Evaluation of early antibiotics use in non-severe COVID-19 patients admitted with low risk of bacterial infection

Xiaoxv Yin

Department of Social Medicine and Health Management, School of Public Health, Tongji Medical College, Huazhong University of Science and Technology
<https://orcid.org/0000-0002-5020-2984>

Li Liu

Office of Academic Research, The Central Hospital of Wuhan, Tongji Medical College, Huazhong University of Science and Technology

Xing Xu

Department of Social Medicine and Health Management, School of Public Health, Tongji Medical College, Huazhong University of Science and Technology

Lei Huang

Office of Academic Research, The Central Hospital of Wuhan, Tongji Medical College, Huazhong University of Science and Technology

Ping Jing

Department of Neurology, The Central Hospital of Wuhan, Tongji Medical College, Huazhong University of Science and Technology

Hui Li

Department of Social Medicine and Health Management, School of Public Health, Tongji Medical College, Huazhong University of Science and Technology

Nan Jiang

Department of Social Medicine and Health Management, School of Public Health, Tongji Medical College, Huazhong University of Science and Technology

Jing Wang

Department of Social Medicine and Health Management, School of Public Health, Tongji Medical College, Huazhong University of Science and Technology

Zuxun Lu

Department of Social Medicine and Health Management, School of Public Health, Tongji Medical College, Huazhong University of Science and Technology

Yanhong Gong (✉ gongyanhong@hust.edu.cn)

Department of Social Medicine and Health Management, School of Public Health, Tongji Medical College, Huazhong University of Science and Technology
<https://orcid.org/0000-0002-7838-1996>

Nian Xiong (✉ nianxiong@hust.edu.cn)

Department of Neurology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology

Changjun Li (✉ hydlcj@163.com)

Department of Neurology, The Central Hospital of Wuhan, Tongji Medical College, Huazhong University of Science and Technology

Research Article

Keywords: COVID-19, antibiotics, non-severe, progression, length of stay, secondary bacterial infections, mortality

Posted Date: July 2nd, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-39522/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License. [Read Full License](#)

Abstract

The use of antibiotics is common in the treatment of COVID-19, but adequate evaluation is lacking. This study aimed to evaluate the effect of early antibiotic use in non-severe COVID-19 patients admitted with low risk of bacterial infection. The multi-center retrospective cohort study included 1613 non-severe COVID-19 inpatients admitted with low risk of bacterial infection. During the follow-up of 30 days, the proportion of patients progressed into severe type COVID-19 in the early antibiotics use group was almost 1.5 times than that of the comparison group. In the mixed-effect model, the early use of antibiotics was associated with higher probability of developing severe type, staying in the hospital for over 15 days, and secondary infection. However, it was not significant association with mortality rate. Analysis with propensity score-matched cohort displayed similar results. It is suggested that antibiotic use should be avoided unless absolutely necessary in non-severe COVID-19 patients, particularly in the early stages.

Introduction

The coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread rapidly worldwide since December 2019¹. This pandemic has brought a major challenge to the current global health systems². However, except for treatment experience of earlier strains of coronavirus, severe acute respiratory syndrome (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), there are no specific treatments against COVID-19 to date³.

The use of antibiotics is common in the treatment of COVID-19. A recent review found that bacterial/fungal co-infection was present in only 8% of patients with COVID-19, however, 72% received antibacterial therapy⁴. The possible explanation is that the clinical symptoms of COVID-19 are similar to those of bacterial pneumonia, such as coughing, fever, and fatigue⁵. Moreover, 44.3% of COVID-19 patients showed increase of C-reactive protein⁶. When these disease diagnoses cannot be effectively identified, clinicians usually give empirical or prophylactic antibiotic treatments against COVID-19. And some national guidelines and cases series have suggested the use of broad spectrum antibiotics or the benefit of atypical antibiotic cover^{7,8}.

