Clinical characteristics of Coronavirus Disease 2019 in Hangzhou, China: the combination of lopinavir/ritonavir, interferon, and arbidol may be a well choice for antiviral therapy in common cases

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Research article

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Abstract

Background

Since December 2019, when Coronavirus Disease 2019 (COVID-19) emerged in Wuhan, China, it is currently causing outbreaks in many countries worldwide. No specific therapeutics have yet been proven effective for the treatment of COVID-19.

Methods

A retrospective, single-center case series study was conducted in a designated hospital for special treatment of COVID-19 in Hangzhou, China. Clinical characteristics of COVID-19 patients were described and compared between the common and severe groups. Multiple linear regression and sensitivity analysis was conducted to evaluate the antiviral effects of the 3-drug combination therapy (lopinavir/ritonavir, interferon, and arbidol).

Results

One hundred and ten confirmed COVID-19 patients were enrolled, including 99 common cases and 11 severe cases. The mean age was 43.1 years and 54.5% were female. Severe patients might be older ($P < 0.01$), and have more coexisting disorders ($P < 0.01$), lower levels of lymphocyte counts ($P = 0.016$), blood sodium ($P = 0.039$) and chloride ($P < 0.01$), and higher levels of C reactive protein and procalcitonin (both $P < 0.01$). Multiple linear regression and sensitivity analysis indicated that both in Model 1 and Model 2, after adjusted by confounding factors, significant associations between completing the 3-drug combination antiviral therapy (vs. incompleting) and a shorter hospital staying time could be seen ($B = -5.970$, 95% CI, $-9.222, -2.718$, $P < 0.01$, in Model 1; and $B = -5.948$, 95% CI, $-10.622, -1.274$, $P = 0.014$, in Model 2).

Conclusions

Severe patients might be older and have more comorbidities. The combination of lopinavir/ritonavir, interferon, and arbidol may be a well choice for antiviral therapy, especially in adult common cases.

Background

As of March 15, 2020, the total number of global cases with coronavirus disease 2019 (COVID-19) reported by the World Health Organization (WHO) was 153,517 with 5,735 deaths [1], since early December 2019 when the first pneumonia cases of unknown origin were identified in Wuhan, the capital city of Hubei province, China [2]. In addition, 72,469 confirmed cases of COVID-19 with 2,531 deaths were reported outside of China [1]. One hundred and forty-three countries, territories or areas had reported
confirmed cases of COVID-19 globally [1]. The WHO has recently characterized COVID-19 outbreak as pandemic and the risk assessment was “very high” globally [3]. The pathogen has been identified and currently been named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which has a phylogenetic similarity to SARS-CoV [4, 5]. So far, there is presently no vaccine or specific antiviral drugs recommended for coronavirus infection except for meticulous supportive care [6–8].

China reported 81,077 COVID-19 cases with 3,218 deaths, as of March 15, 2020 [9]. The vast majority of cases were in Hubei Province, especially in Wuhan, the capital city of Hubei Province [9]. Zhejiang Province reported 1231 COVID-19 cases, ranked in the top 3 provinces outside of Hubei Province in mainland China [9]. Hangzhou, as the capital city of Zhejiang Province, is an important imported metropolis in the COVID-19 epidemic, given that the current COVID-19 outbreak is moving rapidly. Up to March 15, 2020, Hangzhou reported 182 COVID-19 cases [9]. As recently published researches on the epidemic features of COVID-19 were mostly from Wuhan, China, we now reported the clinical characteristics of COVID-19 in an imported city, Hangzhou, China.

In this retrospective study, we consecutively enrolled 110 patients with SARS-CoV-2 positive in a designated hospital to treat COVID-19 in Hangzhou. The aims of this study were to analyze the demographic, epidemiological and clinical characteristics of the COVID-19 cases in Hangzhou and to evaluate the effects of the 3-drug combination antiviral therapy on hospital staying time, which included lopinavir and ritonavir tablets (LPV/r), recombinant interferon α-2b, and arbidol.

**Methods**

**Study design**

This was a retrospective, single-center case series study. We consecutively enrolled patients with COVID-19 in Xixi Hospital of Hangzhou, which was the center for diagnosis and treatment of infectious diseases and one of two the designated hospitals for special treatment of COVID-19 in Hangzhou, China, from January 20 to March 9, 2020. Up to March 9, 2020, there had been 113 hospitalized patients with COVID-19 in our hospital, including 13 patients currently in the hospital and 100 patients discharged. Among them, 3 patients were excluded in our study because they were the cases whose SARS-CoV-2 ribonucleic acid (RNA) was found positive again after discharge. Patients flow could be seen in Fig. 1. The objectives of this study were to describe the clinical characteristics of the enrolled patients and to evaluate the effects of the 3-drug combination antiviral therapy. This study was approved by the Ethics Committee of Xixi Hospital of Hangzhou and the written informed consent was waived because of the retrospective nature of the study and the urgent need to collect data.

**Data sources**

Cases were diagnosed based on the WHO interim guidance [10]. All the enrolled patients were confirmed SARS-CoV-2 positive by real-time reverse-transcriptase polymerase-chain-reaction (RT-PCR) or high-
throughput sequencing assay for nasal and pharyngeal swab specimens in Hangzhou Center for Disease Control (CDC) [2]. Demographic information, epidemiological characteristics (including exposure history), clinical characteristics (including comorbidities, initial signs, duration of fever, length of hospital stay, and duration with pharyngeal swab nucleic acid positive), chest computed tomographic (CT) scan, and laboratory findings of each patient were extracted from the electronic medical record system of Xixi Hospital of Hangzhou. Two independent reviewers (D.Y. and J.Y.) extracted the data. All differences were resolved by evaluating the eligibility of the original data and discussion prior to the final analysis.

