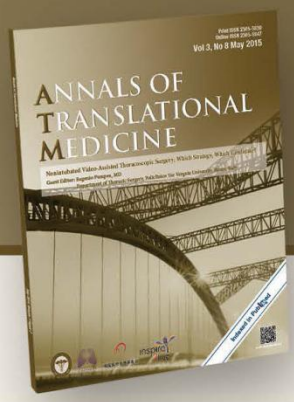
ANNALS OF TRANSLATIONAL MEDICINE



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Peer Review File

Article information: http://dx.doi.org/10.21037/atm-20-4960

Reviewer's comments

This is a retrospective, single-center case series study that enrolled 165 consecutive hospitalized COVID-19 patients from December 19, 2019 to February 2, 2020 who were followed up until March 25, 2020 from a designated hospital in Wuhan. Zhongnan Hospital is one of the major tertiary teaching hospitals in Wuhan.
Patients were grouped by a baseline degree of severity: non-severe (mild, general combined) and severe (severe, critical combined).
The study presents descriptive analysis of (1) drug utilization, (2) disease progression and (3) adverse events of COVID-19 patients.
It is of great importance to describe what medications front-line physicians have been using to treat COVID-19 patients with a focus on medication choices, combinations and safety issues. However, the outcome level of data based on the medication choice is not provided in this study. The authors reported overall death rate and death rate based on disease severity, general data on disease progression, general report of ADE, but this is not linked/analyzed based on the medications used to assist physicians with clinical decision making.

Abstract Results
(1) Drug utilization 92.7% antivirals, 98.8% antibacterials, 68.5% glucocorticoids, 55.2% traditional Chinese medicine (TCM).
a. The total kinds of drug administered to severe subgroup 26, IQR 18-39 were 11 more than non-severe subgroup 15, IQR 10-24
b. The first two common combination were antiviral +glucocorticoid+TCM 49.1%, antiviral + glucocorticoid 13.9%

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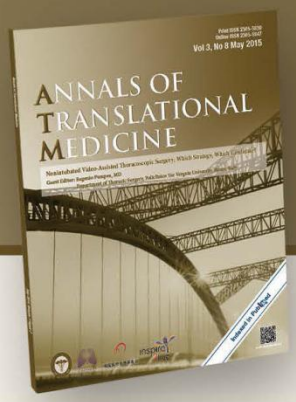

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c. Compared with non-severe cases, severe cases received more glucocorticoids 88.5 vs 66.2%, P=0.02, less TCM, and suffered higher percentage of death 34.6 vs 7.2%, P=0001
(2) At the end of the follow-up, 24 (14.5%) died, 13 (7.9%) had elevated liver enzymes and 49 patients (29.7%) presented worsen kidney function

Comment 1: disease progression is not discussed in abstract, and this seems to be the end point. This data presented in the manuscript, but worth including in the abstract.
Reply 1: Thanks for raising this point. We have added a discussion about disease progression in the Abstract (see Page 2, line 48-50). Further, we have added results disease progression of patients under different drug therapy (please see Table 3).
Changes in the text: At the end of the follow-up, 130 (78.8%) patients had been discharged, and 24 (14.5%) died. There were 13 patients (7.9%) who had elevated liver enzymes and 49 patients (29.7%) presented worsen kidney function during the follow-up.

Comment 2: Reported in the study adverse events (ADE) of COVID-19 patients include elevated liver enzymes and worsen kidney function. Both can be presentation/manifestation of COVID-19 itself or associated sepsis. How this was distinguished, ADE vs COVID-related presentation/worsening? The manuscript in the discussion section comments on the almost universal use of antibacterials that cause unneglectable proportion of liver injury or kidney injury… which antibacterials? This clarification on which antibacterials (moxifloxacin, amoxicillin, flucloxacillin) appears only in the discussion… Please, include in table 2 distribution of antibacterials since 98.9% of the patients received antibacterials
Reply 2: Thanks for the reviewer's comments. In this study, the association between adverse events in patients and their medication regimens were independently evaluated by two senior clinical pharmacists. The basic criteria for distinguishing AEs with COVID-19 related presentation is to exclude any patient who is characterized by liver or kidney injury history and presents abnormal liver or kidney function on admission. We have added the above description (i.e. criteria for assessing AEs) into the revised manuscript (see Page 8, Line 206-210).

