Revised: 11 January 2021 | Accepted: 12 January 2021

DOI: 10.1002/jmv.26798

RESEARCH ARTICLE

JOURNAL OF MEDICAL VIROLOGY WILEY

Clinical efficacy of methylprednisolone and the combined use of lopinavir/ritonavir with arbidol in treatment of coronavirus disease 2019

Qi Xia[1,2] | Wanrong Dai[3] | Kaijin Xu[1] | Qin Ni[1] | Yongtao Li[1] | Jun Liu[1] | Hong Zhao[1] | Yongzheng Guo[1] | Liang Yu[1] | Ping Yi[1] | Junwei Su[1] | Guanjing Lang[1] | Jingjing Tao[1] | Ding Shi[1] | Wenrui Wu[1] | Xiaoxin Wu[1] | Yan Xu[1] | Min Xu[1] | Ling Yu[1] | Xiaoyan Wang[1] | Hongliu Cai[1] | Qiang Fang[1] | Jianying Zhou[1] | Yunqing Qiu[1] | Lanjuan Li[1,2]

[1]Department of Infectious Disease, State Key Laboratory for Diagnosis and Treatment of Infectious Diseases, National Clinical Research Center for Infectious Diseases, Collaborative Innovation Center for Diagnosis and Treatment of Infectious Diseases, The First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou, Zhejiang, China

[2]Key Laboratory for Biomedical Engineering of Ministry of Education, Zhejiang University, Hangzhou, Zhejiang, China

[3]The First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou, Zhejiang Province, China

Correspondence
Lanjuan Li and Qi Xia, State Key Laboratory for Diagnosis and Treatment of Infectious Diseases, National Clinical Research Center for Infectious Diseases, Collaborative Innovation Center for Diagnosis and Treatment of Infectious Diseases, The First Affiliated Hospital, College of Medicine, Zhejiang University, 79# Qingchun Road, Hangzhou 310003, Zhejiang Province, China.
Email: xiaqi@zju.edu.cn and ljli@zju.edu.cn

Funding information
Ministry of Science and Technology of the People's Republic of China, 13th Five-Year National Science and Technology Major Project, Grant/Award Number: 2018ZX10715-013-003; Ministry of Science and Technology of the People's Republic of China, 13th Five-Year National Key Research and Development Program of China, Grant/Award Number: 2019YFC0840600 and 2019YFC0840609; Fundamental Research Funds for the Central Universities

Abstract

This study aims to comparatively analyze the therapeutic efficacy upon multiple medication plans over lopinavir/ritonavir (LPV/r), arbidol (ARB), and methylprednisolone on patients with coronavirus disease 2019 (COVID-19). Totally, 75 COVID-19 patients admitted to The First Affiliated Hospital, Zhejiang University School of Medicine from January 22, 2020 to February 29, 2020 were recruited and grouped based on whether or not LPV/r and ARB were jointly used and whether or not methylprednisolone was used. Indexes including body temperature, time for nucleic acid negative conversion, hospital stays, and laboratory indexes were examined and compared. For all patients, there were no significant differences in the change of body temperature, the time for negative conversion, and hospital stays whether LPV/r and ARB were jointly used or not. While for severe and critically severe patients, methylprednisolone noticeably reduced the time for negative conversion. Meanwhile, the clinical efficacy was superior on patients receiving methylprednisolone within 3 days upon admission, and the duration of hospital stays was much shorter when methylprednisolone was given at a total dose of 0–400 mg than a higher dose of >400 mg if all patients received a similar dose per day. Nonetheless, no significant changes across hepatic, renal, and myocardial function indexes were observed. LPV/r combined with ARB produced no noticeably better effect on COVID-19 patients relative to the single-agent treatment. Additionally, methylprednisolone was efficient in severe and critically severe cases,

and superior efficacy could be realized upon its early, appropriate, and short-term application.

KEYWORDS

arbidol, coronavirus, COVID-19, lopinavir/ritonavir, methylprednisolone

1 | INTRODUCTION

The novel coronavirus pneumonia (officially named as coronavirus disease 2019 [COVID-19]) that outbroke in December 2019 is highly contagious with a relatively low cure rate, and patients always develop fever, cough, myalgia, fatigue, and diarrhea when they get infected.[1] Due to the failure of virus strain isolation, emerging evidence that the impact caused by the outbreak is more dramatic than initially thought and the presence of international transmission that has been driven by travelers, the ongoing COVID-19 outbreak has posed great challenges for the Public Health Laboratory.[2] Therefore, it is urgent to carry out research on the prevention of coronavirus disease.