Severe COVID-19 is an important cause of death in confirmed patients⁹. However, in fact most COVID-19 patients have mild clinical symptoms in the early stages. A report of 72,314 cases by the Chinese Center for Disease Control and Prevention showed that 81% of COVID-19 patients were classified as non-severe patients¹⁰. When non-severe patients were admitted, their specific symptoms with COVID-19 were not obvious, and laboratory confirmation could not be obtained quickly due to the limited ability of nucleic acid testing. Therefore, it is anticipated that during the COVID-19 pandemic an increased number of non-severe patients will require commencement on empirical antibiotic therapy. In viral infections, empirical or prophylactic antibiotic treatment has long been controversial^{11,12}. Reliable evidence on whether antibiotic treatment has an impact on progression and outcome in patients with non-severe COVID-19 is required. However, there is a lack of research.

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

Results

Overall, 2501 patients were admitted to 4 hospitals in Hubei Province, China. According to the inclusion/exclusion criteria, after excluding 888 patients, eventually 1613 patients were included in the analysis (Fig. 1). Among them, 996 patients received antibiotics within 48 hours after admission (EAU group) and 617 did not receive antibiotics or received antibiotics exceeding 48 hours after admission (NEAU group). The median age at diagnosis in NEAU group was 57 year-old and 54 in EAU group and the difference was statistically significant ($P = 0.0028$). Around 55% of the patients were female in both groups. Compared with the NEAU group, the EAU group had higher prevalence of cough and fever, but lower prevalence of hypertension. In Addition, the EAU group had a higher percentage of patients receiving antiviral therapies (96.29% vs. 82.01%; $P < 0.0001$) than patients in the NEAU group.

Progression to severe type COVID-19

During the follow-up of 30 days, out of the 1613 patients admitted with non-severe type COVID-19, 498 patients progressed into severe type. The proportion of patients progressed into severe type COVID-19 in the EAU group was almost 1.5 times than that of NEAU group (36.24% vs 22.20%; $P < 0.0001$). In the mixed-effect Cox model treating site as a random effect, after adjusting for age, gender, comorbidities and in-hospital medications (antiviral drugs), the early use of antibiotics was associated with higher probability of developing severe type (adjusted HR = 1.87, 95% CI: 1.53–2.29) (Fig. 2A, Table2).

Further analysis was done with propensity score-matched datasets, in which 1222 patients were included, with 611 patients in NEAU group were matched with 611 patients in the EAU group at a ratio of 1:1. The results remained consistent, showing higher risk of turning into severe type in EAU group (adjusted HR = 1.67, 95% CI: 1.35–2.09) (Fig. 2B, Table2).

Length of stay

The average length of stay in EAU group was 18 days and NEAU group 13 days ($P < 0.0001$). In the mixed-effect model, the use of antibiotics was associated with higher risk of staying in the hospital for over 15 days (adjusted OR = 2.34, 95% CI: 1.88–2.92) (Table2). In propensity score-matched cohort analysis, higher risk was also observed for patients administered with antibiotics within 48 hours after admission (adjusted OR = 2.20, 95% CI: 1.72–2.80).

Secondary bacterial infection

The incidence rates of secondary bacterial infection during 30 days of in-hospital follow-up in the EAU group and NEAU group were 20.42% and 12.22% respectively ($P = 0.0007$). The mixed-effect model showed that the patients in the EAU group was at higher risk of experiencing secondary infection (adjusted OR = 1.90, 95% CI: 1.32–2.75) (Table2). Analysis with propensity score-matched cohort displayed similar results (adjusted OR = 1.69, 95% CI: 1.14–2.51).

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

During a 30-day follow-up duration, 40 died out of the 1613 patients with COVID–19. There was no significantly difference in risk of all-cause mortality during 30 days of in-hospital follow-up between EAU group and NEAU group (1.62% [10/617] vs. 3.01% [30/996]; $P = 0.08$). The mixed-effect model (adjusted OR = 1.98, 95% CI: 0.94–4.19) and analysis with propensity score-matched cohort (adjusted OR = 1.62, 95% CI: 0.71–3.70) displayed similar results.