All the 110 patients were included in the CT imaging analysis, which was performed according to a recent study by two experienced radiologists with over 10-year experience (Y.Z. and Z.H.C.), and in case of disagreement, they would consult to reach an agreement [11]. Briefly, lesion distribution, including left lung (upper or lower lobe), and right lung (upper, middle or lower lobe), lesion location, including peripheral, central or involving both peripheral and central locations, and lesion density, including ground glass opacity, consolidation, thickness of interlobular and intralobular septa, enlarged lymph nodes within the mediastinum and pleural effusion, were analyzed.

**Study definitions**

The incubation period was defined as the interval between the potential earliest date of contact of the transmission source (wildlife or person with suspected or confirmed case) and the potential earliest date of symptom onset (i.e., cough, fever, fatigue, or myalgia). And the summary statistics of incubation periods were calculated based on patients who had clear information regarding the specific date of exposure.

The status of negative pharyngeal swab specimen was defined as that two consecutive pharyngeal swab specimens were both negative, and the interval time of the two specimens should be at least 24 hours. Based on this definition, the duration with pharyngeal swab specimen positive was defined as the interval between the earliest date with a pharyngeal swab specimen positive and the first time with a pharyngeal swab specimen negative.

For the clinical cure criteria in China [12], if the patient's body temperature has returned to normal for more than 3 days, the respiratory symptoms have improved significantly, the lung imaging has shown well absorption of inflammation, and the nucleic acid test for respiratory pathogens has been negative for two consecutive times with sampling interval at least 24 hours, the patient could be discharged or transferred to the corresponding departments to treat other diseases.

For antiviral therapy, all patients of 18 years or older were treated by the combinations of three drugs, if there were no contraindications: lopinavir and ritonavir tablets (lopinavir 200 mg/ritonavir 50 mg), 2 tablets at a time, twice a day; recombinant interferon α-2b, 5 million units at a time, adding 2 milliliter normal saline, spray inhalation, twice a day; and arbidol hydrochloride tablets, 200 mg at a time, three times a day. The course of the antiviral therapy was at least 10 days. If the patient could not complete the 10-day, three-drug antiviral therapy, because of the side effects of any of the 3 drugs or other reasons, it
was defined as incomplete antiviral therapy. Side effects of the antiviral therapy were defined as common side effects of any of the 3 drugs, after excluding other possible causes.

A non-pneumonia case was defined as a confirmed case by RT-PCR with fever and/or respiratory symptoms, but no radiographic evidence of pneumonia. An asymptomatic case was defined as a confirmed case with normal body temperature or minor discomfort. A mild case was defined as a confirmed case with fever, respiratory symptoms and radiographic evidence of pneumonia, while a severe case was defined as a mild case with dyspnea or respiratory failure. Common cases included all patients except the severe cases.

**Statistical analysis**

Continuous variables were expressed as the means and standard deviations or medians and ranges as appropriate. Categorical variables were summarized as the counts and percentages in each category. To compare the continuous variables for data of different patient groups, a two-tailed \( t \)-test or Mann-Whitney \( U \) test was used as appropriate. Ch-square tests or Fisher’s exact tests were used for categorical variables as appropriate. Multiple linear regression analysis was used to estimate the independent effects of the 10-day, 3-drug antiviral therapy on hospital staying time. To conduct sensitivity analysis, two models, Model 1 and Model 2, were established. Model 1 \((n = 93)\) included all the discharged cases of 18 years or older, while Model 2 included 51 cases after excluded important confounding factors from Model 1. All statistical analysis was performed with SPSS software version 19.0. \( P \)-value (two-sided) less than 0.05 was considered statistically significant.

**Results**

**Demographic, epidemiological and clinical characteristics**

As seen in Figure 1, 113 patients with COVID-19 had been hospitalized in our hospital up to March 9, 2020. The 113 patients included 13 patients currently in the hospital and 100 patients discharged. Especially, there were 3 patients whose SARS-CoV-2 RNA was found positive again after discharge among the 13 patients currently in hospital, and these 3 patients were also included in the 100 patients discharged, given their first hospitalization. We excluded the 3 repeatedly hospitalized cases in the analysis. The total number of severe patients was 11 \((11/110, 10\%)\), and the total number of common patients was 99 \((99/110, 90\%)\), which included 89 patients discharged and 10 patients currently in the hospital. The total number of non-pneumonia cases was 14 \((14/110, 12.7\%)\). The total number of asymptomatic cases was 4 \((4/110, 3.6\%)\) that included 2 patients \((2/110, 1.8\%)\), asymptomatic and with no radiologic evidence.

As seen in Table 1, the age was 43.1 ± 16.9 years of the 110 patients and 8 patients were younger than 18 years old \((8/110, 7.3\%)\). Female patients \((60/110, 54.5\%)\) were more than male patients \((50/110, 45.5\%)\). Most patients came from Zhejiang Province \((79/110, 71.8\%)\). Nine patients were smokers \((9/110, 8.2\%)\). The most common exposure to the source of transmission was contacting people who were
confirmed with COVID-19 (47/110, 42.7%). There were more family-clustering patients (57/110, 51.8 %). The median incubation period was 6.5 (0–26) days. Coexisting disorders could be seen in 24.5% of all patients (27/110). The most common initial manifestation was fever (63/110, 57.3%). The most common temperature range was 37.5–38.0 degrees centigrade (42/110, 38.2%). The median duration of fever during hospitalization was 7 (1–18) days. There were significant differences between the common group and the severe group in age and coexisting disorders (both \( P < 0.01 \)).

