Antiviral Abidol is Associated with the Reduction of In-Hospital Mortality in COVID-19 Patients

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Abstract
Objective: Coronavirus disease 2019 (COVID-19) is a global public health crisis. There are no specific antiviral agents for the treatment of SARS-CoV-2. Information regarding the effect of Abidol on in-hospital mortality is scarce. The present study aimed to evaluate the treatment effect of Abidol for patients with COVID-19 before and after propensity score matching (PSM).

Methods: This retrospective cohort study analyzed 1019 patients with confirmed COVID-19 in China from December 22, 2019 to March 13, 2020. Patients were divided to Abidol (200 mg, tid, 5–7 days, n = 788, 77.3%) and No-Abidol (n = 231, 22.7%) groups. The primary outcome was the mortality during hospitalization.

Results: Among 1019 COVID-19 patients, the age was (60.4 ± 14.5) years. Abidol-treated patients, compared with No-Abidol-treated patients, had a shorter duration from onset of symptoms to admission, less frequent renal dysfunction, lower white blood cell counts (lymphocytes <0.8) and erythrocyte sending rate, lower interleukin-6, higher platelet counts and plasma IgG and oxygen saturation, and less frequent myocardial injury. The mortality during hospitalization before PSM was 17.9% in Abidol group and 34.6% in No-Abidol (hazard ratio (HR) = 2.610, 95% confidence interval (CI): 1.980–3.440), all seen in severe and critical patients. After PSM, the in-hospital death was 13.6% in Abidol group and 28.6% in No-Abidol group (HR = 2.728, 95% CI: 1.598–4.659).

Conclusions: Abidol-treatment results in less in-hospital death for severe and critical patients with COVID-19. Further randomized study is warranted to confirm the findings from this study.

Keywords: Abidol-treatment results in less in-hospital death for severe and critical patients with COVID-19. Further randomized study is warranted to confirm the findings from this study.

Introduction
The first series of patients infected with a new coronavirus in late December 2019 were reported in January 2020.[1] With the successful isolation of its structure, this virus was soon named SARS-CoV-2, and the disease was named coronavirus disease 2019 (COVID-19) in February 2020 by the World Health Organization (WHO).[2] Furthermore, COVID-19 is now a worldwide pandemic, with >1 million patients infected and >60,000 deaths. Epidemiology studies have reported that while people at any age are susceptible, aging patients have a higher incidence of all-cause death.[3,4] Unfortunately, there is a lack of specific antiviral treatments recommended for COVID-19, and no vaccine is currently available. Therefore, identifying the drug specifically for SARS-
CoV-2 is critical for the response to the 2019-nCoV outbreak. To this end, screening from existing antiviral drugs or compounds is one impending method to discover the potential antiviral treatment of SARS-CoV-2. Neuraminidase inhibitors, such as Remdesivir, peptide, Abidol, RNA synthesis inhibitors, and anti-inflammatory drugs could be the drug treatment options for COVID-19 patients. However, the efficacy and safety of those drugs for SARS-CoV-2 have not been confirmed clinically. Since the first report on February 4, 2020, by Lanjuan Li et al showing the in vitro inhibitory effect on SARS-CoV-2 of Abidol (takefoto.cn), Abidol was recommended by Chinese management guideline for COVID-19 (version 6.0) and was used after that for some patients. Accordingly, the present retrospective cohort study analyzed the treatment effect of Abidol in COVID-19 patients from China.

Methods

Patient population

Between December 22, 2019 and March 14, 2020, 1166 hospitalized patients with SARS-CoV-2 infections from 4 hospitals (Tongji Hospital, Tongji Medical College, Huazhong University of Science & Technology, Wuhan, Hubei; Wuhan First Hospital, Wuhan, Hubei; Tianyou Hospital, Wuhan University of Science & Technology, Wuhan, Hubei; Nanjing First Hospital, Nanjing Medical University, Nanjing, Jiangsu) were screened. Patients who underwent non-Abidol antiviral treatment were excluded. Of the remaining patients, 147 patients were further excluded: 6 re-hospitalized after a polymerase chain reaction (PCR) positive examination, 57 with the incomplete medical record, and 84 not hospitalized after a polymerase chain reaction (PCR) positive examination. In the end, 1019 patients were included in this retrospective cohort study. COVID-19 was defined according to the sixth version of interim guidelines by The National Health Commission of China. Patients were then classified into the Abidol group and the No-Abidol group. The ethic committees of all the 4 hospitals approved the study protocol. Informed consent was not required for this retrospective cohort analysis.