Liver function, kidney function and fibrinolytic activity

As shown in Table 3, adjusting for patients' sex, age, comorbidities, and whether or not received antiviral drugs), the DID estimator was negative and statistically significant at the 5% level in ALB and A/G, and it was positive and statistically significant in ALT, UA, and D-Di. The albumin and A/G decreased by 1.5 g/L and 0.1, respectively; while ALT, UA, and D-Di increased by 22.6 U/L, 23.6 $\mu\text{mol/L}$, and 1.9 $\mu\text{g/mL}$ FEU, respectively. The effect of early antibiotics use on other blood examination indicators was not significant in this study.

Discussion

Our study found that in the absence of clear evidence of bacterial infection, early empirical or prophylactic antibiotic treatment augmented the risk of progression from non-severe to severe, increased the incidence of secondary bacterial infections, and prolonged hospitalization in non-severe COVID–19 patients. In addition, there was no significant difference in mortality rate between the non-severe COVID–19 patients who received antibiotics early and those who did not.

The composition of balanced gut microbiota has a significant influence on the effectiveness of lung immunity¹⁵. Disruption of gut microbiota has been shown to impair pathogen clearance capability in the lung and increase susceptibility to influenza virus infection in lungs¹⁶. Coincidentally, the SARS-CoV–2 receptor ACE2 is highly expressed on human small intestinal enterocytes, but small intestinal enterocytes can be readily infected by SARS-CoV and SARS-CoV–2^{17,18}. Previous studies showed that antibiotic use in SARS-CoV–2-infected individuals may exacerbate dysbiosis of the gut microbiota and contribute to further lung injury^{16,19}. Thus, the imbalance of gut microbiota caused by early antibiotic use might have a potential impact on the progression of non-severe COVID–19 patients.

Studies warned antibiotic treatment without clear evidence of bacterial infection might lead to cytokine storms and septic shock²⁰. Antibiotics themselves can stimulate the immune cells to secrete pro-inflammatory cytokines (such as TNF- α , IL–1, IL–2 and IL–6), and increase the Toll-like receptor 4 (TLR4) expression^{21–23}. It means that the release of pro-inflammatory factors due to antibiotics may contribute to cytokine storm which accompanies COVID–19. The systemic inflammatory response syndrome (SIRS) caused by the release of a high number of pro-inflammatory cytokines leads to vascular system damage and extensive microthrombosis^{24–26}. Moreover, some pro-inflammatory factors such as IL–6 and TNF- α inhibit the synthesis of albumin in the liver^{27–29}. Albumin is involved in the regulation of coagulation function, and hypoproteinemia can lead to hypercoagulability³⁰. In our study, the use of antibiotics resulted in a decrease in albumin and an increase in D-dimer, which indicated that increased release of pro-inflammatory factors caused by antibiotics may exacerbate hypoproteinemia and secondary fibrinolysis hyperactivity. Our study also showed a significant association between early antibiotics use and drug-induced liver injury. So we cannot rule out the effect of liver function damage on albumin and d-dimer levels. According to the above, the intensification of cytokine release, hypoproteinemia and D-dimer elevation caused by antibiotics may also contribute to the progression of COVID–19.

This study also found that the rate of secondary bacterial infection during hospitalization in the COVID–19 patients treated with antibiotics early is significantly higher than that in patients who did not (20.42% vs. 12.22%). The possible reasons for this as follow: first, imbalance of gut microbiota, release of pro-inflammatory factors and other mechanisms caused by antibiotic use damaged human immunity in early admitted COVID–19 patients, which could increase the risk of nosocomial bacterial infection; second, the invasion of patients' own opportunistic bacteria was also one of the reasons for secondary bacterial infection. A study reported that almost all of COVID–19 patients who died were complicated by secondary bacterial infection³¹. Thus, reducing empiric or prophylactic antibiotic treatment in early admitted COVID–19 patients may reduce the risk of secondary bacterial infection even death in these patients.