**Laboratory and radiologic findings at presentation**

As seen in Table 2, severe patients might have lower level of lymphocyte counts \( (P = 0.016) \), sodium \( (P = 0.039) \) and chloride \( (P < 0.01) \), and higher level of C reactive protein and procalcitonin (both \( P < 0.01 \)). Radiologic features included ground glass opacity (88/110, 88%), consolidation (61/110, 55.5%), thickness of interlobular (75/110, 68.2%) and intralobular (45/110, 40.9%) septa, air bronchogram (61/110, 55.5%), and pleural effusion (18/110, 16.4%). As seen in Table 3, lesions could be seen in all the 5 lobes of the lung, including left upper lobe (53/110, 48.2%), left lower lobe (68/110, 61.8%), right upper lobe (50/110, 45.5%), right middle lobe (43/110, 39.1%), and right lower lobe (79/110, 71.8%). And within lobes, peripheral and peripheral involving central lesions were more common.

**Treatment and clinical outcome**

As seen in Table 2, more patients had completed the 3-drug combination antiviral therapy in the 93 discharged patients of 18 years or older (74/93, 79.6%). Side effects of any of the 3 antiviral drugs seemed more common in the common cases group (55.6% in the common group vs. 9.1% in the severe group, \( P < 0.01 \)). Seventeen (17/99, 17.2%) patients interrupted antiviral therapy owing to side effects of any of the 3 drugs in the common group, while 1 patient in the severe group (1/11, 0.9%). The use of systemic corticosteroids, immunoglobin, and antibiotics were all more common in severe patients (all \( P < 0.01 \)). Hospital staying time seemed longer in the common group (median, 14, range, 3–29, in the common group, and median, 5, range, 1–25, in the severe group, \( P = 0.014 \)), with potential causes that there might be more severe patients transferred to the superior hospital (4/99, 4.0%, in the common group, and 6/11, 54.5%, in the severe group) when they got worse. The median duration with pharyngeal swab specimen positive was 11.5 (2–28) days.

To investigate the associations between the 3-drug combination antiviral therapy (complete vs. incomplete) and hospital staying time (days), multiple linear regression was performed. And to conduct sensitivity analysis, two models, Model 1 and Model 2 (see Table 4 and Supplementary Table 1), were established. Model 1 included 93 discharged patients of 18 years or older (3-drug combination antiviral therapy, complete, \( n = 74 \), and incomplete, \( n = 19 \)) with complete data of hospital staying time, and the adjusted potential confounding factors included gender, age, coexisting disorders, COVID-19 status
Discussion

Given the limited knowledge of the novel pathogen, SARS-CoV-2, and the current worldwide outbreak of COVID-19, effective treatment options are urgently needed. In the present study, we summarized the clinical characteristics of COVID-19 patients in Hangzhou, China, an important imported metropolis outside Wuhan. Our data indicated the effectiveness of the 3-drug combination of LPV/r, recombinant interferon α-2b, and arbidol on COVID-19, especially in adult common cases.

As seen in Fig. 1, the total number of non-pneumonia cases was 14 (14/110, 12.7%). And especially, 4 cases were asymptomatic, including 2 patients with radiologic evidence and 2 patients without radiologic evidence. Under the same definition of non-pneumonia cases, the ratio of non-pneumonia cases in all symptomatic cases (except severe patients) was about 14.7% (14/95, see Fig. 1) in our study, higher than another research in Beijing, China, conducted by Tian and colleagues (5.4%, 11/203) [13]. And a study from Shenzhen, China, including 55 asymptomatic cases at the time of hospital admission, indicated that the majority of them developed to be mild or ordinary COVID-19 during hospital [14]. Altogether, these data might reflect the characteristics of patients at different stages of SARS-CoV-2 infection, or very few patients might have a subclinical infection. From the perspective of controlling the epidemic, these findings suggested that the absence of clinical symptoms could not rule out the diagnosis of SARS-CoV-2 infection. Persons with a clear history of exposure to SARS-CoV-2, regardless of clinical symptoms, should be considered for medical observation, home isolation, and further examination [15].

There were 3 cases (3/110, 2.7%) whose SARS-CoV-2 RNA was found to be positive again after discharge in our study. Some case reports also suggested this phenomenon [16, 17]. Zhou and colleagues suggested some possible reasons to explain this status in their recent review [18]: 1) Virological properties of SARS-CoV-2 were not sufficiently understood given that it was just discovered recently; 2) Some host factors, such as the immune function status or coexisting disorders, might influence the control of the virus in the body; 3) Use of systemic corticosteroids might be related to the recurrence of SARS-CoV-2 RNA; 4) The tests results had been false negative when the patients were discharged; 5)
Secondary infection of SARS-CoV-2 might occur in some patients. In addition, another noteworthy phenomenon was that some patients had a long duration of viral shedding. In our study, the longest time with pharyngeal swab specimen positive was 28 days. And the longest duration of viral shedding was 37 days in a recent study by Zhou and colleagues [19]. People with positive SARS-CoV-2 RNA of respiratory tract specimens are the infectious source of COVID-19. During treatment or follow-up after discharge, the level and duration of infectious virus replication are important factors in assessing the risk of transmission and guiding decisions regarding the isolation of patients and the length of antiviral treatment. Data above indicated that SARS-CoV-2 RNA of respiratory tract specimens might be persistent or recurrent positive during the course, calling for further researches on dynamic profile and infectivity assessment of SARS-CoV-2 infection.

Severe patients seemed older and to have more coexisting disorders, lower levels of lymphocyte counts, sodium and chloride, and higher levels of C reactive protein and procalcitonin (see Table 1 and Table 2). These findings were consistent with the results of other studies with larger sample sizes [19–21]. Researches from Wuhan, China, indicated that older age (odds ratio 1.10, 95% CI 1.03–1.17, per year increase; \( P = 0.0043 \)) was an independent risk factor for in-hospital death [19] and showed more comorbidities and higher plasma levels of C reactive protein in severe cases [22]. These data indicate that older persons, particularly those with multimorbidity, are at high risk of being severer or death if infected by SARS-CoV-2. The elderly should be one of the key groups for infection prevention.

