retrospective cohort design to analyse the effects of antibiotic use within 48 h of admission on disease progression, length of stay and mortality rate to provide clinical evidence for the formulation of prescription and management strategies of antibiotic therapy for patients with COVID-19.

## 2. Materials and methods

### 2.1. Ethical approval

This study was conducted in accordance with the Declaration of Helsinki and approved by the Medical Ethics Committee of Tongji Medical College, Huazhong University of Science and Technology (Ref. 2020IECA252). The requirement for informed consent was waived by the Ethics Committee. Only pseudonymized data with no risk of identification were used for the analyses. The authors only had access to anonymized data, and had no interaction with patients or patient samples.

### 2.2. Study design and patients

This multi-centre retrospective cohort study analysed information on hospitalized patients with COVID-19 admitted to four hospitals in Hubei Province, China.

The diagnosis of COVID-19 was based on the interim guidance of the World Health Organization, and the Diagnosis and Treatment Protocol for COVID-19 Patients released by the National Health Commission of China [18,19]. All confirmed cases of COVID-19 included in this study were diagnosed by physicians based on epidemiological history, clinical symptoms, laboratory examination, aetiology, serological examination and chest imaging. In total,

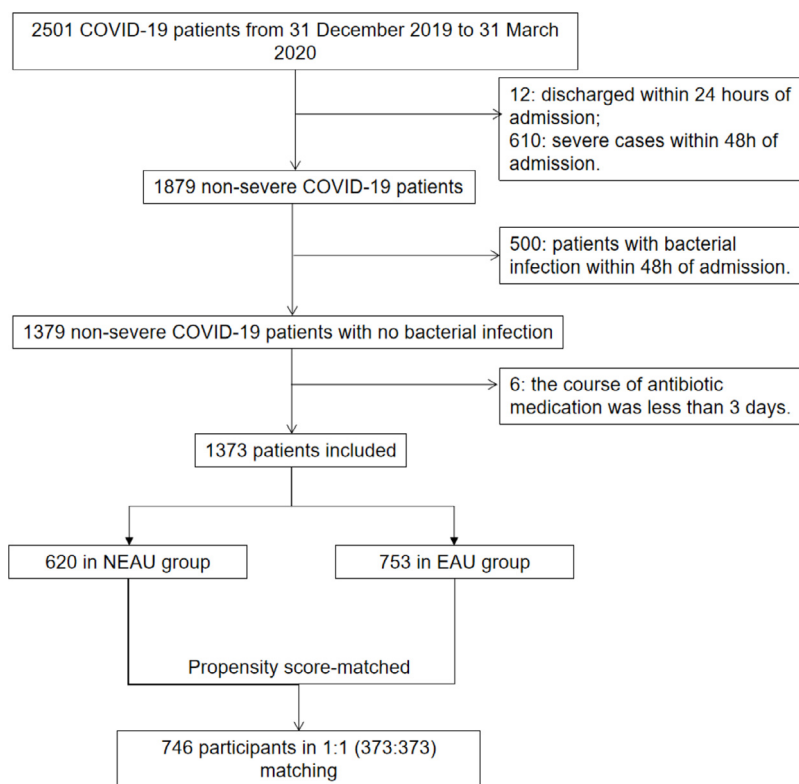
2,501 patients with COVID-19 were admitted to four hospitals in Hubei Province from 31 December 2019 to 31 March 2020. Patients were followed-up until 5 April 2020. The treatments received by the patients were standard of care in accordance with the Diagnosis and Treatment Protocol for COVID-19 Patients. This study aimed to analyse the effects of early antibiotic use on disease progression, length of stay and mortality rate among patients with COVID-19 without bacterial co-infection. In this study, early antibiotic use was defined as antibiotic use within 48 h of admission with a course of medication  $\geq 3$  days. Based on the definition of the Diagnosis and Treatment Protocol for COVID-19 Patients, there were four clinical classifications of patients with COVID-19: (1) mild cases: mild clinical symptoms and no evidence of pneumonia on chest radiology; (2) moderate cases: fever and respiratory symptoms and chest radiology suggestive of pneumonia; (3) severe cases: cases meeting any of the following criteria – respiratory rate  $\leq 30$  breaths per min, oxygen saturation  $\leq 93\%$  in a resting state, ratio of arterial partial pressure of oxygen and oxygen concentration  $\leq 300$  mmHg, and  $>50\%$  lesion progression in lung imaging within 24–48 h; and (4) critical cases: cases meeting any of the following criteria – respiratory failure requiring mechanical ventilation, other organ failure, shock or death. For this study, patients were grouped into two categories: severe (severe and critical cases) and non-severe (mild and moderate cases). Bacterial infection was defined using both clinical and laboratory data [20–22]; three physicians involved in the treatment of COVID-19 performed a chart review of the electronic medical records of patients, and determined bacterial infection using the majority rule. Indicators of bacterial infection were either significant positive microbiological cultures (e.g. blood, sputum, urine, stool, tracheal secretions) or a clinical picture that strongly suggested bacterial infection (e.g. radiological or laboratory tests).

