

# Protocol for a retrospective cohort study for evaluating the early antibiotics use in non-severe COVID-19 patients

## **Xiaoxv Yin**

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

## **Nan Jiang**

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

## **Jing Wang**

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

## **Zuxun Lu**

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

## **Yanhong Gong** (✉ [gongyanhong@hust.edu.cn](mailto:gongyanhong@hust.edu.cn))

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

## **Nian Xiong** (✉ [nianxiong@hust.edu.cn](mailto:nianxiong@hust.edu.cn))

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

**Changjun Li** (✉ [hydlcj@163.com](mailto:hydlcj@163.com))

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

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## Method Article

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# Abstract

The use of antibiotics is common in the treatment of COVID-19, but adequate evaluation is lacking. We aimed to evaluate the efficacy of antibiotic use in non-severe COVID-19 patients, particularly in patients admitted with low risk of bacterial infection. This is a multi-center retrospective cohort study. Patients are screened strictly according to the inclusion/exclusion criteria and are divided into two groups based on antibiotics exposure. The exposure is defined as the treatment of antibiotics prescribed within 48 hours after admission, with a course of treatment  $\geq 3$  days; and patients in this group are classified as early antibiotic use group. Otherwise, patients are classified as the non early antibiotic use group. The primary end point of the study is progressing from non-severe type COVID-19 into severe type. This is the first protocol to put a focus on the transformation of the severity of the disease, based on a multi-center retrospective cohort design.

## Introduction

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 therapy.<sup>1</sup> The possible explanation is that the clinical symptoms of COVID-19 are similar to those of bacterial pneumonia, such as coughing, fever, and fatigue.<sup>2</sup> Moreover, 44.3% of COVID-19 patients showed increase of C-reactive protein.<sup>3</sup> 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.<sup>4,5</sup>

Severe COVID-19 is an important cause of death in confirmed patients.<sup>6</sup> 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 patients.<sup>7</sup> 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.<sup>8,9</sup> 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 will 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.

## Reagents

Not applicable because this is a retrospective cohort study and all the data is provided by hospitals

## Equipment

Not applicable because this is a retrospective cohort study and all the data is provided by hospitals

## Procedure

We collected information of hospitalized patients with COVID-19 admitted to four hospitals in Hubei Province, China from 31<sup>st</sup> December, 2019 to 31<sup>st</sup> March, 2020. The demographic information, clinical symptoms, medical history, in-hospital medication, and clinical outcomes obtained from the electronic medical system. Laboratory data were collected from the laboratory information system. Any missing or uncertain records will collate and clarify through communication with involved health-care providers or patients and their families. Patients are screened strictly according to the inclusion/exclusion criteria and are divided into two groups according to their exposure to antibiotics within 48 hours after admission. Patients receiving antibiotic treatment within 48 hours after admission, with a course of treatment  $\geq 3$  days are classified as early antibiotic use group (EAU group). Otherwise, patients are classified as non early antibiotic use group (NEAU group). The outcomes of interest will be recorded during a follow-up of 30 days for each patients.

## Troubleshooting

### Problems may occur

As this study is a retrospective cohort study, there might exist the following problems:

1. Missing or uncertain records.
2. Selection bias.

### Solution

1. Any missing or uncertain records will collate and clarify through communication with involved health-care providers or patients and their families.
2. Propensity score-matched analysis will be used to reduce the selection bias between exposure group and control group.

## Time Taken

From 31<sup>st</sup> December, 2019 to 31<sup>st</sup> March, 2020

# Anticipated Results

Early empirical or prophylactic antibiotic treatment augments the risk of progression from non-severe to severe, increases the incidence of secondary bacterial infections, prolongs hospitalization and increases mortality rate in non-severe COVID-19 patients.

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## Figures

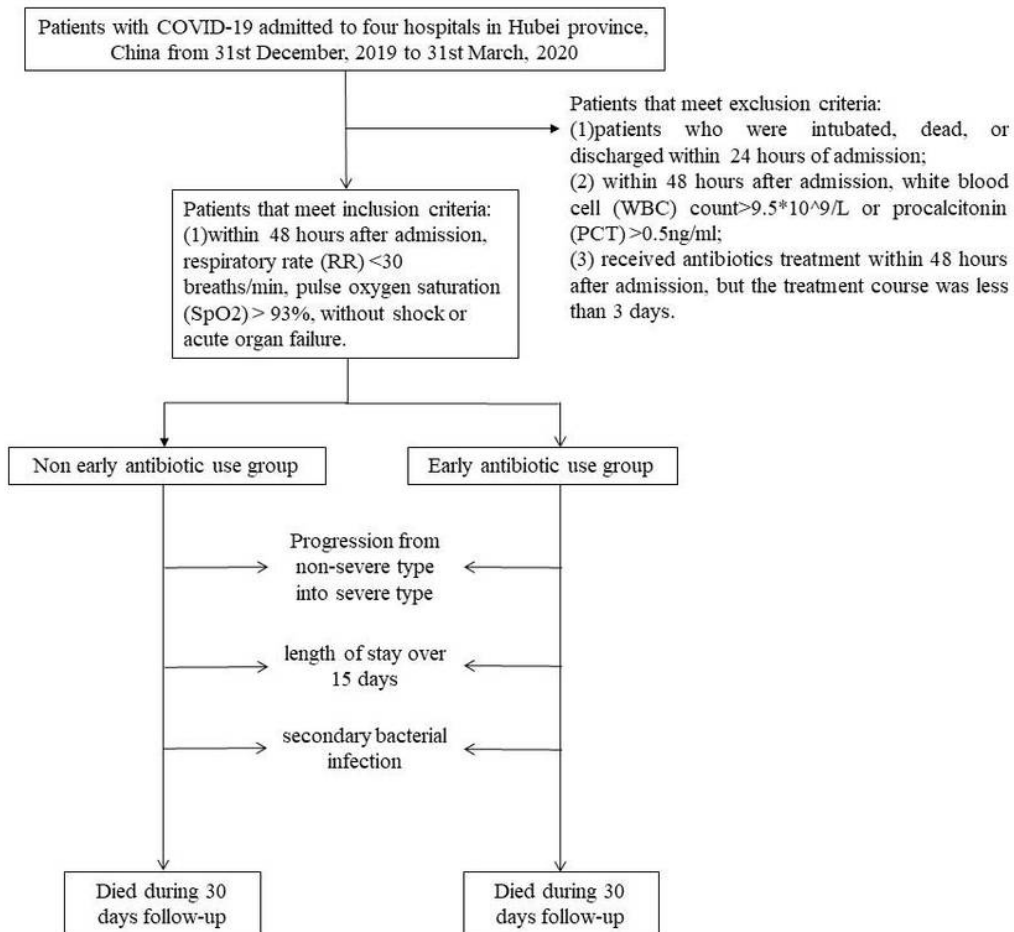


Figure 1

Flow chart of the protocol