Judging from the CT imaging data, lesions being simultaneously present in more than one lobe or with more than one radiologic feature could be seen in a considerable number of patients (see Table 3). And within lobes, peripheral and peripheral involving central lesions were more common. These radiologic characteristics were similar to other reports [15, 23]. However, we must note that the CT findings of COVID-19 are variable. Some patients have no initial abnormal lung findings and can be misdiagnosed with other common diseases. Sixteen patients in our study had no CT evidence of pneumonia, including 14 non-pneumonia cases and 2 cases, asymptomatic and no radiologic evidence (see Fig. 1). Therefore, epidemiological history, clinical manifestations, and the RT-PCR detection of the viral RNA from a respiratory tract sample can be considered to represent the comprehensive analysis necessary to diagnose SARS-CoV-2 infection [24]. Especially, for cases of high clinical suspicion of SARS-CoV-2 infection with a negative RT-PCR result, the combination of repeated swab tests and CT examinations can be helpful for diagnosis. CT images and the detection of nucleic acid can mutually complement each other in the diagnosis of COVID-19.

Up to now, no specific treatment has been recommended for coronavirus infection [8]. Given the urgency of the COVID-19 outbreak and the absence of definitive antiviral drugs or vaccines, diverse treatment regimes have been explored for the treatment of COVID-19, such as oseltamivir, ganciclovir, LPV/r, remdesivir, chloroquine phosphate, herbal treatments, and passive immunization [8, 25–29]. Some of these treatments may have been tried out of desperation, and among these, some show initial promise.
Approved protease inhibitors including lopinavir and ritonavir have been reported to be active against SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV). They were also potential virally targeted agents for SARS-CoV-2 [7]. A study in the early stage of the SARS-CoV-2 epidemic in Wuhan, China, showed the initial therapeutic effect of arbidol, with a higher discharge rate in the arbidol-treated group compared to the arbidol-untreated group [22]. In addition, a recent retrospective cohort study showed that arbidol and LPV/r combination therapy was associated with a significant elevated negative conversion rate of coronavirus test in 7-day and 14-day and significantly improved the chest CT scans in 7-day, compared with LPV/r monotherapy [30]. Pegylated interferon α-2a and − 2b, approved for the treatment of hepatitis B virus (HBV) and hepatitis C virus (HCV) infection, had the potential activity to stimulate innate antiviral responses in patients infected with SARS-CoV-2 [7]. In our hospital, since the beginning of the SARS-CoV-2 epidemic in Hangzhou, all COVID-19 patients of 18 years or older were treated with the combination of LPV/r, recombinant interferon α-2b, and arbidol, if no contraindications. The course was at least 10 days. Our results showed that completing the 3-drug combination antiviral therapy was an independent related factor to a shorter hospital staying time, both in the whole group including common and severe patients and in the group excluding important confounding factors (see Table 4). Especially, given that 82 cases in Model 1 (82/93, 88.2%) were common cases and the 51 cases in Model 2 were all common cases, we draw the conclusion cautiously that the adult common COVID-19 patients might benefit from the 3-drug combination antiviral therapy. Meanwhile, another issue that needed attention was the side effects of antiviral drugs. In our study, 50.9% of the patients reported side effects of any of the 3 antiviral drugs, while 16.4% of the patients discontinued at least one of the 3 antiviral drugs because of side effects. Overall, prospective or even randomized researches with larger sample sizes are called for to evaluate the efficacy and tolerance of the 3-drug combination antiviral therapy in COVID-19 patients. And phase 3 or 4 clinical trials for LPV/r, arbidol or recombinant interferons in the treatment of COVID-19 are currently in progress [7, 19]. These might help to stratify patients to improve efficacy and reduce side effects.

Notably, a recent randomized clinical trial comparing LPV/r monotherapy plus standard care with standard care alone indicated that no benefit was observed with LPV/r treatment beyond standard care in hospitalized adult patients with severe COVID-19 [29]. This trial included only the severe cases with “an oxygen saturation (Sao₂) of 94% or less while they were breathing ambient air or a ratio of the partial pressure of oxygen (Pao₂) to the fraction of inspired oxygen (Fio₂) (Pao₂:Fio₂) at or below 300 mg Hg”. In our study, there were more common cases. As seen in the “Treatment and clinical outcome, Results” section and Supplementary Table 1, Model 1 included 93 patients, including only 11 severe cases and 51 cases in Model 2 were all common cases. In addition, in our study, patients were treated with 3-drug combination therapy, not with one drug monotherapy. There was a hypothesis that reducing the viral load as soon as possible might benefit the delay of the progression of lung lesions. A combination of two or three antiviral drugs might facilitate the rapid decline of viral load. These two differences between the resent clinical trial and our study might cause differences in treatment effects. And in the clinical trial conducted by Doctor Cao and colleagues, in the modified intention-to-treat analysis, which excluded three patients with early death, the between-group difference in the median time to clinical improvement
(median, 15 days vs. 16 days) was significant, although modest [29]. As the authors discussed in their article [29], further studies should be done to answer these questions: “whether earlier LPV/r treatment in COVID-19 could have clinical benefit?”, “whether LPV/r treatment given at a certain stage of illness can reduce some complications in COVID-19?”, and “whether combining LPV/r with other antiviral agents, as has been done in SARS and is being studied in MERS-CoV might enhance antiviral effects and improve clinical outcomes?”. Corresponding to these questions, in our study, most patients were common cases and combination therapy including LPV/r was evaluated. So the results of our research might be a well complement to the research conducted by Doctor Cao and colleagues.