The inclusion criteria were patients hospitalized with COVID-19 and admitted to the four hospitals in Hubei, China from 31 December 2019 to 31 March 2020. Exclusion criteria were: (1) patients discharged within 24 h of admission; (2) cases that became severe within 48 h of admission; (3) patients with bacterial infection within 48 h of admission; and (4) patients who received antibiotics within 48 h of admission, but whose medication course was  $< 3$  days.

Demographic information, clinical symptoms, medical history, in-hospital medication and clinical outcomes were obtained from the electronic medical system. Laboratory data (white blood cell count, procalcitonin, C-reactive protein, aspartate aminotransferase, alanine aminotransferase, albumin, albumin/globulin ratio, serum creatinine, blood urea, uric acid and D-dimer) were collected from the laboratory information system. Personal identification (ID) information including name and ID was anonymized, and a new study ID was generated for each patient.

### 2.3. Antibiotic exposure and outcomes

Antibiotic exposure was defined as commencing antibiotics within 48 h of hospital admission, with a course of duration  $\geq 3$  days; patients in this group were classified as the early antibiotic use group (EAU group). Otherwise, patients were classified as the non-early antibiotic use group (NEAU group). To further compare the efficacy of different classes of antibiotics, the following four situations of antibiotic administration were analysed in the subgroup analysis: (1) fluoroquinolones (J01M) alone; (2) cephalosporins (J01D) alone; (3) other classes of antibiotics alone, including penicillins (J01C) alone, macrolides (J01FA) alone, nitroimidazoles (J01XD) alone, aminoglycosides (J01G) alone, oxazolidinones (J01XX) alone, and lincosamides (J01FF) alone; and (4) a combination of two or more classes of antibiotics. Patients administered penicillins alone, macrolides alone, nitroimid-



**Figure 1.** Flowchart of patient enrolment. Patients with non-severe coronavirus disease 2019 (COVID-19) include mild cases and moderate cases. Patients with severe COVID-19 include severe cases and critical cases. Patients with the following two conditions were designated as bacterial infections in this study: (i) patients with positive microbiological cultures, including blood, sputum, urine, stool and tracheal secretions; and (ii) patients with no evidence of positive microbiological cultures, but in whom the clinical picture radiological evidence laboratory tests strongly suggest bacterial infection. NEAU, non-early antibiotic use; EAU, early antibiotic use.

idazoles alone, aminoglycosides alone, oxazolidinones alone and lincosamides alone were grouped together because of the small number of cases in each group. As azithromycin had been recommended as a therapeutic regimen for cases of COVID-19 [12,14], the effect of azithromycin was also analysed in a subgroup analysis. The study outcomes were: (1) progression from non-severe COVID-19 to severe COVID-19; (2) length of stay > 15 days; and (3) all-cause mortality during 30 days of in-hospital follow-up.