To know more about the COVID-19, some similar respiratory diseases, such as severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), which happened before can be studied for reference. Coronaviruses that cause SARS and MERS (SARS-CoV and MERS-CoV) are two types of viruses present in humans in the early 21th century characterized by a high rate of transmissibility and fatality. SARS which broke out in 2002 caused 8422 infectious worldwide by August 15, 2003 and 916 deaths with a fatality rate of around 10%.[3,4] While for MERS, the fatality rate was up to 35%.[5] However, we do not know whether the COVID-19 epidemic is similar to SARS/MERS or manifests different clinical characteristics. At present, no specific antiviral drugs or vaccines available for COVID-19 have been developed which prompts us to find suitable therapeutic medicine as soon as possible.

In view of the treatment experience towards SARS and MERS, 20 drugs that could be potentially active against the COVID-19 virus are identified. Among the drugs, lopinavir (LPV), ritonavir (RTV), and arbidol (ARB) are the three drugs commonly used in clinical treatment. LPV is a protease inhibitor against HIV-1 and its half-life period can be prolonged upon inhibition of cytochrome P4507 and combined use with RTV. RTV is a type of broad-spectrum antiviral drug as well as a nucleotide analog prodrug that has superior in vitro antiviral activity across various RNA viruses. As a therapeutic drug, RTV is also able to greatly reduce severe lung pathology.[6] It is proven that the combined use of lopinavir/ritonavir (LPV/r) and interferon β makes an effect in patients infected with SARS-CoV.[7] ARB is a small indole-derivative molecule and has been used in the prevention and treatment of influenza and other respiratory viral infections.[8] As well, ARB is a broad-spectrum antiviral drug and is effective in process of anti-influenza viruses by targeting the hemagglutinin fusion machinery.[9] Although LPV, RTV, and ARB are reported to play a part in patients with SARS/MERS, their role in COVID-19 has not been demonstrated.

Other than the anti-viral drugs, some hormone drugs may produce a certain effect on the COVID-19 virus as well. Methylprednisolone is a non-halogenated corticosteroid characterized by relatively high intrinsic activity with a methyl group at C6.[10] It is established that treatment efficacy can be affected from various aspects, including the severity of the disease, time to interventional treatment, the dosage of hormone drugs, and the duration time. As reported, hormonotherapy used in the treatment of patients with severe acute respiratory distress syndrome (ARDS) is able to reduce pulmonary fibrosis and prevent progressive pathological deterioration.[11] Through previous studies, we can see that the application of glucocorticoids (GCs) can lead to a significant decrease in mortality of adult patients with severe pneumonia, while the use of corticosteroids can contribute to a shorter time of clinical cure, length of hospital, and intensive care unit (ICU) stays, with no respiratory failure or shock developed upon the bout of pneumonia, as well as the incidence of pneumonia complications.[12] Hence, it is also significant to study the possible clinical efficacy that methylprednisolone may produce on patients with COVID-19.

Here, we performed an observational retrospective study on patients with COVID-19 who received diverse medication plans over LPV/r, ARB, and methylprednisolone. Roughly, differences in body temperature, time for nucleic acid negative conversion, hospital stays, and laboratory indexes were comparatively analyzed in patients with different medication plans. Based on the observational results, therapeutic effects of methylprednisolone and the combined use of LPV/r and ARB were then evaluated. Overall, our research findings may help clinicians apply LPV/r, ARB, and methylprednisolone these three types of drugs in a more reasonable manner.

2 | MATERIALS AND METHODS

2.1 | Subjects inclusion and grouping

A total of 75 patients with COVID-19 who were admitted to The First Affiliated Hospital, Zhejiang University School of Medicine in the period of January 22 to February 29, 2020 were enrolled and their respiratory tract nucleic acid (nCoV-RNA here) testing turned out to be positive as detected by a quantitative polymerase chain reaction. The cohort was comprised of 41 males and 34 females with an average age of 51.6 ± 15.0 years old.

All subjects were identified as mild ($n = 4$), moderate ($n = 22$), severe ($n = 39$), and critically severe ($n = 10$) patients according to the following criteria:

(1) Mild cases: the clinical symptoms are mild with no pneumonia manifestations appeared in imaging.
(2) Moderate cases: fever and respiratory symptoms are developed and pneumonia manifestations can be found in imaging.
(3) Severe cases: adults who meet one of the following criteria are identified as severe cases: respiratory rate (RR) ≥30 times/min; the figure oxygen saturation under the resting state, $SpO_2 \leq 93\%$; arterial partial pressure of oxygen (PaO_2)/oxygen concentration (FiO_2) ≤300 mmHg; patients who have noticeable lesion progression >50% within 24–48 h are treated as severe cases.
(4) Critically severe cases: patients who are in line with one of the criteria below: respiratory failure that requires mechanical ventilation; presence of shock; other organ failure which needs monitoring and treatment in ICU.