There were several notable limitations in our study. Firstly, respiratory tract specimens were detected by RT-PCR, while results reporting is qualitative rather than quantitative in the clinical practice. This would cause the loss of some information. For example, the dynamic profile of SARS-CoV-2 RNA load could not be carefully observed. Secondly, the viral load in the serum was not detected in the clinical practice. That was a potentially useful marker related to the severity of COVID-19. Thirdly, this was a retrospective study, so recall bias might exist. That would influence the accuracy of the evaluation of some parameters, such as the incubation period. Meanwhile, this retrospective character also had advantages. For example, most patients had been discharged, which allowed us to obtain relatively complete data including the hospital staying time.

**Conclusions**

In summary, we described the clinical characteristics of COVID-19 patients in Hangzhou, China. Our data suggested that the 3-drug combination of LPV/r, recombinant interferon α-2b, and arbidol might be a well choice for antiviral therapy of COVID-19, especially in adult common patients.

**List Of Abbreviations**

CDC: Center for Disease Control; COVID-19: Coronavirus Disease 2019; CT: computed tomographic; HBV: hepatitis B virus; HCV: hepatitis C virus; LPV/r: lopinavir and ritonavir tablets; MERS-CoV: Middle East respiratory syndrome coronavirus; RNA: ribonucleic acid; RT-PCR: reverse-transcriptase polymerase-chain-reaction; SARS-CoV: severe acute respiratory syndrome coronavirus; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; WHO: World Health Organization.

**Declarations**

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**Authors’ contributions**
Z.Y. and J.Y. conceived and designed the study. D.Y. and J.Y. extracted the clinical data. Y.Z. and Z.H.C. extracted the CT imaging data. Z.Y., J.Y., M.W., K.Z., S.Z., B.X., J.H., Z.C., D.Y., Y.Z., Z.H.C., and S.L. analyzed data. Z.Y. and J.Y. wrote this manuscript. All authors reviewed and approved the final manuscript.

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**Availability of data and materials**

The datasets used and analyzed during the current study available from the corresponding author on reasonable request.

**Ethics approval and consent to participate**

This study was approved by the Ethics Committee of Xixi Hospital of Hangzhou and the written informed consent was waived because of the retrospective nature of the study and the urgent need to collect data.

**Consent for publication**

Not applicable.

**Competing interests**

The authors declare that they have no competing interests.

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References

1. WHO: Coronavirus disease 2019 (COVID-19) Situation Report – 55. 2020.
2. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X et al: Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet (London, England) 2020, 395(10223):497-506.
3. WHO: Coronavirus disease (COVID-19) outbreak. 2020.
4. Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, Wang W, Song H, Huang B, Zhu N et al: Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet (London, England) 2020, 395(10224):565-574.
5. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, Zhao X, Huang B, Shi W, Lu R et al: A Novel Coronavirus from Patients with Pneumonia in China, 2019. The New England journal of medicine 2020, 382(8):727-733.
6. de Wit E, van Doremalen N, Falzarano D, Munster VJ: SARS and MERS: recent insights into emerging coronaviruses. Nature reviews Microbiology 2016, 14(8):523-534.
7. Li G, De Clercq E: Therapeutic options for the 2019 novel coronavirus (2019-nCoV). Nature reviews Drug discovery 2020, 19(3):149-150.
8. Cunningham AC, Goh HP, Koh D: Treatment of COVID-19: old tricks for new challenges. Critical care (London, England) 2020, 24(1):91.
9. Chinese Center for Disease Control and Prevention: Distribution of new coronavirus pneumonia. 2020.
10. WHO: Clinical management of severe acute respiratory infection when Novel coronavirus (nCoV) infection is suspected: interim guidance. Jan 28, 2020.
11. Xu YH, Dong JH, An WM, Lv XY, Yin XP, Zhang JZ, Dong L, Ma X, Zhang HJ, Gao BL: Clinical and computed tomographic imaging features of novel coronavirus pneumonia caused by SARS-CoV-2. The Journal of infection 2020.
12. National Health Commission of the People's Republic of China: New coronavirus pneumonia prevention and control program (5nd ed.). 5 February 2020. (in Chinese)
13. Tian S, Hu N, Lou J, Chen K, Kang X, Xiang Z, Chen H, Wang D, Liu N, Liu D et al: Characteristics of COVID-19 infection in Beijing. The Journal of infection 2020.
14. Wang Y, Liu Y, Liu L, Wang X, Luo N, Ling L: Clinical outcome of 55 asymptomatic cases at the time of hospital admission infected with SARS-Coronavirus-2 in Shenzhen, China. The Journal of
15. Xu X, Yu C, Qu J, Zhang L, Jiang S, Huang D, Chen B, Zhang Z, Guan W, Ling Z et al: Imaging and clinical features of patients with 2019 novel coronavirus SARS-CoV-2. European journal of nuclear medicine and molecular imaging 2020.

16. Qu YM, Cong HY: Positive result of Sars-Cov-2 in sputum from a cured patient with COVID-19. Travel medicine and infectious disease 2020:101619.

17. Chen D, Xu W, Lei Z, Huang Z, Liu J, Gao Z, Peng L: Recurrence of positive SARS-CoV-2 RNA in COVID-19: A case report. International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases 2020.

18. Zhou Ling, Liu Kui, Huiguo L: Cause analysis and treatment strategies of "recurrence" with novel coronavirus pneumonia (covid-2019) patients after discharge from hospital. Chinese Journal of Tuberculosis and Respiratory Diseases 2020, 43. (in Chinese)

19. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X et al: Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet (London, England) 2020.

20. Wei-jie Guan, Zheng-yi Ni, Yu Hu, Wen-hua Liang, Chun-quan Ou, Jian-xing He, Lei Liu, Hong Shan, Chun-liang Lei, David S.C. Hui et al: Clinical characteristics of 2019 novel coronavirus infection in China. medRxiv 2020.

21. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui DSC et al: Clinical Characteristics of Coronavirus Disease 2019 in China. The New England journal of medicine 2020.