#### 2.4. Statistical analyses

Data are presented as median and interquartile range (IQR), or number and percentage, as appropriate. Comparisons of parameters between the two groups were conducted with the Wilcoxon–Mann–Whitney test for continuous variables. For categorical variables, Pearson's  $\chi^2$  test or Fisher's exact test was used. The risk of outcomes of interest was calculated using the Cox proportional hazard model if hazard curves for the EAU and NEAU groups were proportional (determined by the Kaplan–Meier curve) or logistic regression. Site was modelled as a random effect in the mixed-effect Cox model and random effect logistic regression. Factors associated with disease severity were adjusted in the multivariate analysis, including basic demographic characteristics (age and gender), symptoms (cough and fever), comorbidities [hypertension, diabetes, malignancy, chronic obstructive pulmonary disease (COPD) and coronary heart disease] and treatments [antiviral drugs, non-steroidal anti-inflammatory drugs (NSAIDs), steroids, immunomodulators and biologics]. The following variables were included for propensity score matching: basic demographic characteristics (age and gender), symptoms (cough and fever), vital signs (diastolic blood pressure and respiratory rate), comorbidities (hy-

pertension, diabetes, malignancy and COPD), treatments (antiviral drugs, NSAIDs, steroids, immunomodulators and biologics) and laboratory data on admission (white blood cell count, lymphocyte percentage and C-reactive protein). Two cohorts were matched at a ratio of 1:1 with a caliper width of 0.15. The balance among covariates was evaluated by estimating the standardized differences between two groups before and after matching. Only those with absolute value < 0.1 were considered as qualified matching. A sensitivity analysis was conducted to evaluate the robustness of propensity-score-matched cohort analyses. This additional analysis of the full dataset included the propensity score as a continuous variable in the model to adjust for differences in patient characteristics. For all comparisons, differences were tested using two-tailed tests, and  $P < 0.05$  was considered to indicate statistical significance.

The difference-in-difference (DID) methodology was employed to evaluate the impact of antibiotic use on liver function, kidney function and fibrinolytic activity, while controlling for confounding factors in linear regression analysis. The model was also adjusted for basic demographic characteristics (age and gender), symptoms (cough and fever), comorbidities (hypertension, diabetes, malignancy, COPD and coronary heart disease) and treatments (antiviral drugs, NSAIDs, steroids, immunomodulators and biologics). All analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA) and R 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria).

### 3. Results

Overall, 2,501 patients with COVID-19 were admitted to four hospitals in Hubei Province, China. Of these, 1,128 patients were

**Table 1**  
Characteristics of patients in early antibiotic use (EAU) and non-early antibiotic use (NEAU) groups before and after propensity score matching.