Our study provided a timely evaluation of the use of antibiotics among non-severe COVID–19 patients with a strict inclusion and exclusion standard. It was the first to put a focus on the transformation of the severity of the disease. This study provides evidence-based support for optimizing antibiotic use guidelines in COVID–19 patients. The study also has some limitations. First, as this study was a retrospective study, the missing of some parameters might lead to the deviation of our observation results. For example, the absence of white blood cell counts and procalcitonin (PCT) data in 404 patients after 48 hours may lead to a bias in secondary infection rates. Second, in this study, we were unable to retrieve pre-hospital self-medication, especially the use of antibiotics, from the electronic medical record system, so we could not observe their effect on the changes in patients' condition and prognosis. Third, according to our data, 62 antibiotics, belonging to 16 major classes of antibiotics, were used in the currently enrolled COVID–19 patients from four hospitals in Hubei province. Due to diversity of the types of antibiotics used clinically and the different courses of treatment, we were unable to specifically assess the

potential impact of a particular antibiotic. Forth, there are regional and ethnic limitations. Large clinical cohort studies targeting different regions and ethnic groups are needed to further explore the impact of early antibiotic use on COVID-19 patients.

Conclusion

This study found that early empirical or prophylactic antibiotic treatment against non-severe COVID-19 patients is significantly associated with the risk of progression from non-severe to severe, secondary bacterial infections, and prolonged hospitalization. Furthermore, non-severe COVID-19 patients received antibiotics was more prone to Hypoproteinemia and D-dimer elevation. Regarding the above-mentioned effects of antibiotic use, we suggest that antibiotic use should be avoided unless absolutely necessary in non-severe COVID-19 patients, particularly in the early stages.

Methods

Ethical Statement

This study was approved by the Medical Ethics Committee of Tongji Medical College, Huazhong University of Science and Technology. The requirement for informed consent was waived by the Ethics Committee. Only pseudonymized data with no risk of identification were used for our analyses.

Study design and patients

This multi-center retrospective cohort study analyzed information on hospitalized patients with COVID-19 admitted to four hospitals in Hubei Province, China, the Central Hospital of Wuhan of Tongji Medical College, Huazhong University of Science and Technology, Wuhan Red Cross Hospital, the Central Hospital of Enshi Tujia and Miao Autonomous Prefecture and Lichuan People's Hospital.

The diagnosis of COVID-19 was confirmed according to the WHO interim guidance and the Diagnosis and Treatment Protocol for Coronavirus Pneumonia (trial version 7) released by National Health Commission of China^{13,14}. A total of 2501 patients with COVID-19 were admitted to four hospitals in Hubei Province from 31st December, 2019 to 31st March, 2020. Patients were followed up until 5th April, 2020. Based on the definition of the Protocol, patients were divided into non-severe and severe type according to the respiratory rate, pulse oxygen saturation and acute organ failure. Patients had severe disease if they had any of the following criteria: respiratory rate (RR) ≥ 30 breaths/min, pulse oxygen saturation (SpO₂) $\leq 93\%$, shock, or acute organ failure.

In this study, early antibiotic use was defined as patients receiving antibiotic treatment within 48 hours after admission. Since COVID-19 patients and bacterial pneumonia patients all have clinical symptoms such as cough, fever, elevated C-reactive protein and pulmonary imaging changes, patients with white blood cell (WBC) count $< 9.5 \times 10^9/L$ ($3.5 - 9.5 \times 10^9/L$) and procalcitonin (PCT) $< 0.5 \text{ ng/ml}$ ($0 - 0.5 \text{ ng/ml}$: a low rate of bacterial infection) within 48 hours after admission were defined as having a low risk of bacterial infection. Therefore, the inclusion criteria contained: 1) patients with SARS-CoV-2 infection who were admitted to the above-mentioned hospitals in Hubei, China from 31st December 2019 to 31st March, 2020; 2) within 48 hours after admission, respiratory rate (RR) < 30 breaths/min, pulse oxygen saturation (SpO₂) $> 93\%$, without shock or acute organ failure. The exclusion criteria contained: 1) patients who were intubated, dead, or discharged within 24 hours of admission; 2) within 48 hours after admission, white blood cell (WBC) count $\geq 9.5 \times 10^9/L$ or procalcitonin (PCT) $\geq 0.5 \text{ ng/ml}$; 3) received antibiotics treatment within 48 hours after admission, but the treatment course was less than 3 days.