Data collection

All epidemiological, demographic, clinical, laboratory, treatment, and outcome data were extracted from electronic medical records using a standardized data collection form. The raw data were carefully checked by 2 staff members. Any difference in definition was adjudicated by 1 person who was unaware of the study design. Clinical outcomes after discharge from these 4 hospitals were not recorded.

Laboratory examinations

Routine blood tests on admission included blood cell counts, cytokines, high-sensitive cardiac troponin I (hs-cTNI), hepatic and renal function, erythrocyte sedimenting rate (ESR), hs-C reactive protein (CRP), interleuking-6 (IL-6), IgG and IgM, and N-terminal-pro brain natriuretic peptide (NT-proBNP). Repeat measurements were done at 48 to 72 hours (2nd measurement) after admission and 24 hours before discharge (3rd measurement) or just before death.

COVID-19 PCR examination

Three to 6 hours after admission, routine throat- or nose-swabs were recommended for all patients. Nasopharyngeal swabs were done for 12 patients in March 2020. The PCR procedure has been described elsewhere. Briefly, all swabs were delivered to the Chinese Center for Disease Control and Prevention, the Chinese Academy of Medical Science, and the Wuhan Institute of Virology, Chinese Academy of Sciences for testing until January 12, 2020. Since then, our 4 hospitals were able to perform real-time reverse transcription PCR (RT-PCR). A PCR re-examination was performed every 3 days until discharge.

Definitions

The primary outcome was the mortality during hospitalization. Coexisting cardiovascular disease (CVD) included coronary heart disease, hypertension, hyperlipidemia, diabetes, stroke, and arrhythmias treated by medications or an implanted permanent pacemaker. Due to some patients had severe symptoms on admission, the history of heart failure was not collected in this analysis. Patients with hs-cTnI concentration above the 99th centile were classified as having acute myocardial injury. Hypoproteinemia was defined as blood albumin level <25 g/L. Indications for continuous renal replacement therapy (CRRT) were stark increase in inflammation and the occurrence of acute kidney injury defined according to the Kidney Disease: Improving Global Outcomes (KDIGO), Clinical Practice Guidelines. Mechanical ventilation was used for patients with acute respiratory distress syndrome according to the Berlin definition. Antibiotic use was recommended for patients with evidence of secondary bacterial infections and ventilator-associated pneumonitis. Extracorporeal membrane oxygenation (ECMO) was recommended if oxygen saturation could not be improved by mechanical ventilation. Three typical computed tomography (CT) findings (ground glass opacities, consolidation, and bilateral pulmonary infiltration with reticular pattern or crazy paving pattern) were collected from COVID-19 patients.

Use of Abidol

Abidol (Shiyao Company, Shijiazhuang, Hebei province, China) was prescribed according to physician’s discretion, at 200mg, 3 times per day, no longer than 7 days. For patients who underwent Abidol treatment, no any other antiviral agent was allowed to be used. All patients in this analysis did not participate in any clinical study comparing the treatment effect and safety between different antiviral drugs.

Criteria for discharge

The criteria for discharge for all patients were the absence of a fever for at least 72 hours, substantial improvement in lung CT, significant clinical improvement of symptoms, and negative PCR tests from at least 2 samples at least 24 hours apart.