Parameters	Unmatched (n=1373)				P-value <sup>b</sup>	Matched (N=746) <sup>a</sup>				P-value <sup>b</sup>
	NEAU		EAU			NEAU		EAU		
<b>n</b>	620		753			373		373		
	Mean	SD	Mean	SD		Mean	SD	Mean	SD	
Age (years)	55.1	17.4	49.0	16.7	<0.0001	53.3	16.8	51.5	17.8	0.1596
Length of stay (days)	14.6	7.2	17.8	7.8	<0.0001	15.2	7.3	16.7	7.8	0.0059
<b>Laboratory test</b>										
White blood cell count (10 <sup>9</sup> /L)	5.7	1.6	5.2	2.1	<0.0001	5.6	1.6	5.5	2.0	0.4127
Lymphocyte percentage (%)	30.1	9.2	28.3	10.5	0.0009	29.8	9.4	29.8	10.9	0.9834
Procalcitonin (ng/L)	0.1	0.2	0.1	0.3	0.6396	0.1	0.2	0.1	0.4	0.6687
C-reactive protein (mg/L)	5.2	13.9	12.0	17.6	<0.0001	6.1	13.9	7.0	9.9	0.3103
<b>Vital signs</b>										
Pulse	83.7	13.5	85.9	13.5	0.0346	84.0	13.8	86.0	13.8	0.1275
SBP	131.6	17.3	125.2	14.1	<0.0001	129.1	16.8	126.5	15.1	0.0970
DBP	79.3	10.8	76.9	9.0	0.0016	78.5	11.1	77.7	9.5	0.4487
Respiratory rate	19.5	1.8	19.7	2.0	0.0493	19.5	1.8	19.7	2.0	0.1173
	n	%	n	%		n	%	n	%	
<b>Gender</b>					0.0154					0.7649
Female	331	53.39	451	59.89		222	59.52	226	60.59	
Male	289	46.61	302	40.11		151	40.48	147	39.41	
<b>Symptom</b>										
Cough	247	39.84	383	50.86	<0.0001	167	44.77	162	43.43	0.7124
Fever	279	45.00	501	66.53	<0.0001	207	55.50	199	53.35	0.5565
<b>Comorbidity</b>										
Hypertension	212	34.19	169	22.44	<0.0001	100	26.81	101	27.08	0.9342
Malignancy	25	4.03	44	5.84	0.1264	16	4.29	16	4.29	1.0000
Diabetes	98	15.81	76	10.09	0.0015	44	11.80	46	12.33	0.8221
COPD	37	5.97	45	5.98	0.9948	24	6.43	25	6.70	0.8825
Coronary heart disease	60	9.68	47	6.24	0.0181	27	7.24	28	7.51	0.8886
<b>Treatment</b>										
Antivirus drugs	503	81.13	718	95.35	<0.0001	341	91.42	341	91.42	1.0000
NSAIDs	137	22.10	226	30.01	0.0009	73	19.57	92	24.66	0.0937
Steroids	89	14.35	317	42.10	<0.0001	71	19.03	91	24.40	0.0757
Immunomodulators	30	4.84	233	30.94	<0.0001	27	7.24	32	8.58	0.4976
Biologics	140	22.58	340	45.15	<0.0001	90	24.13	100	26.81	0.4006
All-cause death (30 days)	11	1.77	12	1.59	0.7953	6	1.61	4	1.07	0.5243
Progression to severe disease (30 days)	136	21.94	239	31.74	<0.0001	87	23.32	115	30.83	0.0211

SD, standard deviation; SBP, systolic blood pressure; DBP, diastolic blood pressure; COPD, chronic obstructive pulmonary disease; NSAIDs, non-steroidal anti-inflammatory drugs.

<sup>a</sup> Propensity score matching was conducted to adjust for basic demographic characteristics (age and gender), symptoms (cough and fever), vital signs (DBP and respiratory rate), comorbidities (hypertension, diabetes, malignancy and COPD), treatments (antiviral drugs, NSAID, steroids, immunomodulators and biologics) and laboratory data on admission (white blood cell count, lymphocyte percentage and C-reactive protein).

<sup>b</sup> P-values were calculated by Chi-squared test or Fisher's exact test.