The demographic information, clinical symptoms, medical history, in-hospital medication, and clinical outcomes were obtained from the electronic medical system. Laboratory data (WBC count, PCT, aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin (Alb), albumin /globulin ration (A/G), serum creatinine (Scre), blood urea (BUN), uric acid (UA), D dimer (D-Di)) were collected from the laboratory information system. The personal identification information including name and ID was anonymized and a new study ID was generated for each patient to avoid the possibility of identifying individual patient.

Exposure and outcomes

The exposure in this study was defined as the treatment of antibiotics prescribed within 48 hours after admission, with a course of treatment ≥ 3 days; and patients in this group were classified as early antibiotic use group (EAU group). Otherwise, patients were defined as the non early antibiotic use group (NEAU group). The antibiotics were identified using the Anatomic Treatment and Chemical classification, code J01. The study outcomes were: 1) progressing from non-severe type COVID-19 into severe type; 2) length of stay over 15 days; 3) secondary bacterial infection (WBC count $> 9.5 \times 10^9/L$ or PCT $> 0.5 \text{ ng/ml}$) during 30 days of in-hospital follow-up. 4) all-cause death during 30 days of in-hospital follow-up.

Statistical analyses

Data are presented as the medians and interquartile ranges (IQRs), or numbers and percentages (%), as appropriate. Comparison of parameters between two groups were conducted with the Wilcoxon-Mann-Whitney-Test for continuous variables. For categorical variables, Pearson's χ^2 test or Fisher's exact tests were used. The risk of outcomes of interest was calculated by 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 modeled as a random effect in the mixed-effect Cox model and random effect logistic regression. Multivariate analyses were all adjusted for age, gender, comorbidities (hypertension and diabetes), and treatment (antivirus drugs). Based on potential confounding factors associated with the exposure to antibiotics, including age, gender, comorbidities (hypertension and diabetes), and symptoms

(cough and fever), propensity score-matched cohorts were established. The EAU group and its matched control unit was set to have the same proportion of female/male patients.

The difference-in-difference (DID) methodology was employed to evaluate the impact of antibiotics use on liver function, kidney function, and fibrinolytic activity, while controlling for confounding factors in linear regression analysis. The DID approach has been widely used to examine outcome measures for treatment groups and comparison groups that are not randomly assigned. The DID estimations from linear regression models were able to capture the net effects of the early antibiotics use, where a negative or positive estimate from the DID models would indicate that a measure of blood examination indicator decreased or increased more over time in patients EAU group than those in NEAU group. The model were also adjusted for age, gender, comorbidities (hypertension and diabetes), and treatment (antivirus drugs). All analyses were performed using SAS 9.4 (by SAS Institute Inc., Cary, NC, USA).

Declarations

Data availability

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

Acknowledgements

This study was funded by the Fundamental Research Funds for the Central Universities (No. 2016YXMS224), Huazhong University of Science and Technology.

Authors contributions

XY, YG, NX, and CL were responsible for the conception, design, and writing of the manuscript. LL, LH, and PJ 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.

Competing interests

The authors declare no conflicts of interest.