22. Wang Z, Yang B, Li Q, Wen L, Zhang R: Clinical Features of 69 Cases with Coronavirus Disease 2019 in Wuhan, China. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 2020.

23. Han R, Huang L, Jiang H, Dong J, Peng H, Zhang D: Early Clinical and CT Manifestations of Coronavirus Disease 2019 (COVID-19) Pneumonia. AJR American journal of roentgenology 2020:1-6.

24. Joob B, Wiwanitkit V: Computed Tomographic Findings in COVID-19. Korean journal of radiology 2020.

25. CC L, TP S, WC K, HJ T, PR H: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): the epidemic and the challenges. International journal of antimicrobial agents 2020:105924.

26. Gao J, Tian Z, Yang X: Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. Bioscience trends 2020, 14(1):72-73.

27. Luo H, Tang QL, Shang YX, Liang SB, Yang M, Robinson N, Liu JP: Can Chinese Medicine Be Used for Prevention of Corona Virus Disease 2019 (COVID-19)? A Review of Historical Classics, Research Evidence and Current Prevention Programs. Chinese journal of integrative medicine 2020.

28. De Clercq E, Li G: Approved Antiviral Drugs over the Past 50 Years. Clinical microbiology reviews 2016, 29(3):695-747.
29. Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, Ruan L, Song B, Cai Y, Wei M et al: A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19. *The New England journal of medicine* 2020.

30. Deng L, Li C, Zeng Q, Liu X, Li X, Zhang H, Hong Z, Xia J: Arbidol combined with LPV/r versus LPV/r alone against Corona Virus Disease 2019: a retrospective cohort study. *The Journal of infection* 2020.

**Tables**
Table 1. Demographic, epidemiological, and clinical characteristics of 110 patients with COVID-19

| Characteristics | All patients (n = 110) | Common cases (n = 99) | Severe cases (n = 11) | P-value |
|----------------|------------------------|-----------------------|----------------------|---------|
| **Age, means ± SD, years** | 43.1 ± 16.9 | 41.6 ± 16.3 | 56.5 ± 17.1 | < 0.01 |
| **Sex, No. (%)** | | | | 1.000 |
| Male | 50 (45.5) | 45 (45.5) | 5 (45.5) | | |
| Female | 60 (54.5) | 54 (54.5) | 6 (54.5) | | |
| **Native place ¹, No. (%)** | | | | 0.86 |
| Zhejiang province | | | | |
| Hangzhou | 75 (68.2) | 67 (67.7) | 8 (72.7) | | |
| Other cities in Zhejiang province | 4 (3.6) | 4 (4) | 0 | | |
| Hubei province | | | | |
| Wuhan | 7 (6.4) | 6 (6.1) | 1 (9.1) | | |
| Other cities in Hubei province | 8 (7.3) | 8 (8.1) | 0 | | |
| Other provinces | 16 (14.5) | 14 (14.1) | 2 (18.2) | | |
| **Smoking history, yes** | | | | 0.59 |
| Not available | 18 (16.4) | 15 (15.2) | 3 (27.3) | | |
| Travelling to or living in Wuhan or other epidemic areas | 31 (28.2) | 28 (28.3) | 3 (27.3) | | |
| Contacting people who were confirmed with COVID-2019 | 47 (42.7) | 45 (45.5) | 2 (18.2) | | |
| Contacting people who had travelled to or lived in Wuhan or other epidemic areas in the past 14 days | 14 (12.7) | 11 (11.1) | 3 (27.3) | | |
| **Clustering** | | | | 0.47 |
| Not available | 35 (31.8) | 30 (30.3) | 5 (45.5) | | |
| Family | 57 (51.8) | 53 (53.5) | 4 (36.4) | | |
| Work | 12 (10.9) | 11 (11.1) | 1 (9.1) | | |
| Others | 6 (5.5) | 5 (5.1) | 1 (9.1) | | |
| **Incubation period, median (range), days** | 6.5 (0–26) | 7 (0–26) | 4 (0–8) | 0.12 |
| **Coexisting disorders, No. (%)** | | | | < 0.01 |
| Any | 27 (24.5) | 20 (20.2) | 7 (63.6) | | |
| Malignancies | 3 (2.7) | 3 (3) | 0 | | |
| Auto-immune diseases | 2 (1.8) | 2 (2) | 0 | | |
| Metabolic diseases and hypertension ² | 16 (14.5) | 12 (12.1) | 4 (36.4) | | |
| Others ³ | 6 (5.5) | 3 (3) | 3 (27.3) | | |
| **Initial manifestations** | | | | 0.69 |
| None | 4 (3.6) | 4 (4) | 0 | | |
| Nasal obstruction | 4 (3.6) | 4 (4) | 0 | | |
| Fever | 63 (57.3) | 55 (55.6) | 8 (72.7) | | |
| Fatigue | 3 (2.7) | 3 (3) | 0 | | |
| Dry cough | 11 (10) | 11 (11.1) | 0 | | |
| Productive cough | 10 (9.1) | 8 (8.1) | 2 (18.2) | | |
| Chest tightness | 4 (3.6) | 3 (3) | 1 (9.1) | | |
| Sore throat | 8 (7.3) | 8 (8.1) | 0 | | |
| Others 4 | 3 (2.7) | 3 (3) | 0 |
|----------|---------|-------|---|
| **The maximum temperature during hospitalization, degrees centigrade, No. (%)** |         |       |   |
| < 37.5   | 34 (30.9) | 32 (32.3) | 2 (18.2) |
| 37.5 - 38.0 | 42 (38.2) | 39 (39.4) | 3 (27.3) |
| 38.1 - 39.0 | 30 (27.3) | 25 (25.3) | 5 (45.5) |
| > 39.0   | 4 (3.6) | 3 (3) | 1 (9.1) |
| **Duration of fever during hospitalization, median (range), days** | 7 (1–18) | 7 (1–18) | 7 (2–11) |