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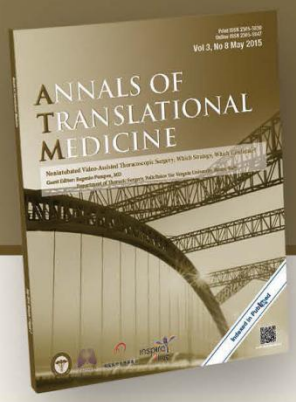

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In the discussion section, we commented on the almost universal use of antibacterials that may cause an unneglectable proportion of liver injury or kidney injury, but we were not completely attributed to these observed AEs to the use of antibacterials. We have modified the relevant comments in the discussion section of the revised manuscript (see Page 11, Line 283-285, and Page 12, Line 286-288). Also, there are a total of 36 antibacterials. We have added the distribution of antibacterials (at the 3rd-level ATC code) into Table 2 of the revised manuscript (see Table 2 on Page 16).
Changes in the text: Deleted text “The widespread use of antibacterials, together with multiple drugs, should alert the clinicians to pay attention to the potential ADEs” and “caused by antibacterials (e.g., moxifloxacin, amoxicillin sodium/flucloxacillin sodium). Actually, these safety signals have also been reported by drug instructions and previous studies” from page 11. And added text “Interestingly, these safety signals have also been reported by some antibacterials instructions and previous studies” on page 11.

Comment 3: Not clear based on what analysis of the data this conclusion is made? There is no analysis to review disease progression based on medication use, death based on medications used, single medication vs combination, etc. Might be worth to present this analysis… Just reporting on which medications were used without looking at the outcome level of data based on meds is not very beneficial. Description of medication choices and dosing does not really provide useful data for clinical decision making in the future….
Reply 3: Thanks for raising these points. This statement came from some of our earlier analyses and current analysis based on the real-world clinical practice, however, the relationship between patient outcome and medication use appeared to have changed after we collected longer follow-up data. We have added results for outcomes of patients treated with different medications (please see Table 3, page 18-19). However, since only 165 patients were included, our results should be interpreted with caution. More robust evidence about the safety and efficacy of drugs for COVID-10 from studies with much bigger sample size is needed in the future.

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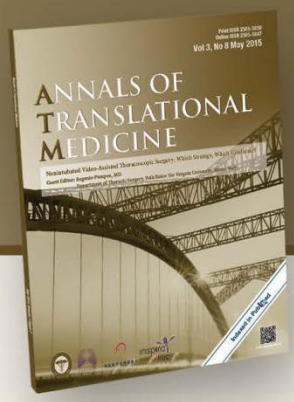

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Manuscript

Comment1: All patients enrolled in this study were diagnosed according to the WHO interim guidance. Was COVID-19 positive test was a requirement? Did the study enroll negative COVID-19 pts but high clinical suspicion, based on imaging findings, etc? Would be good to be clear on this, not sure if all readers will go to the references 23, 24 to clarify this…

Reply 1: Thanks for the reviewer's comment. All patients enrolled in this study were confirmed to be COVID-19 positive by viral test on admission. We didn't enroll any patients who tested negative for COVID-19 here. For clearness, we have added the above description into the revised manuscript. (See Page 4, Line 87-88)

Changes in the text: All patients enrolled in this study were confirmed to be COVID-19 positive by viral test on admission, according to the World Health Organization (WHO) interim guidance.

Comment 2: What is the MDAR reporting checklist (re-abbreviate/clarify MDAR)?

Reply 2: Thank you for this comment. MDAR is short for Materials Design Analysis Reporting Checklist, which is a tool for authors, editors and others seeking to adopt the MDAR framework for transparent reporting in manuscripts and other outputs for studies in the life sciences. We added the relevant description at the end of the Introduction. (See Page 3, Line 80-81)

Comment 3: Inclusion/exclusion criteria not specified. Was there any patients excluded? Generally, each study clarifies excluded patients if any.

Discussion includes the following value of the study "real world evidence for clinical decision-makers? Not sure how this can be extrapolated from the description provided. Just description of which medications were used cannot really help with decision-making unless patient outcome data presented in some way based on the medication choices and not just overall death rate, ADE rate, disease progression rate.

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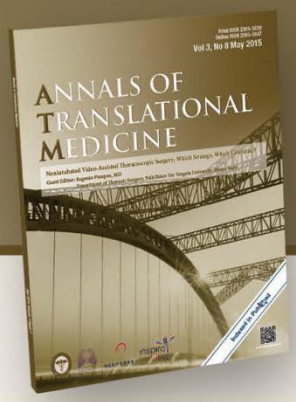

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Reply 3: Thanks for the reviewer's comments. The COVID-19 confirmed patients who are younger than 18 years old and diagnosed with bacterial pneumonia are excluded from this study. We have added these exclusion criteria into the revised manuscript (see Page 4, Line 87-88).
As we all know, RCT is time-consuming and costly, making it unsuitable for timely evidence needed in facing the rapidly spreading COVID-19 pandemic. In the contract, the real-world, including electronic medical records, can be accessed and analyzed much more quickly. Our results indicated that medication use in the early stage of the pandemic was somewhat arbitrary and some kinds of drugs might be helpful to reduce mortality (for example some kinds of antibacterials). Changes in the text: All patients were followed up to March 25, 2020, and were ≥ 18 years old and not diagnosed with bacterial pneumonia.