Statistical analysis

Categorical variables were reported as numbers and percentages and were compared using the χ² test or Fisher’s exact test. Continuous variables were presented as the mean ± the standard deviation (SD) or median (Q1, Q3). The Student’s t test or Wilcoxon rank sum scores for non-normally distributed data were used to compare continuous variables. Time-to-first event curves were generated using Kaplan-Meier analysis and
compared using the log-rank test. Since disease severity was associated with in-hospital mortality in patients with COVID-19,[2–4,16] subsequently, patients were grouped into general (mild), severe, and critical subgroups,[9] between them the difference in death during hospitalization was then compared. Cox regression model was created to identify the independent factors of in-hospital mortality after inputting all the variables in Tables 1–3. Because of the broader discrepancy in baseline and treatment variables [Tables 1–3] between patients treated with and without Abidol, propensity score matching (PSM), using logistic regression with membership in the 2 groups according to the nearest rule, was used for comparison of the primary endpoint between 2 groups. One patient in the Abidol group matched 1 patient in the No-Abidol group, with a matching tolerance of 0.10. All statistical tests were two-sided, and a P-value <0.05 was considered statistically significant. All analyses were performed using SPSS version 24.0 (SPSS Institute Inc., Chicago, Illinois, USA).

Results

Baseline clinical characteristics

Of 1019 patients in this study, 788 (77.3%) were assigned in Abidol and 231 (22.7%) in No-Abidol groups [Table 1]. Baseline clinical characteristics were comparable between Abidol and No-Abidol groups.

| Variable                     | Abidol (n=788) | No-Abidol (n=231) | Unadjusted OR (95% CI) | P     |
|------------------------------|---------------|-------------------|------------------------|-------|
| Age (years), mean ± SD       | 60.8±14.1     | 59.0±15.7         | 0.2 (0.4–0.4)          | 0.097 |
| Male gender, n (%)           | 420 (53.3)    | 118 (51.1)        | 0.9 (0.7–1.2)          | 0.652 |
| Time to admission (days), mean±SD | 12.1±7.9   | 14.3±10.2         | 1.1 (1.4–1.7)          | <0.001|
| Heart rate (beats/min), mean ± SD | 90.2±16.4   | 91.9±21.3         | 3.8 (1.1–11.7)         | 0.193 |
| SBP (mmHg), mean ± SD        | 129.9±19.7    | 130.6±26.6        | 4.9 (0.3–19.9)         | 0.690 |
| DBP (mmHg), mean ± SD        | 79.3±12.2     | 79.9±16.8         | 7.7 (2.3–13.1)         | 0.533 |
| Smoker, n (%)                | 85 (10.8)     | 26 (12.1)         | 0.9 (0.6–1.4)          | 0.551 |
| At least one CVD, n (%)      | 357 (45.3)    | 103 (44.6)        | 0.4 (0.3–1.5)          | 0.309 |
| Two or more CVD, n (%)       | 124 (15.7)    | 40 (17.3)         | 0.2 (0.1–1.3)          | 0.145 |
| Hypertension, n (%)          | 285 (36.2)    | 83 (35.9)         | 0.9 (0.7–1.4)          | 1.000 |
| Diabetes, n (%)              | 121 (15.4)    | 36 (15.6)         | 0.9 (0.7–1.5)          | 0.917 |
| Hyperlipidemia, n (%)        | 19 (2.4)      | 2 (0.9)           | 2.8 (0.6–12.1)         | 0.191 |
| Coronary artery disease, n (%) | 62 (7.9)     | 19 (8.2)          | 0.9 (0.6–1.6)          | 0.809 |
| Previous PCI, n (%)          | 30 (3.8)      | 10 (4.3)          | 0.9 (0.4–1.8)          | 0.701 |
| Stroke, n (%)                | 23 (2.9)      | 5 (2.2)           | 1.3 (0.5–3.6)          | 0.652 |
| Atrial fibrillation, n (%)   | 6 (0.8)       | 2 (0.9)           | 0.9 (0.2–4.4)          | 1.000 |
| COPD, n (%)                  | 37 (4.7)      | 9 (3.9)           | 1.2 (0.8–1.8)          | 0.764 |
| Renal dysfunction, n (%)     | 12 (1.5)      | 10 (4.3)          | 0.3 (0.1–0.8)          | 0.017 |
| Symptoms, n (%)              | 642 (81.5)    | 184 (79.7)        | 1.1 (0.7–1.6)          | 0.700 |
| Fever                        | 588 (74.6)    | 157 (67.9)        | 1.4 (0.9–1.9)          | 0.074 |
| Cough                        | 234 (29.7)    | 61 (26.4)         | 1.2 (0.8–1.8)          | 0.408 |
| Dyspnea                      | 121 (15.4)    | 28 (12.1)         | 1.3 (0.8–2.0)          | 0.288 |
| Muscular soreness            | 120 (15.2)    | 36 (15.6)         | 0.9 (0.6–1.5)          | 0.836 |
| Diarrhea                     | 32 (4.4)      | 5 (2.2)           | 1.9 (0.7–4.9)          | 0.230 |
| Chest pain                   | 274 (34.8)    | 38 (16.5)         | 0.05 (0.04–0.07)       | <0.001|
| Disease severity, n (%)      | 356 (45.2)    | 107 (47.2)        | 0.69 (0.4–1.2)         | 0.390 |