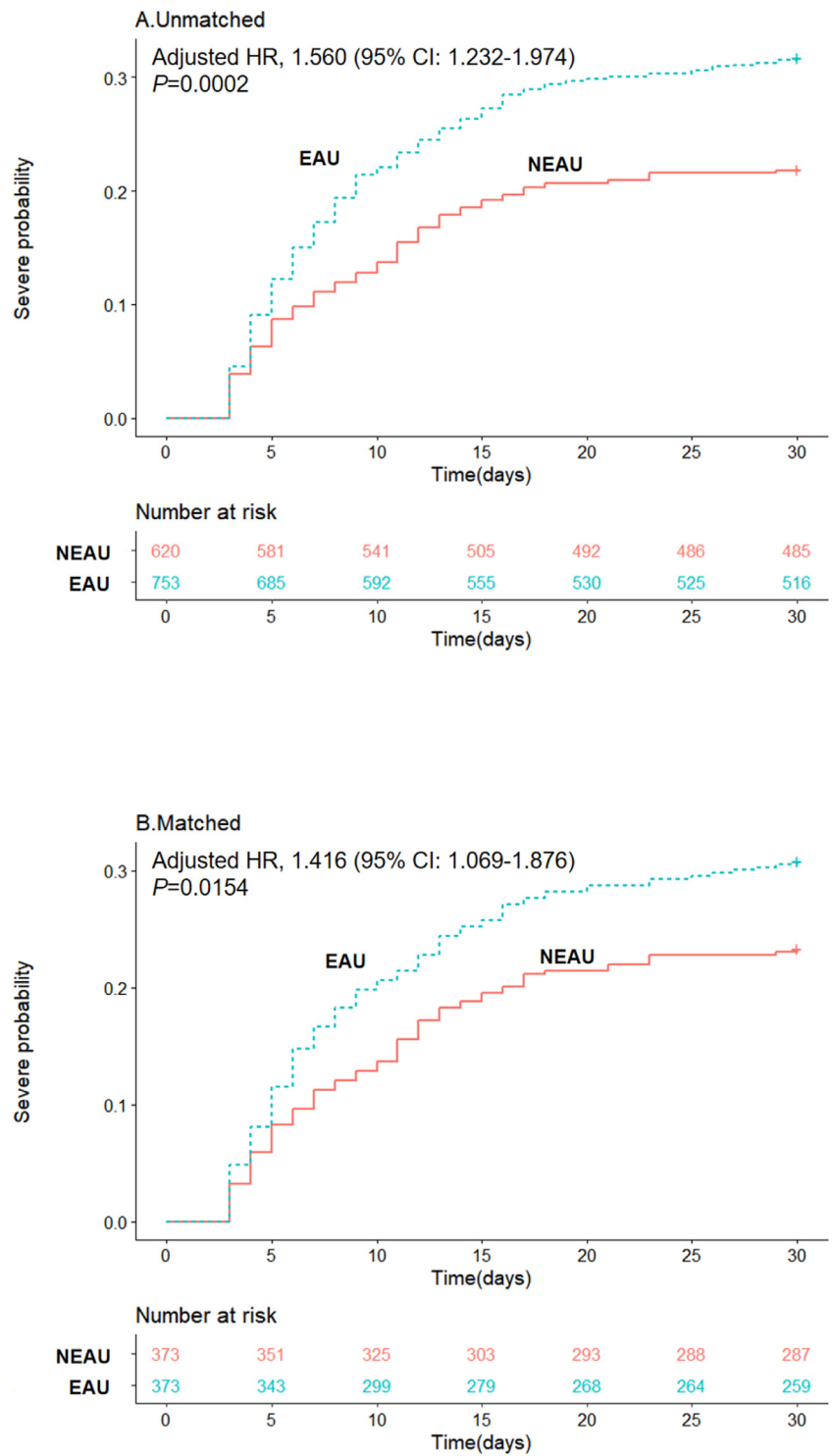
excluded, so 1,373 patients with non-severe COVID-19 without bacterial infection were included in the analysis (Figure 1). There were 753 patients in the EAU group and 620 patients in the NEAU group. In the EAU group, 438 patients received fluoroquinolones alone, 124 patients received cephalosporins alone, 38 patients received other antibiotics alone, and 153 patients received a combination of antibiotics. The mean ages of patients in the NEAU and EAU groups were 55.1 [standard deviation (SD) 17.4] and 49.0 (SD 16.7) years, respectively ( $P < 0.0001$ ). Over 50% of the patients were female in both groups. Compared with the NEAU group, the EAU group had higher prevalence rates of cough and fever, but lower prevalence rates of hypertension, diabetes and coronary heart disease. A higher proportion of the EAU group received antiviral therapies (95.35% vs 81.13%;  $P < 0.0001$ ). After propensity score matching, the two cohorts were balanced with no significant difference (Table 1). The standard mean differences shrank within the range of  $\pm 0.1$ , indicating good balance (Figure S1, see online supplementary material). Among the patients in the EAU group, eight different antibiotic classes were administered. The most frequently prescribed class of antibiotics was fluoroquinolones ( $n = 573$ , 76.10%), followed by cephalosporins ( $n = 191$ , 25.37%) and penicillins ( $n = 89$ , 11.82%) (Table S1, see online supplementary material). The frequencies of individual antibiotics prescribed are shown in Table S2 (see online supplementary material); the single most commonly pre-

scribed antibiotic was moxifloxacin, accounting for 37.84% of prescriptions.