Here, mild and moderate cases were collectively referred to as mild cases, while severe and critically severe cases were called severe cases jointly. Afterward, patients were sub-grouped into four groups based on their therapeutic regimens: combination of LPV/r and ARB/un-combination and methylprednisolone/control groups.

2.2 | Therapeutic regimens

For patients in the combination group and un-combination group, the medication plan was designed as below: LPV/r tablet was given two tablets once per 12 h, by oral. While ARB was given 200 mg three times daily, by oral. For patients receiving methylprednisolone, methylprednisolone was given by intravenous injection one or two times per day with a total accumulative dose of 0.75–1.5 mg/kg.

2.3 | Evaluation indexes

(1) Body temperature: changes in body temperature are monitored daily upon admission for consecutive 10 days and the highest temperature is taken.
(2) Blood routine and abnormal lymphocyte: total hemoglobin count (Hb, g/L), total white blood cell count (WBC, 10^9/L), neutrophil count (10^9/L), and lymphocyte count (10^9/L).
(3) Hepatic, renal and myocardial function indexes: C-reactive protein (CRP, mg/L), total cholesterol (mmol/L), albumin (g/L), total bilirubin (μmol/L), direct bilirubin (μmol/L), alanine aminotransferase (ALT, U/L), aspartate aminotransferase (AST, U/L), creatine kinase isoenzyme (CK-MB, U/L), creatine phosphokinase (CPK, U/L), and glomerular filtration rate (GFR, ml/min).
(4) Immune related indexes: immunoglobulin M (IGM, mg/dl), IGA (mg/dl), IGG (mg/dl), TNF-γ (pg/ml), interleukin-10 (IL-10, pg/ml), IL-6 (pg/ml), IL-2 (pg/ml), and IL-4 (pg/ml).
(5) Procalcitonin examination: procalcitonin (PCT, ng/ml).
(6) Pulmonary computed tomography (CT) imaging: pulmonary CT scan for baseline evaluation was usually performed upon admission and required a review 2–3 days after if ideal therapeutic efficacy is not reached, but 5–7 days after if the symptoms are stable or improved after treatment. For critically severe patients, portable chest X-ray is recommended daily.
(7) Normal range for the indexes used in this study: CRP, 131–172 g/L; total Hb, 131–17 g/L; total WBC, $4–10 \times 10^9$/L; neutrophil, $2–7 \times 10^9$/L; lymphocyte, $0.8–4.0 \times 10^9$/L; IGM, 30–220 mg/dl; IGA, (100–420) mg/dl; IGG, (860–1740) mg/dl; TNF-γ, 0–20.06 pg/ml; IL-10, 0–2.31 pg/ml; IL-6, 0–6.61 pg/ml; IL-2, 0–4.13 pg/ml; IL-4, 0–8.37 pg/ml; PCT, 0–0.05 ng/ml; ALT, 9–50 U/L; AST: 15–40 U/L; CK-MB, 2–25 U/L; CPK, 50–310 U/L; albumin, 40–55 g/L; total cholesterol, 3.14–5.86 mmol/L; total bilirubin, 0–26 μmol/L; direct bilirubin, 0–8 μmol/L; values out of the normal range is considered abnormal.

2.4 | Statistical analysis

All data were processed on SPSS 22.0. Enumeration data between groups were comparatively analyzed using Fisher's precise test, while part of the data was presented as mean ± standard deviation (*SD*) with *t* test applied for verification. $p < .05$ was set as the threshold for statistical significance.

3 | RESULTS

3.1 | Comparative analysis toward body temperature in different treatment groups

As most patients had developed fever upon admission, the change of body temperature was taken as an important indicator and monitored daily from the beginning of treatment for consecutive 10 days. It turned out that no matter for mild or severe patients, the change of body temperature showed no significant difference between patients receiving combination treatment and single-agent treatment (Figure 1A,B; $p > .05$). Consistently, in methylprednisolone and control groups, the body temperature also exhibited no noticeable difference (Figure 1C,D; $p > .05$). These results demonstrated that the body temperature of patients with COVID-19 was not greatly affected by methylprednisolone or LPV/r combined with ARB.