Table 1

Baseline clinical characteristics of Abidol and No-Abidol group before PSM

COPD: Chronic obstructive pulmonary disease; CVD: Cardiovascular disease; DBP: Diastolic blood pressure; PCI: Percutaneous coronary intervention; PSM: Propensity score matching; SBP: Systolic blood pressure; SD: Standard deviation.

Laboratory findings

Routine blood count tests demonstrated a less white blood cell count and percentage of lymphocytes <0.8, lower cTnl leading to less myocardial injury, lower ESR and IL-6, and higher plasma IgG in the Abidol group than the No-Abidol group (all P<0.05) [Table 2]. Abidol was less frequently prescribed for patients with IL-6 >7 pg/mL (26.0% vs. 33.3%, P=0.033).

On admission, the oxygen saturation of No-Abidol group was (84.4% ± 12.9%) compared to (95.4% ± 11.3%) in the Abidol group (P=0.002), but no significant difference in the percentage of oxygen saturation <90% between 2 groups. Three typical findings (ground glass opacity, consolidation, and bilateral infiltration) from lung CT scans were comparable between Abidol and No-Abidol groups.

Treatment strategies

Antibiotics were administered to 84.0% in Abidol group but only 68.4% in No-Abidol group (P<0.001), with 4-quinolones (76.8%) mostly used among patients in the Abidol group (vs. 49.8%, P<0.001) and with cephalosporin (37.7%) and carbapenem antibiotics (12.6%) mostly used in the No-Abidol group (vs. 23.9%, vs. 4.3%, all P<0.001). Glucocorticoids were
also much more commonly administered to patients in the No-Abidol group than in the Abidol group. In contrast, angiotensin receptor blockers (ARB) was more prescribed for Abidol group.

During hospitalization, mechanical ventilation was performed in 37.7% of patients in the No-Abidol group, compared to 19.9% of patients in the Abidol group (P < 0.001) [Table 3]. ECMO was used in 7 patients; 4 (1.7%) in No-Abidol and 3 (0.4%) in Abidol groups (P = 0.049).

**Mortality during hospitalization**

Of the 1019 patients before PSM, 221 (21.7%) died during hospitalization, with 141 (17.9%) in the Abidol group and 80 (34.6%) in the No-Abidol group (P < 0.001) [Table 3] [Figure 1A]. The time from admission to death in the No-Abidol group was (10.3 ± 8.6) days, which was delayed by 3 days after Abidol treatment (P = 0.828). Of 221 deaths, there was no death among general (mild) patients. Abidol use was associated with significant reduction of in-hospital death in patients defined as severe or critical (32.6%), particularly in severe patients (0.3%), compared to those in No-Abidol group (64.5%, P < 0.001 and 1.7%, P = 0.013).

By PSM, 147 pairs of patients matched [Supplemental Tables 1 and 2, http://links.lww.com/CD9/A3] with a c-statistics of 0.825. Of them, 62 (21.1%) died during hospitalization, with 20 (13.6%) in the Abidol group and 42 (28.6%) in the No-Abidol group (P < 0.001) [Figure 1B] [Table 3]. The time from admission to death was non-significantly different between 2 groups (P = 0.280).