1 Native place, the place of one's birth or origin; 2 Metabolic diseases include diabetes mellitus and hyperlipidemia; 3 Including liver or heart diseases and osteoarticular diseases; 4 Including abdominal pain, diarrhea, and soreness.
Table 2. Laboratory findings, treatment, and clinical outcome of 110 patients with COVID-19

| Characteristics                                      | Normal Range | All patients (n = 110) | Common cases (n = 99) | Severe cases (n = 11) | P-value |
|------------------------------------------------------|--------------|------------------------|-----------------------|-----------------------|---------|
| **Laboratory findings**                              |              |                        |                       |                       |         |
| White blood cell count, median (range), 10^9/L        | 3.50 – 9.50  | 5.295 (2.12 – 16.67)   | 5.33 (2.12 – 16.67)   | 4.98 (2.97 – 9.7)     | 0.58    |
| Neutrophil, median (range), 10^9/L                   | 1.80 – 6.30  | 3.3 (0.4 – 13.44)      | 3.2 (0.4 – 13.44)     | 3.78 (1.97 – 8.97)    | 0.346   |
| Lymphocyte count, means ± SD, 10^9/L                 | 1.10 – 3.20  | 1.42 ± 0.79            | 1.48 ± 0.79           | 0.88 ± 0.5            | 0.016   |
| Hemoglobin, means ± SD, g/L                          | 115 – 150    | 136.99 ± 18.15         | 137.0 ± 18.8          | 136.8 ± 10.9          | 0.974   |
| C reactive protein, median (range), mg/L             | 0 – 10       | 8 (1.0 – 203.0)        | 8 (1.0 – 203)         | 55 (8 – 94)           | < 0.01  |
| Procalcitonin, median (range), ng/mL                 | 0 – 0.500    | 0.03 (0.02 – 1.46)     | 0.028 (0.02 – 0.33)   | 0.056 (0.022 – 1.46)  | < 0.01  |
| Lactate dehydrogenase, median (range), U/L           | 120 – 250    | 187 (0 – 1200)         | 182 (0 – 1200)        | 291 (25 – 805)        | 0.158   |
| Alanine aminotransferase, median (range), U/L        | 7 – 40       | 25 (7 – 97)            | 25 (12 – 97)          | 29 (7 – 58)           | 0.131   |
| Aspartate aminotransferase, median (range), U/L      | 13 – 35      | 19 (8 – 227)           | 18 (8 – 227)          | 28 (11 – 59)          | 0.147   |
| Alkaline phosphatase, median (range), U/L            | 30 – 120     | 73 (0 – 210)           | 71 (0 – 210)          | 75 (0 – 111)          | 0.527   |
| Total bilirubin, median (range), μmol/L              | 3.42 – 20.52 | 9.04 (1.23 – 58.24)    | 8.94 (1.23 – 58.24)   | 11.73 (4 – 38.45)     | 0.368   |
| Blood urea nitrogen, median (range), mmol/L          | 2.6 – 7.5    | 4.1 (2 – 11.8)         | 4 (2 – 8.7)           | 4.3 (2.1 – 11.8)      | 0.148   |
| Creatinine, means ± SD, μmol/L                       | 41 – 81      | 63.51 ± 19.21          | 63.1 ± 19.3           | 66.8 ± 19.1           | 0.549   |
| Sodium, means ± SD, mmol/L                           | 137 – 147    | 137.42 ± 2.61          | 137.7 ± 2.3           | 135 ± 3.7             | 0.039   |
| Potassium, means ± SD, mmol/L                        | 3.50 – 5.30  | 3.82 ± 0.45            | 3.84 ± 0.45           | 3.65 ± 0.42           | 0.202   |
| Chloride, means ± SD, mmol/L                         | 99 – 110     | 102.68 ± 2.82          | 102.9 ± 2.6           | 100.4 ± 3.8           | < 0.01  |
| Creatine kinase, median (range), U/L                 | 24 – 170     | 66 (5 – 3290)          | 64.5 (5 – 3290)       | 86 (31 – 183)         | 0.203   |
| Creatine kinase–MB, median (range), U/L              | 0 – 25       | 11 (1 – 46)            | 11 (1 – 46)           | 14 (7 – 23)           | 0.268   |
| Type B natriuretic peptide, median (range), pg/mL    | 0 – 125      | 33.5 (6 – 1821)        | 33 (6 – 1821)         | 94 (19 – 1449)        | 0.05    |
| Blood lactic acid levels, median (range), mmol/L     | 0.7 – 2.1    | 1.5 (0.4 – 4.7)        | 1.5 (0.4 – 3.4)       | 1.41 (0.9 – 4.7)      | 0.361   |
| D-dimer, median (range), mg/L                        | 0 – 0.55     | 1.07 (0.12 – 4.19)     | 1.07 (0.12 – 4.19)    | 1.74 (0.78 – 1.97)    | 0.441   |

| Treatment, No. (%)                                   |              |                        |                       |                       |         |
|------------------------------------------------------|--------------|------------------------|-----------------------|-----------------------|---------|
| Antiviral therapy                                   |              |                        |                       |                       |         |
| Completing the 3-drug combination                    | 74 (79.6)    | 65 (79.3)              | 9 (81.8)              | >                     |         |
Not completing the 3-drug combination 19 (20.4) 17 (20.7) 2 (18.2) 0.05

Side effects of any of the 3 drugs, yes, No. (%) 56 (50.9) 55 (55.6) 1 (9.1) < 0.01

 Interruption of antiviral treatment owing to side effects of any of the 3 drugs, No. (%) 18 (16.4) 17 (17.2) 1 (0.9) 0.688