References

1. Lai CC, Shih TP, Ko WC, Tang HJ, Hsueh PR. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): The epidemic and the challenges. *Int J Antimicrob Agents*. **55**, 105924 (2020).
2. Zhu N, Zhang D, Wang W, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. *N Engl J Med*. **382**, 727-33 (2020).
3. Rismanbaf A. Potential Treatments for COVID-19. a Narrative Literature Review. *Arch Acad Emerg Med*. **8**, e29 (2020).
4. Rawson TM, Moore LSP, Zhu N, et al. Bacterial and fungal co-infection in individuals with coronavirus: A rapid review to support COVID-19 antimicrobial prescribing. *Clin Infect Dis* (2020). published online May 2. DOI: 10.1093/cid/ciaa530.
5. Wang D, Hu B, Hu C, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA*. **323**, 1061-9 (2020).
6. Li LQ, Huang T, Wang YQ, et al. COVID-19 patients' clinical characteristics, discharge rate, and fatality rate of meta-analysis. *J Med Virol* (2020). published online Mar 12. DOI: 10.1002/jmv.25757.
7. Gautret P, Lagier JC, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *Int J Antimicrob Agents* (2020). published online Mar 20. DOI: 10.1016/j.ijantimicag.2020.105949.
8. Zheng YX, Chen J, Kong DC, et al. [Pathogenic characteristics of hospitalized severe acute respiratory infections in Shanghai, China, 2015-2017]. *Zhonghua Liu Xing Bing Xue Za Zhi*. **40**, 911-916 (2019). (in Chinese)
9. Richardson S, Hirsch JS, Narasimhan M, et al. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. *JAMA*. **323**, 2052-9 (2020).
10. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72314 Cases From the Chinese Center for Disease Control and Prevention. *JAMA* (2020). published online Feb 24. DOI: 10.1001/jama.2020.2648.
11. Mason S, Devincenzo JP, Toovey S, Wu JZ, Whitley RJ. Comparison of antiviral resistance across acute and chronic viral infections. *Antiviral Res*. **158**, 103-12 (2018).
12. Reardon S. Antibiotic treatment for COVID-19 complications could fuel resistant bacteria. 2020. <https://www.sciencemag.org/news/2020/04/antibiotic-treatment-covid-19-complications-could-fuel-resistant-bacteria> (accessed May 1, 2020)

13. World Health Organization. Laboratory testing for 2019 novel coronavirus (2019-nCoV) in suspected human cases Interim guidance. 2020. <https://www.who.int/publications-detail/laboratory-testing-for-2019-novel-coronavirus-in-suspected-human-cases-20200117> (accessed May 1, 2020)
14. National Health Commission of the People's Republic of China. New Coronavirus Pneumonia Prevention and Control Program (version 7.0). <http://www.nhc.gov.cn/yzygj/s7653p/202003/46c9294a7dfe4cef80dc7f5912eb1989/files/ce3e6945832a438eaae415350a8ce964.pdf> (accessed April 29, 2020. in Chinese).
15. Bingula R, Filaire M, Radosevic-Robin N, et al. Desired Turbulence? Gut-Lung Axis, Immunity, and Lung Cancer. *J Oncol*. 5035371 (2017).
16. Fagundes CT, Amaral FA, Vieira AT, et al. Transient TLR activation restores inflammatory response and ability to control pulmonary bacterial infection in germfree mice. *J Immunol*. **188**, 1411-20 (2012).
17. Perlot T, Penninger JM. ACE2 - from the renin-angiotensin system to gut microbiota and malnutrition. *Microbes Infect*. **15**, 866-73 (2013).
18. Lamers MM, Beumer J, van der Vaart J, et al. SARS-CoV-2 productively infects human gut enterocytes. *Science*. (2020). published online May 1. DOI: 10.1126/science.abc1669.
19. Boursi B, Mamtani R, Haynes K, Yang YX. Recurrent antibiotic exposure may promote cancer formation—Another step in understanding the role of the human microbiota? *Eur J Cancer*. **51**, 2655-64 (2015).
20. Hantoushzadeh S, Norooznezhad AH. Inappropriate Antibiotic Consumption as a Possible Cause of Inflammatory Storm and Septic Shock in Patients Diagnosed with Coronavirus Disease 2019 (COVID-19). *Arch Med Res*. (2020). published online Apr 4. DOI: 10.1016/j.arcmed.2020.03.015.
21. Hantoushzadeh S, Anvari Aliabad R, Norooznezhad AH. Antibiotics, pregnancy, and fetal mental illnesses: where is the link? *Am J Obstet Gynecol*. **222**, 639-640 (2020).
22. Alkharfy KM, Kellum JA, Frye RF, Matzke GR. Effect of ceftazidime on systemic cytokine concentrations in rats. *Am J Obstet Gynecol*. **44**, 3217-9 (2000).
23. Cecconi M EL, Levy M, Rhodes A. Sepsis and septic shock. *Lancet* 2018. 392: 75-87.
24. Chousterman BG, Swirski FK, Weber GF. Cytokine storm and sepsis disease pathogenesis. *Semin Immunopathol*. **39**, 517-28 (2017).
25. Tian S, Hu W, Niu L, Liu H, Xu H, Xiao SY. Pulmonary Pathology of Early-Phase 2019 Novel Coronavirus (COVID-19) Pneumonia in Two Patients With Lung Cancer. *J Thorac Oncol*. **15**, 700-4 (2020).
26. Joob B, Wiwanitkit V. Pulmonary Pathology of Early Phase 2019 Novel Coronavirus Pneumonia. *J Thorac Oncol*. **15**, e67 (2020).
27. Buck M, Zhang L, Halasz NA, Hunter T, Chojkier M. Nuclear export of phosphorylated C/EBPbeta mediates the inhibition of albumin expression by TNF-alpha. *EMBO J*. **20**, 6712-23 (2001).
28. Doweiko JP, Nompoggi DJ. Role of albumin in human physiology and pathophysiology. *JPEN J Parenter Enteral Nutr*. **15**, 207-11 (1991).
29. Smith JTLB, inventor ALDERBIO HOLDINGS LLC (Las Vegas, NV, US), assignee. Antagonists of IL-6 to raise albumin and/or lower CRP United States. 2016.
30. Blanloeil Y, Trossaert M, Rigal JC, Rozec B. [Effects of plasma substitutes on hemostasis]. *Ann Fr Anesth Reanim*. **21**, 648-67 (2002).
31. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. **395**, 1054-62 (2020).