3.2 | Comparative analysis on the time to negative nucleic acid test, hospital stays, and pulmonary imaging

After analysis on the body temperature, the time for nCoV-RNA turned to negative and hospital stays were recorded and compared. As for the combination and un-combination groups, there was no

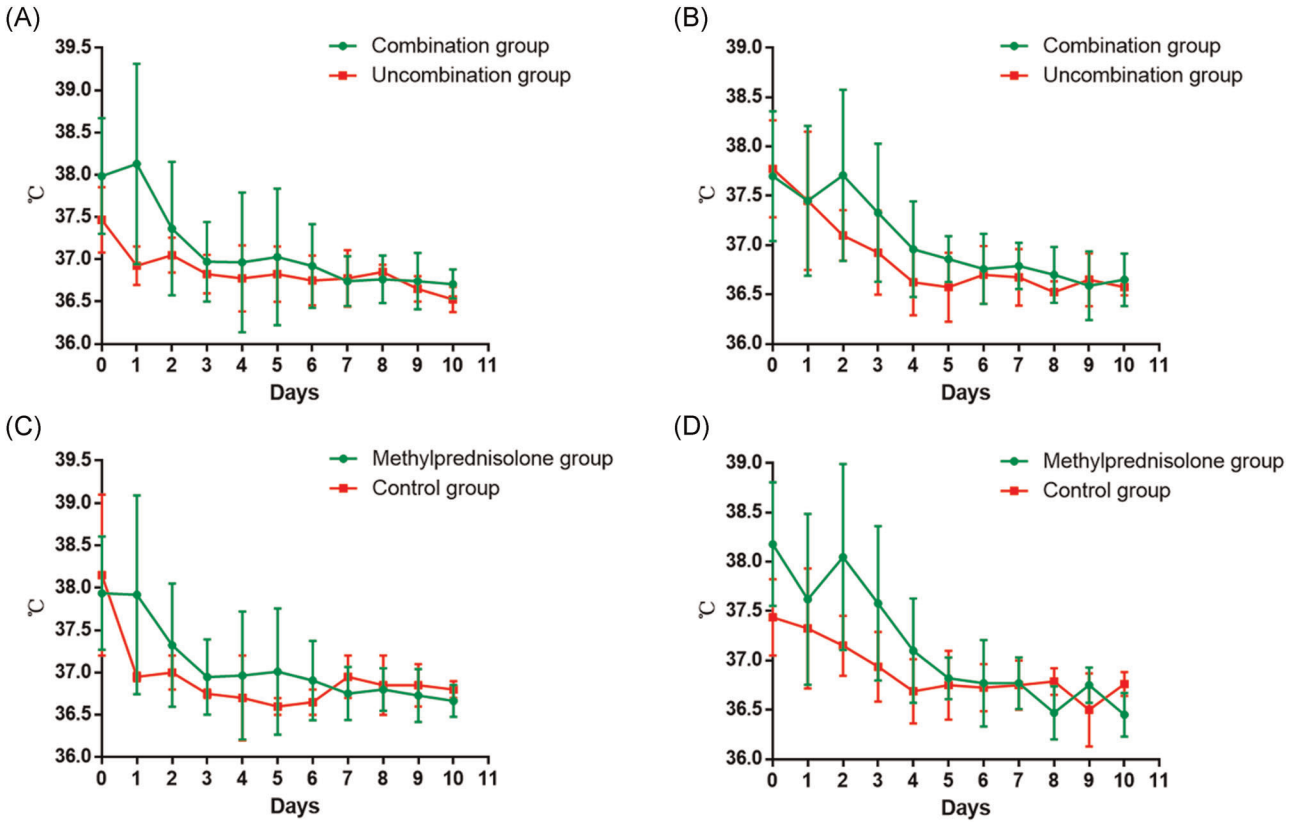

FIGURE 1 Changes on body temperature of patients in each treatment group within the first 10 days upon admission. (A–D) Changes on the temperature of (A,C) critical patients and (B,D) patients with mild symptoms in (A,B) combination/un-combination groups and (C,D) methylprednisolone/control groups

significant difference towards these two indexes in both mild and severe patients (Table 1; $p > .05$). Similarly, no remarkable difference in the duration of hospital stays was observed in mild and severe patients in methylprednisolone and control groups (Table 1; $p > .05$). While for severe patients, the time for nCoV-RNA converted to negative was greatly variate in two groups (Table 1; $p < .05$). It suggested that methylprednisolone was beneficial for early negative conversion in severe patients.