### 3.1. Progression to severe COVID-19

During the 30-day follow-up period, 375 of the 1,373 patients admitted with non-severe COVID-19 progressed to severe disease. The proportion of patients who progressed to severe COVID-19 was higher in the EAU group compared with the NEAU group (31.74% vs 21.94%;  $P < 0.0001$ ) (Table 1). In the mixed-effect Cox model treating site as a random effect, the early use of antibiotics was associated with higher probability of progression to severe COVID-19 [adjusted hazard ratio (HR) 1.555, 95% confidence interval (CI) 1.227–1.970] (Figure 2A and Table 2).

Further analysis was conducted with propensity-score-matched datasets, in which 746 patients were included. In total, 373 patients in the NEAU group were matched with 373 patients in the EAU group at a ratio of 1:1. The results remained consistent, showing higher risk of progression to severe COVID-19 in the EAU group (adjusted HR 1.416, 95% CI 1.069–1.876) (Figure 2B and Table 2). The sensitivity analysis of the full dataset by including the propensity score as a continuous variable showed consistent results with the results of propensity-score-matched cohorts (adjusted HR 1.449, 95% CI 1.128–1.861) (Table 3).



**Figure 2.** Kaplan-Meier curves for cumulative probability of progression to severe coronavirus disease 2019 (COVID-19) during the 30-day follow-up period in the early antibiotic use (EAU) and non-early antibiotic use (NEAU) groups among 1373 patients in unmatched cohorts and 746 patients in matched cohorts. HR, hazard ratio; CI, confidence interval.

### 3.2. Length of stay

The average length of stay was 17.8 days (SD 7.8) for the EAU group and 14.6 days (SD 7.2) for the NEAU group ( $P < 0.0001$ ) (Table 1). In the mixed-effect model, antibiotic use was associated with higher risk of staying in hospital for >15 days [adjusted odds ratio (OR) 1.827, 95% CI 1.389–2.403]. In propensity-score-matched cohort analysis, higher risk was also observed for patients administered antibiotics within 48 h of admission (adjusted OR 1.784,

95% CI 1.279–2.487) (Table 2). The sensitivity analysis of the full dataset showed consistent results with the results of propensity-score-matched cohorts (adjusted OR 1.664, 95% CI 1.244–2.227) (Table 3).

### 3.3. All-cause mortality during 30 days of in-hospital follow-up

During the 30-day follow-up period, 23 of 1,373 patients with COVID-19 died. There was no significant difference in the risk of

**Table 2**  
Relative risks for outcomes in early antibiotic use (EAU) or non-early antibiotic use (NEAU) groups under the mixed-effect model before and after propensity score matching.

	Unmatched (n=1373)				Matched (n=746) <sup>a</sup>							
	Crude <sup>b</sup>		Mixed-effect model <sup>c</sup>		Crude <sup>b</sup>		Mixed-effect model <sup>c</sup>					
	HR	95% CI	P-value	HR	95% CI	HR	95% CI	P-value				
Progression to severe disease	1.560	1.232	1.974	0.0002	1.555	1.227	1.970	1.876	1.416	1.069	1.876	0.0154
	OR	95% CI		P-value	OR	95% CI		OR	95% CI	OR	95% CI	P-value
Length of stay > 15 days	1.711	1.308	2.240	<0.0001	1.827	1.389	2.403	2.328	1.784	1.279	2.487	0.0007
All-cause mortality (30 days)	3.070	1.008	9.348	0.0484	3.051	1.001	9.301	5.909	1.190	0.237	5.969	0.8324