Tables

Table 1. Characteristics of patients in early antibiotics use and non-early antibiotics use groups before and after propensity score matching

Paratmeters	Unmatched (N=1613)					Matched (1:1)				
	NEAU		EAU		P- value ^a	NEAU		EAU		P- value ^a
N	617		996			611		611		
	Median	IQR	Median	IQR		Median	IQR	Median	IQR	
Age (years)	57	44-66	54	38-66	<0.01	57	44-66	56	40-67	0.50
Length of stay (days)	13	9-20	18	12-26	<0.01	13	9-20	17	11-25	<0.01
	N	%	N	%		N	%	N	%	
Gender					0.43					1.00 ^b
Female	332	53.81	556	55.82		326	53.36	326	53.36	
Male	285	46.19	440	44.18		285	46.64	285	46.64	
Symptom										
Cough	259	41.98	507	50.90	<0.01	259	42.39	249	40.75	0.56
Fever	296	47.97	699	70.18	<0.01	295	48.28	329	53.85	0.05
Comorbidity										
Hypertension	215	34.85	287	28.82	0.01	213	34.86	205	33.55	0.63
Diabetes	101	16.37	144	14.46	0.30	100	16.37	95	15.55	0.70
Treatment										
Anti-virus drugs	506	82.01	959	96.29	<0.01	502	82.16	574	93.94	<0.01
Secondary bacterial infection (30 days) ^c	43	12.22	175	20.42	<0.01	43	12.32	99	19.26	<0.01
All-cause death (30 days)	10	1.62	30	3.01	0.08	10	1.64	16	2.62	0.23
Progression to severe type (30 days)	137	22.20	361	36.24	<0.01	137	22.42	211	34.53	<0.01

NEAU=Non early antibiotic use; EAU=Early antibiotic use; IQR=Interquartile range;

^a The P value was calculated by Chi-square test or Fisher's exact test

^b Equal ratio of gender was set when two groups were propensity score-matched.

^c 404 and 359 patients had no information on secondary bacterial infection for the unmatched and matched participants, respectively.