Considering the above findings, we further analyzed the effect of methylprednisolone on the time for nCoV-RNA converted to negative and hospital stays by means of operating methylprednisolone treatment within different time periods. As the results suggested in Table 1, there was a significant difference between severe patients undergoing methylprednisolone treatment within 3 days upon admission and after 3 days with regard to the time for negative conversion and hospital stays ($p < .05$), while no difference was observed in mild patients ($p > .05$). Thus, we could see that methylprednisolone treatment could significantly reduce the time for negative conversion and hospital stays for severe patients, yet showed no remarkable effect in patients with mild symptoms. Moreover, we further treated severe patients with methylprednisolone in a variate dosage with four groups set for comparative analysis. Results plotted in Figure 2 unveiled that an increased dose of methylprednisolone could contribute to a decreased time of negative conversion, yet the time for hospital stays was reduced first and then increased. It was worth noting that when the total dose was higher than 400 mg, despite the significant reduction of negative conversion time, the nCoV-RNA would be repeatedly converted to positive, in turn resulting in the remarkable prolong of hospital stays (around 24 days) (Figure 2). In view of this, we considered that methylprednisolone at a routine dose (0–400 mg) would produce superior efficacy on severe patients. Nevertheless, methylprednisolone in our study was usually used in severe and critically severe patients at a dose of 0.75–1.5 mg/kg per day, and our study found that a total dose of either 0–200 mg or 200–400 mg of methylprednisolone presented no significant difference in therapeutic efficacy on patients (Figure 2). Hence, we believed that under the circumstance that a certain dose range of methylprednisolone was given to each patient per day, prolonged use of methylprednisolone was not much efficient in severe patients. Overall, we proposed that methylprednisolone should be used at a routine dose with a short-term duration as early as possible.

A pulmonary imaging test is vital for diagnosis, efficacy monitoring, and evaluation upon discharge of patients with COVID-19. Hence, we conducted such tests on our subjects upon admission as well as during treatment. As unveiled by the imaging, the time to achieve improved lesions the first time was not

TABLE 1 Comparative analysis on the time for nCoV-RNA converted to negative and hospital stays of patients in each treatment groups

	Severe							Mild						
	Combination			Un-combination				Combination			Un-combination			
	Case	Average	SD	Case	Average	SD	*p* value	Case	Average	SD	Case	Average	SD	*p* value
Negative conversion time	36	7.75	3.70	13	5.85	2.85	.1000	19	6.16	3.89	6	5.50	4.93	.7365
Hospital stays	36	18.36	6.35	13	15.31	6.69	.1030	20	16.05	8.48	6	13.83	8.70	.5811
	Methylprednisolone			Control				Methylprednisolone			Control			
	Case	Average	SD	Case	Average	SD	*P* value	Case	Average	SD	Case	Average	SD	*P* value
Negative conversion time	46	6.59	3.22	3	13.00	6.08	.0027	10	5.90	2.88	15	6.07	4.79	.9209
Hospital stays	46	17.15	6.39	3	23.67	8.14	.0976	10	18.60	9.29	16	13.63	7.47	.1457
	Methylprednisolone treatment within 3 days upon admission			Methylprednisolone treatment after 3 days upon admission				Methylprednisolone treatment within 3 days upon admission			Methylprednisolone treatment after 3 days upon admission			
	Case	Average	SD	Case	Average	SD	*P* value	Case	Average	SD	Case	Average	SD	*P* value
Negative conversion time	30	5.70	2.91	16	8.25	3.19	.0089	7	5.14	2.19	3	7.67	4.04	.2223
Hospital stays	30	15.60	5.93	16	20.06	6.37	.0223	7	16.43	7.00	3	23.67	13.65	.2836

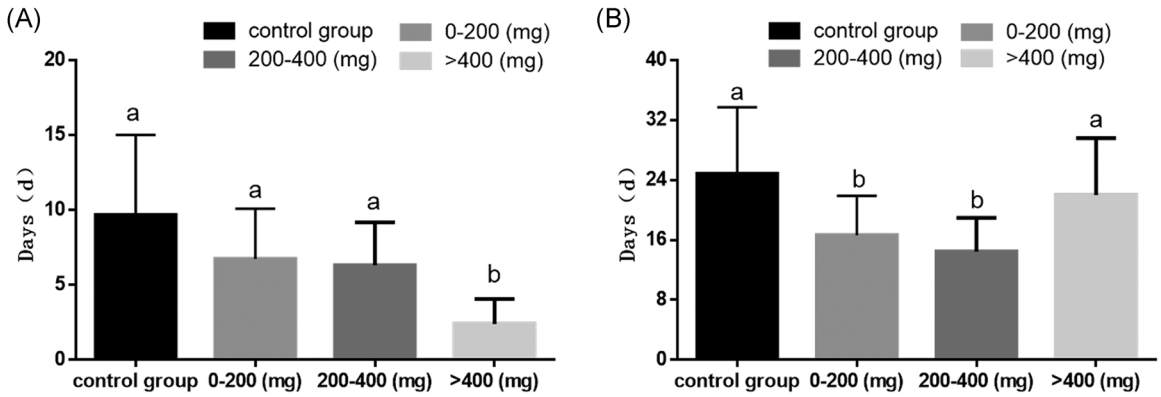

FIGURE 2 Effect of methylprednisolone in a variate dosage on severe patients in terms of negative conversion time and hospital stays. The time for (A) negative conversion and (B) hospital stays of severe patients in methylprednisolone and control groups