OR, odds ratio; CI, confidence interval; HR, hazard ratio; COPD, chronic obstructive pulmonary disease; NSAIDs, non-steroidal anti-inflammatory drugs.  
<sup>a</sup> Propensity score matching was conducted to adjust for basic demographic characteristics (age and gender), symptoms (cough and fever), vital signs (diastolic blood pressure and respiratory rate), comorbidities (hypertension, diabetes, malignancy and COPD), treatments (antiviral drugs, NSAIDs, steroids, immunomodulators and biologics) and laboratory data on admission (white blood cell count, lymphocyte percentage and C-reactive protein).  
<sup>b</sup> Crude estimations were adjusted for basic demographic characteristics (age and gender), symptoms (cough and fever), comorbidities (hypertension, diabetes, and coronary heart disease, malignancy and COPD) and treatments (antiviral drugs, NSAIDs, steroids, immunomodulators and biologics).  
<sup>c</sup> Site (hospital) was modelled as a random effect in the multi-variate analyses.

all-cause mortality during the 30-day follow-up period between the EAU group and the NEAU group [1.59% (12/753) vs 1.77% (11/620);  $P=0.7953$ ] (Table 1). The mixed-effect model (adjusted OR 3.051, 95% CI 1.001–9.301) and analysis with propensity-score-matched cohorts (adjusted OR 1.190, 95% CI 0.237–5.969) displayed similar results (Table 2).

### 3.4. Subgroup analysis

There was no evidence of improved health outcomes in patients who received any class of antibiotics (Tables S3 and S4, see online supplementary material). Of particular note, there was no significant difference in progression to severe COVID-19 (adjusted HR 2.225, 95% CI 0.862–5.745) or length of stay (adjusted HR 1.515, 95% CI 0.441–5.201) between patients who received azithromycin and those who did not receive antibiotics after propensity score matching (Table S4, see online supplementary material). The case number was too low for assessment of the effect of azithromycin on survival.

### 3.5. Liver function, kidney function and fibrinolytic activity

After adjusting for covariates, the DID estimator was negative and statistically significant at the 1% level for albumin, and it was positive and statistically significant for D-dimer. Albumin decreased by 2.5 g/L in the EAU group and by 1.4 g/L in the NEAU group. D-dimer increased by 1.7  $\mu\text{g/mL}$  fibrinogen equivalent units (FEU) in the EAU group and decreased by 0.1  $\mu\text{g/mL}$  FEU in the NEAU group (Table S5A, see online supplementary material). However, the effect of early antibiotic use on blood examination indicators was not significant in the propensity-score-matched cohorts (Table S5B, see online supplementary material).

## 4. Discussion

This study found that early use of antibiotics in patients with non-severe COVID-19 without bacterial infection was associated with progression to severe COVID-19 and longer length of hospital stay, and had no effect on 30-day survival. Subgroup analysis showed that this held for all antibiotic types.

Antibiotic use was common among patients with COVID-19 in the early phase of the pandemic [5]. One possible explanation for the adverse impact of antibiotics is dysbiosis, which occurs within 4–7 days of antibiotic use [23,24]. Considering that the length of stay of patients in the EAU group was 17.8 days, dysbiosis is certainly temporally feasible. Microbial balance has a positive impact on lung immunity. The gut microbiome can activate G-protein-coupled receptors to inhibit inflammation in the lung via its metabolisms, such as short-chain fatty acids to reduce lung injury [25–27]. By affecting the composition and function of the microbiome, antibiotic use has been proven to undermine the ability of the lungs to clear pathogens and make the lungs more vulnerable to viral infection [28–31].

Previous studies have suggested that antibiotic treatment without bacterial infection could cause a cytokine storm and a septic-shock-like picture [32–36]. This release of pro-inflammatory cytokines may promote immune dysfunction and tissue damage, and increase susceptibility to infection [37]. In the context of COVID-19, antibiotic exposure – by adding to the release of pro-inflammatory cytokines – could be associated with higher risk of progression from non-severe to severe disease.

The finding that azithromycin was not associated with lower risk of progression to severe COVID-19 or reduced length of stay is consistent with a multi-centre retrospective cohort study in New York [11]. A Spanish observational study also found no significant association between azithromycin and length of stay in patients

**Table 3**

Relative risks for outcomes in early antibiotic use (EAU) and non-early antibiotic use (NEAU) groups while including the variable propensity as a covariate in the mixed-effect model ( $n=1373$ ).