Table 2. Relative risks for outcomes in early antibiotics or non-early antibiotics group under mixed-effect model before and after propensity-score matching

	Unmatched								Matched (1:1) ^a							
	Crude ^b				Mixed-effect Model ^b				Crude				Mixed-effect Model			
	HR	95% CI		<i>P</i> value	HR	95% CI		<i>P</i> value	HR	95% CI		<i>P</i> value	HR	95% CI		<i>P</i> value
Progression to severe type	1.87	1.53	2.29	<0.01	1.87	1.53	2.29	<0.01	1.67	1.35	2.08	<0.01	1.67	1.35	2.09	<0.01
	OR	95% CI		<i>P</i> value	OR	95% CI		<i>P</i> value <td>OR</td> <td>95% CI</td> <td></td> <th><i>P</i> value<td>OR</td><td>95% CI</td><td></td><th><i>P</i> value</th></th>	OR	95% CI		<i>P</i> value <td>OR</td> <td>95% CI</td> <td></td> <th><i>P</i> value</th>	OR	95% CI		<i>P</i> value
Length of stay>15 days	2.39	1.92	2.99	<0.01	2.34	1.88	2.92	<0.01	2.27	1.78	2.90	<0.01	2.20	1.72	2.80	<0.01
Secondary bacterial infection (30 days)	1.89	1.31	2.73	<0.01	1.90	1.32	2.75	<0.01	1.72	1.16	2.54	<0.01	1.69	1.14	2.51	<0.01
All-cause death (30 days)	2.13	1.00	4.55	0.05	1.98	0.94	4.19	0.07	1.69	0.73	3.90	0.22	1.62	0.71	3.70	0.25

HR= Hazard ratio; OR= Odds ratio;

^aThe early antibiotics use and non-early antibiotics use groups were matched for age, gender, symptom (cough, fever), comorbidities (hypertension, diabetes).

^bCrude estimations were adjusted for age, gender, treatment, comorbidities (hypertension, diabetes).

^cSite (hospital) was modeled as a random effect in the multivariate analyses.

Table 3. Impact of the antibiotics on blood examination indicators (standard error in parenthesis)

	EAU group			NEAU group			D-in-D ^b
	Before	After	Change ^a	Before	After	Change ^a	
Liver function							
AST (U/L)	29.1(36.2)	37.3(67.7)	8.2	23.3(20.1)	24.9(21.3)	1.6	6.6(5.1)
ALT (U/L)	27.9(43.4)	52.8(98.0)	24.9	29.7(45.6)	32.1(36.1)	2.4	22.6(6.4) ^{**}
ALB (g/L)	38.2(4.8)	35.3(5.2)	-2.9	40.0(4.3)	38.6(5.1)	-1.4	-1.5(0.4) ^{**}
A/G	1.4(0.3)	1.2(0.3)	-0.2	1.5(0.3)	1.4(0.4)	-0.1	-0.1(0.0) ^{***}
Renal function							
Scre(μmmol/L)	87.4(153.8)	94.3(139.6)	6.9	104.4(185.4)	105.5(157.8)	1.1	5.7(14.2)
BUN(mmmol/L)	4.9(4.0)	6.0(5.3)	1.1	5.4(4.3)	6.0(5.5)	0.6	0.6(0.4)
UA(μmmol/L)	267.2(98.5)	299.3(112.0)	32.1	300.8(96.2)	309.3(95.8)	8.5	23.6(9.3) [*]
Fibrinolytic activity							
D-Di (μg/mL.FEU)	1.9(5.2)	4.2(10.4)	2.3	1.5(7.5)	1.9(5.1)	0.4	1.9(0.9) [*]

NEAU=Non early antibiotic use; EAU=Early antibiotic use; AST=Aspartate transaminase; ALT=alanine transaminase; Alb= albumin; A/G=albumin/globulin ratio; Scre=serum creatinine; BUN= blood urea; UA=uric acid; D-Di= D dimer

P*<0.05; *P*<0.01; ****P*<0.0001.

^a The average change was computed from raw data.

^b The D-in-D result was adjusted using D-in-D estimation, the covariates include the age, sex, comorbidities (hypertension and diabetes), and treatment (antivirus drugs).

Figures

Figure 1

Flowchart of the patient enrollment

Figure 2

Kaplain-Meier Curves for cumulative probability of progression to severe type COVID-19 during 30-day follow-up duration in early antibiotics use/non-early antibiotics use cohort among 1613 patients in unmatched and 1222 matched cohort