much variate between patients undergoing methylprednisolone within 3 days (6.70 ± 3.70 days) and after 3 days (8.88 ± 4.62 days) upon admission. While for patients who were given methylprednisolone at a total dose of 0–400 mg or over 400 mg, a significant difference was observed where the time for patients with 0–400 mg was 6.92 ± 3.70 days shorter than 11.00 ± 0.82 days for patients with over 400 mg. Given the findings, methylprednisolone at a routine dose could bring benefits to the improvement of lung lesions.

3.3 | Comparative analysis on the main indexes in severe patients receiving methylprednisolone (0–400 mg) or not

As the above section mentioned, methylprednisolone at a routine dose was able to produce superior therapeutic efficacy on severe patients. In this part, some significant physiological and biochemical indexes of the cohort upon admission (baseline) and discharge tested and recorded on the basis of whether methylprednisolone was used in a routine dosage or not used. In total, 14 relevant indexes, including CRP, total Hb, total WBC, neutrophil, lymphocyte, IGM, IGA, IGG, TNF-γ, IL-10, IL-6, IL-2, IL-4, PCT, were analyzed. Regarding the baseline levels, no noticeable difference in the abnormal proportions (the percentage of severe patients with abnormal indexes in all severe patients of the corresponding group) of all these indexes was monitored between the two groups ($p > .05$). While after treatment, the proportions across CRP, total Hb, lymphocyte, and PCT upon discharge were all decreased in a certain degree relative to baseline values in patients who received methylprednisolone at a total dose of (0IGM, IGA, IGG, TNF-γ, IL-10, IL-6, IL-2, IL-4, PCT400) mg, and such reduction was also seen in some pro-inflammatory factors like IGM, IGG, IL-10, and IL-6. Nonetheless, the proportions in patients who were not treated with methylprednisolone at the time of discharge showed no significant difference with those in patients receiving (0–400) mg dose of methylprednisolone ($p > .05$). Taken together, methylprednisolone at a total dose of 0–400 mg made minor effect on physiological and biochemical indexes in severe patients.

3.4 | Comparative analysis on hepatic, renal, and myocardial function indexes in severe patients receiving methylprednisolone (0–400 mg) or not

To gain more insight into the safety of methylprednisolone, indexes related to hepatic, renal, and myocardial function were tested and recorded to find whether or not toxic and side effects would be developed upon the treatment with methylprednisolone (0–400 mg). Here, total cholesterol, albumin, total bilirubin, direct bilirubin, ALT, AST, CK-MB, CPK were considered. In terms of baseline levels, these indexes in patients of two groups all abnormal at admission, which indicated that COVID-19 would pose a certain effect on the liver, kidney, and myocardium. Besides, the abnormal proportions of these indexes in two groups were not significantly different ($p > .05$). While for the proportions at the time of discharge, only those of total cholesterol (baseline 0.1563 vs. discharge 0.3939) and CPK (baseline 0.2727 vs. discharge 0.7391) were noticeably elevated in severe patients with methylprednisolone at a total dose of 0–400 mg ($p < .05$), yet no remarkable difference was observed in those of other indexes between the two groups ($p > .05$). It suggested that methylprednisolone at a routine dose produced no noticeable toxic and side effects on liver, kidney, and myocardium in COVID-19 patients.

4 | DISCUSSION

The purpose of this study was to comparatively analyze the clinical therapeutic efficacy upon the combined use of LPV/r with ARB and single-agent use of LPV/r or ARB. In the meantime, the efficiency that methylprednisolone may produce in clinical treatment was also discussed.

For detection of coronavirus infection, body temperature is the most noticeable indicator that can be detected at the highest speed. While for COVID-19 virus infection, fever also turns out the main initial symptom as revealed by statistical analysis on 78 patients with COVID-19 reported by Liu Wei et al.[13] and 57 patients (73.1%) sought for treatment due to fever, with a high temperature of 37.3–38 ℃ most common in 31 (39.7%) patients. In addition, patients ($n = 99$) admitted to Wuhan Jinyintan Hospital were analyzed by Chen Nanshan,[14] and it was found that up to 82 cases (83%) manifested fever. Our study signified that the therapeutic efficacy regarding body temperature produced by the combination treatment of LPV/r and ARB in either mild or severe cases showed no significant difference with that caused by single-agent treatment. In the meantime, methylprednisolone also exhibited no superior effect. It could be seen that whether LPV/r and ARB were jointly used or whether methylprednisolone was applied, no noticeable improvement of body temperature was observed in patients with COVID-19.