	Crude <sup>a</sup>			Mixed-effect model <sup>b</sup>			P-value	
	HR	95% CI	P-value	HR	95% CI	P-value		
Progression to severe disease	1.444	1.126	1.853	0.0038	1.449	1.128	1.861	0.0037
	OR	95% CI	P-value	OR	95% CI	P-value		
Length of stay >15 days	1.621	1.217	2.159	0.0010	1.664	1.244	2.227	0.0006
All-cause mortality (30 days)	2.710	0.725	10.136	0.1384	2.733	0.732	10.206	0.1345

OR, odds ratio; CI, confidence interval; HR, hazard ratio.

<sup>a</sup> Crude estimations were adjusted for basic demographic characteristics (age and gender), symptoms (cough and fever), comorbidities (hypertension, diabetes, coronary heart disease, malignancy and chronic obstructive pulmonary disease) and treatment (antiviral drugs, non-steroidal anti-inflammatory drugs, steroids, immunomodulators and biologics).

<sup>b</sup> Site (hospital) was modelled as a random effect in the multi-variate analyses.

with COVID-19 [38]. Moreover, a recent meta-analysis of randomized clinical trials showed no benefit of azithromycin on length of stay [39].

Average changes in the decrease of albumin and the increase in D-dimer were greater in the EAU group compared with the NEAU group. This may be due to increased release of pro-inflammatory factors by antibiotics [33–35]. Several pro-inflammatory factors such as interleukin-6 and tumour necrosis factor- $\alpha$  can inhibit the synthesis of albumin in the liver [40–42]. A decreased level of albumin is involved in the regulation of coagulation function [43]. Pro-inflammatory factors can also lead to systemic inflammatory response syndrome and subsequent damage to the vascular system and extensive microthrombosis [44–46]. Elevation of D-dimer indicates a hypercoagulable state in patient with COVID-19 [47]. However, the differences in the changes of albumin and D-dimer were not significant in the propensity-score-matched cohorts. Further investigation in large clinical trials is needed to assess the influence of antibiotics on liver/renal function and coagulation among patients with COVID-19.

This study does have some limitations. First, it was not possible to retrieve details of pre-admission self-medication with antibiotics. Second, due to limited test availability during the early stages of the pandemic, not all patients in this study had their diagnosis of COVID-19 confirmed virologically. Third, the sample size was too small to determine reliably whether there was any association between antibiotic use and survival. Fourth, as a single-locality study, the possibility of regional or ethnic differences cannot be excluded. Fifth, obesity is known to be associated with increased risk of unfavourable clinical outcomes, including death, in patients with COVID-19 [48–51]. Although body mass index was not addressed directly in this study, obesity-related comorbidities such as diabetes were adjusted in the analysis to partially mitigate the effect of obesity on outcome. Sixth, although a commonly used official definition of severe cases was adopted in this study, some previous studies used admission to an intensive care unit as a standard [52,53]. Seventh, although propensity score matching and additional propensity score matching analysis were used to balance disease severity between the EAU and NEAU groups, it was only possible to adjust for known and measurable confounders. Thus, it was not possible to eliminate selection bias completely caused by unidentified confounders that affected severity of disease. Further randomized clinical trials are needed to verify the impact of early antibiotic use in patients with non-severe COVID-19.

## 5. Conclusion

This study found that early use of antibiotics among patients with non-severe COVID-19 was significantly associated with the risk of progression to severe disease, and prolonged hospitalization. Azithromycin use was not associated with better clinical outcomes. It is suggested that antibiotic use should be avoided in patients

with non-severe COVID-19 in the absence of evidence of bacterial infection.

## Author contributions

XY, NX and YG were responsible for the conception, design and writing of the manuscript. XY, XX and NX were responsible for the acquisition of data and literature research. XX, YG, HL, NJ, JW and ZL were responsible for the analysis and interpretation of data. All authors reviewed and revised the manuscript and approved the final version.

## Declaration of Competing Interest

None declared.

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## Ethical approval

This study was approved by the Medical Ethics Committee of Tongji Medical College, Huazhong University of Science and Technology (Ref. 2020IECA252).

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijantimicag.2021.106462.

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