Use of systemic corticosteroids, yes 19 (17.3) 11 (11.8) 8 (72.7) < 0.01

Use of intravenous immunoglobulin, yes 33 (30) 24 (25.3) 9 (81.8) < 0.01

Use of intravenous antibiotics, yes 29 (26.4) 22 (23.2) 7 (77.8) < 0.01

Hospital staying time, days 13 (1–29) 14 (3–29) 5 (1–25) 0.014

Duration with pharyngeal swab specimen positive, median (range), days 11.5 (2–28) 11 (2–28) 14 (8–19) 0.413

Clinical outcome, No. (%) < 0.01

Being hospitalized 10 (9.1) 10 (10.1) 0

Discharging from hospital 90 (81.8) 85 (85.9) 5 (45.5)

Transferring to the provincial hospital for further treatment 2

1 Lopinavir and ritonavir tablets (lopinavir 200mg/ritonavir 50 mg), 2 tablets at a time, twice a day; recombinant interferon α-2b, 5 million units at a time, spray inhalation, twice a day; and arbidol hydrochloride tablets, 200 mg at a time, three times a day. The course of the antiviral therapy was at least 10 days. 2 Because remission is not obvious since admission, some patients were transferred to the superior hospital. And there had no death of the patients in our and the superior hospital.

Table 3. Location of lesions identified by computerized tomography in 110 patients with COVID-19

| Lobe                  | Total, No (%) | Peripheral  | Central | Peripheral involving central |
|-----------------------|---------------|-------------|---------|----------------------------|
| Left upper lobe       | 53 (48.2)     | 26 (49.1)   | 1 (1.9) | 26 (49.1)                  |
| Left lower lobe       | 68 (61.8)     | 28 (41.2)   | 1 (1.5) | 39 (57.4)                  |
| Right upper lobe      | 50 (45.5)     | 23 (46)     | 3 (6)   | 24 (48)                    |
| Right middle lobe     | 43 (39.1)     | 21 (48.8)   | 1 (2.3) | 21 (48.8)                  |
| Right lower lobe      | 79 (71.8)     | 30 (38)     | 4 (5.1) | 45 (57)                    |
Table 4. Multiple linear regression evaluating the effects of the 3-drug combination antiviral therapy on hospital staying time in patients with COVID-19

| Variable                                | B, (95% CI)          | β   | P-value |
|-----------------------------------------|----------------------|-----|---------|
| **Model 1**                             |                      |     |         |
| Gender                                  | 0.631 (-2.056, 3.318)| 0.048| 0.641   |
| Age                                     | 0.020 (-3.780, 3.819)| 0.001| 0.992   |
| Coexisting disorders                    | -2.191 (-5.709, 1.328)| -0.142| 0.219   |
| COVID-2019 status                       | -4.263 (-9.725, 1.198)| -0.193| 0.124   |
| Use of systemic corticosteroids         | 0.838 (-3.406, 5.083)| 0.048| 0.695   |
| Use of intravenous immunoglobulin       | 1.053 (-2.619, 4.725)| 0.073| 0.57    |
| Use of intravenous antibiotic           | 1.143 (-2.175, 4.461)| 0.076| 0.495   |
| The 3-drug antiviral therapy            | -5.970 (-9.222, -2.718)| -0.369| < 0.01  |
| **Model 2**                             |                      |     |         |
| Gender                                  | 0.316 (-3.325, 3.957)| 0.024| 0.862   |
| Age                                     | 0.656 (-5.416, 6.729)| 0.03 | 0.829   |
| Coexisting disorders                    | -5.233 (-10.898, 0.432)| -0.26| 0.069   |
| The 3-drug antiviral therapy            | -5.948 (-10.622, -1.274)| -0.349| **0.014**|

1 Model 1 included 93 discharged patients of 18 years or older with complete data (3-drug combination antiviral therapy, complete, n = 80, and incomplete, n = 20), and the adjusted factors included gender (male as reference), age (< 60 years old or >= 60 years old, < 60 years old as reference), coexisting disorders (none as reference), COVID-19 status (common or severe, common as reference), use of systemic corticosteroids (no as reference), use of intravenous immunoglobulin (no as reference), use of intravenous antibiotic (no as reference), and the 3-drug therapy (incomplete or complete, incomplete as reference). 2 In model 2 (3-drug combination antiviral therapy, complete, n = 42, and incomplete, n = 9), patients treated with systemic corticosteroids, intravenous immunoglobulin, and intravenous antibiotic were excluded. All 51 patients were common cases. Covariates included gender (male as reference), age (< 60 years old or >= 60 years old, < 60 years old as reference), coexisting disorders (none as reference), and the 3-drug therapy (incomplete or complete, incomplete as reference). 3 Three-drug combination antiviral therapy: all the patients of 18 years or older were treated by the combinations of three drugs, if there was no contraindication, which included lopinavir and ritonavir tablets (lopinavir 200mg/ritonavir 50 mg), 2 tablets at a time, twice a day; recombinant interferon α-2b, 5 million units at a time, spray inhalation, twice a day; and arbidol hydrochloride tablets, 200 mg at a time, three times a day. The course of the antiviral therapy was at least 10 days. If the patient could not complete the 10-day, three-drug antiviral therapy, because of the side effects of any of the 3 drugs or other reasons, it was defined as incomplete antiviral therapy. Abbreviation: B, regression coefficient; β, standard partial regression coefficient; CI, confidence interval for each regression coefficient.

Figures
Figure 1

Patients flow and enrollment. A non-pneumonia case was defined as a confirmed case by RT-PCR with fever and/or respiratory symptoms, but no radiographic evidence of pneumonia. An asymptomatic case was defined as a confirmed case with normal body temperature or minor discomfort. A mild case was defined as a confirmed case with fever, respiratory symptoms and radiographic evidence of pneumonia, while a severe case was defined as a mild case with dyspnea or respiratory failure. Common cases included all the patients except the severe cases.

Supplementary Files

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