Methylprednisolone was reported to play a part in the improvement of pulmonary mechanics and respiratory function in a low dosage upon rescue administration 24 days after the onset of ARDS, which in turn experienced accelerated separation from extracorporeal membrane oxygenation.[15] Additionally, it was reported that the occurrence of clinical adverse complications of SARS patients who underwent treatment with GCs was in a dosage-dependent manner.[16,17] In our study, we also found that short-term use of methylprednisolone at a routine dose of 0–400 mg in an early stage could produce a superior effect on reduction of time for negative conversion as well as hospital stays of patients in severe and critically severe conditions. Moreover, no noticeable toxic and side effects were developed during the methylprednisolone treatment.

Changes in some indexes like cytokines and inflammatory factors can also be seen during the COVID-19 virus infection. Wang Dawei et al.[18] found that most patients occurred noticeable lymphopenia during hospitalization. In the meantime, the count of WBC and neutrophil appeared to be higher in nonsurvivors than those in survivors, suggesting that COVID-19 virus infection might be responsible for cellular immunity deficiency, blood coagulation activation, myocardial injury, liver, and kidney damage. Similarly, Huang Chaolin et al.[19] made a comparative analysis on patients in ICU and routine ward, finding a higher level of plasma IL-2, IL-7, IL-10, GSCF, IP-10, MCP1, MIP1A, and TNF-α in patients in ICU. In our study, the proportions for hepatic, renal, and myocardial function indexes like ALT, AST, GFR, and CK-MB all showed no noticeable difference between the methylprednisolone (routine dose) and control groups, which elucidated that methylprednisolone could produce no noticeable toxic and side effects on liver, kidney, and myocardium in COVID-19 patients. Moreover, the results of pulmonary imaging examination turned out that the application of routine-dose methylprednisolone could contribute to more accelerated absorption of lung lesions in severe and critically severe patients relative to high-dose treatment. Given the result, it could be seen from imaging examination that methylprednisolone at a routine dose was more efficient in patients with severe and critically severe medical conditions.

In conclusion, this study confirmed that the combined use of LPV/r and ARB was not superior to single-agent treatment with LPV/r or ARB in the treatment of patients with COVID-19. In the meantime, methylprednisolone could noticeably reduce the time for negative conversion and hospital stays of severe and critically severe patients and its early use at a routine dose of a short-term duration could produce dramatic therapeutic efficacy, accompanied by accelerated inflammatory absorption and certain alleviation of cytokine storm, with no noticeable toxic and side effects developed. In view of the findings, we suggested that for critically severe patients, routine-dose methylprednisolone of a short-term duration is recommended in clinical diagnosis as early as possible. Nevertheless, some limitations still exist in this study mainly referring to the data missing of some patients during treatment, which led to the results not precise enough. Hence, clinical sample size will be enlarged in future in-depth research for a more precise analysis.

ACKNOWLEDGMENTS

This study was supported by the Ministry of Science and Technology of the People's Republic of China, 13th Five-Year National Science and Technology Major Project (2018ZX10715-013-003), Research on Intelligent Medical Application of Information Platform of Integrated Prevention and Control Demonstration Area Based on "Internet+". Ministry of Science and Technology of the People's Republic of China, 13th Five-Year National Key Research and Development Program of China, 2019YFC0840600 and 2019YFC0840609, Research on cloud platform and intelligent diagnosis and treatment technology for viral hepatitis diagnosis and treatment. Fundamental Research Funds for the Central Universities.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

Conceptualization: Qi Xia. *Methodology*: Wanrong Dai, Kaijin Xu, Qin Ni and Yongtao Li. *Formal analysis and investigation*: Jun Liu, Hong Zhao, Yongzheng Guo, and Liang Yu. *Resources*: Ling Yu, Xiaoyan Wang, Hongliu Cai, and Qiang Fang. *Supervision*: Jianying Zhou and Yunqing Qiu. *Writing – original draft preparation*: Qi Xia, Qin Ni, Ping Yi, Junwei Su, Guanjing Lang, and Jingjing Tao. *Writing – review and editing*: Lanjuan Li, Yongtao Li, Jun Liu, Ding Shi, Wenrui Wu, Xiaoxin Wu, Yan Xu, and Min Xu. *Writing – revised*: Qi Xia, Hong Zhao, Lanjuan Li, Yongzheng Guo, Jianying Zhou, and Yunqing Qiu. Lanjuan Li and Qi Xia gave the final approval of the version to be submitted. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was conducted in accordance with the Helsinki Declaration II and was approved by the Institutional Review Boards of The First Affiliated Hospital, College of Medicine, Zhejiang University.

DATA AVAILABILITY STATEMENT

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

ORCID

Qi Xia http://orcid.org/0000-0002-4693-6088
Lanjuan Li http://orcid.org/0000-0001-9186-4741

REFERENCES

1. WU, YC, Chen CS, Chan YJ. Overview of the 2019 novel coronavirus (2019-nCoV): the pathogen of severe specific contagious pneumonia (SSCP). *J Chin Med Assoc*. 2020;83:217-220. https://doi.org/10.1097/JCMA.0000000000000270
2. Corman VM, Landt O, Kaiser M, et al. Detection of 2019 novel coronavirus (2019-nCoV) by real-time RT-PCR. *Euro Surveill*. 2020;25(3). https://doi.org/10.2807/1560-7917.ES.2020.25.3.2000045
3. Peiris J, Lai S, Poon L, et al. Coronavirus as a possible cause of severe acute respiratory syndrome. *Lancet*. 2003;361:1319-1325. https://doi.org/10.1016/s0140-6736(03)13077-2
4. Cheng VC, Lau SK, Woo PC, Yuen KY. Severe acute respiratory syndrome coronavirus as an agent of emerging and reemerging infection. *Clin Microbiol Rev*. 2007;20:660-694. https://doi.org/10.1128/CMR.00023-07
5. Chafekar A, Fielding BC. MERS-CoV: understanding the latest human coronavirus threat. *Viruses*. 2018;10:93. https://doi.org/10.3390/v10020093
6. Sheahan TP, Sims AC, Leist SR, et al. Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. *Nat Commun*. 2020;11:222. https://doi.org/10.1038/s41467-019-13940-6
7. Martinez MA. Compounds with therapeutic potential against novel respiratory 2019 coronavirus. *Antimicrob Agents Chemother*. 2020;64, https://doi.org/10.1128/AAC.00399-20
8. Blaising J, Polyak SJ, Pecheur EI. Arbidol as a broad-spectrum antiviral: an update. *Antiviral Res*. 2014;107:84-94. https://doi.org/10.1016/j.antiviral.2014.04.006
9. Kadam RU, Wilson IA. Structural basis of influenza virus fusion inhibition by the antiviral drug Arbidol. *Proc Natl Acad Sci U S A*. 2017;114:206-214. https://doi.org/10.1073/pnas.1617020114
10. Torrelo A. Methylprednisolone aceponate for atopic dermatitis. *Int J Dermatol*. 2017;56:691-697. https://doi.org/10.1111/ijd.13485
11. Biffl WL, Moore FA, Moore EE, Haenel JB, McIntyre RC, Burch JM. Are corticosteroids salvage therapy for refractory acute respiratory distress syndrome? *Am J Surg*. 1995;170:591-595. https://doi.org/10.1016/s0002-9610(99)80022-1
12. Stern A, Skalsky K, Avni T, Carrara E, Leibovici L, Paul M. Corticosteroids for pneumonia. *Cochrane Database Syst Rev*. 2017;12:CD007720. https://doi.org/10.1002/14651858.CD007720.pub3
13. Yang M, Li CK, Li K, et al. Chan hematological findings in SARS patients and possible mechanisms (review). *Int J Mol Med*. 2004;14:311-315.
14. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet*. 2020;395:507-513. https://doi.org/10.1016/S0140-6736(20)30211-7
15. Diana P, Money DT, Gelvin MG, Lunardi N. Effective and safe use of glucocorticosteroids for rescue of late ARDS. *Case Rep Crit Care*. 2017;2017:6740532-6740533. https://doi.org/10.1155/2017/6740532
16. Rhodes A, Evans LE, Alhazzani W, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. *Intensive Care Med*. 2017;43:304-377. https://doi.org/10.1007/s00134-017-4683-6
17. Panesar NS. What caused lymphopenia in SARS and how reliable is the lymphokine status in glucocorticoid-treated patients? *Med Hypotheses*. 2008;71:298-301. https://doi.org/10.1016/j.mehy.2008.03.019
18. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA*. 2020;323:1061. https://doi.org/10.1001/jama.2020.1585
19. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395:497-506. https://doi.org/10.1016/S0140-6736(20)30183-5

How to cite this article: Xia Q, Dai W, Xu K, et al. Clinical efficacy of methylprednisolone and the combined use of lopinavir/ritonavir with arbidol in treatment of coronavirus disease 2019. *J Med Virol*. 2021;93:4446-4453. https://doi.org/10.1002/jmv.26798