**Multivariable analysis to identifying independent factors of in-hospital death**

Using Cox regression analysis before PSM [Table 4], critical illness (HR = 3.042; 95% CI: 1.238–7.669; P < 0.001), myocardial injury (HR = 2.561; 95% CI: 1.849–4.548; P < 0.001), Abidol use (HR = 0.268; 95% CI: 0.176–0.407; P < 0.001), and mechanical ventilation (HR = 13.104; 95% CI: 7.221–20.044; P < 0.001) were 4 independent factors of mortality during hospitalization.
Association of Abidol treatment with prognosis

This report provides the treatment effect of antiviral Abidol among patients with COVID-19 in China. Generally, Abidol was more frequently prescribed for general and severe patients but less for critical patients. In the current study, among 1019 patients with COVID-19, 221 patients (21.7%) died during hospitalization. The significant reduction (17.9% vs. 34.6%) in mortality during hospitalization in patients treated by Abidol before PSM was sustained after PSM (13.6% vs. 28.6%), particularly in severe and critical patients. In patients who died during hospitalization, the mean duration from admission to death was 3 days delayed in Abidol treated patients.

Potential mechanisms underlying the benefits of Abidol

Arbidol, also known as umifenovir, is a broad-spectrum antiviral compound developed in Russia[17] and licensed in Russia and China. In the current study, a significant reduction in mortality (17.9% vs. 34.6%) in patients treated by Abidol before PSM was sustained after PSM (13.6% vs. 28.6%), particularly in severe and critical patients. In patients who died during hospitalization, the mean duration from admission to death was 3 days delayed in Abidol treated patients.
China for the prophylaxis and treatment of human influenza A and B infections, plus post-influenza complications,[18] via interacting with virus hemagglutinin (HA), causing an increase in HA stability thereby preventing the pH-induced transition of HA into its a functional fusogenic state.[19] Recently, ARBITR study demonstrated that the effect of Abidol in the treatment of influenza in adults is most pronounced in the acute stage of the disease.[20] More recently, a pool of data confirmed the benefits of Abidol for different diseases induced by viruses, including hepatitis C virus,[21] Zika virus,[22] and Ebola virus.[23] Additionally, Abidol also showed its stronger antioxidant capacity, which could make a profound contribution to the compensation of oxidative stress caused by viral diseases and the therapeutic effect of the drug.[24] The antioxidant capacity of 0.9 μmol/L umifenovir in that study is equaled to the maximum concentration of Abidol in blood after oral administration of 200 mg in our study.[25] In total, antiviral effect, immunomodulation, as well as preventing virus-exacerbated occurrences of bronchial asthma and chronic obstructive pulmonary disease by Abidol[25] all indicated the potential of Abidol for patients with SARS-CoV-2 infection, which was confirmed in an in vitro study led by Lanjuan Li et al,[26] who reported an inhibitory effect of Abidol at high concentration (10–30 μmol/L).

**Considerations of treatment effect of Abidol**

To date, there were 3 studies reported the treatment effect of Abidol for COVID-19 patients.[26-28] Deng et al[26] for the first compared combination of arbidol and lopinavir/ritonavir (LPV/r, n=16) with LPV/r alone (n=17) for COVID-19. After 14 days, 15 (94%) of 16 and 9 (53%) of 17, respectively, SARS-CoV-2 could not be detected, along with improvement in the chest CT scans (69% vs. 29%). Soon after, Wang et al[27] further revealed the efficacy of combining LPV/r, arbidol, and traditional Chinese medicines for SARS-CoV-2, without known the patient sample size. In another report consisting of 69 confirmed patients with COVID-19, arbidol treatment showed the tendency to improve the discharging rate and decrease the mortality rate, in line with the reduction of IL-6.[28] Obviously, in the larger study, we found a sustainable reduction of mortality during hospitalization among patients treated by Abidol, indicating the potential of Abidol in treating SARS-CoV-2 infection.

**Limitations**

Our study suffers several limitations. First, only 1019 patients with confirmed COVID-19 were included, and a more extensive cohort study is needed to verify the real mortality rate. Second, as a retrospective study, some other specific information regarding the side effects of Abidol could not be collected. Third, as reflected by the urgent status in the isolation ward during virus spreading, echocardiography was not routinely performed, leading to the inability to invasively assess cardiac function. Finally, non-randomized controlled trial (RCT) feature of this cohort study allowed the prescription of Abidol at physician’s discretion. Generally, Abidol was more often used in general and severe patients, but less often used in critical patients. This resulted in small patient population for PSM.

**Conclusions**

Abidol treatment is associated with the reduction of in-hospital death for patients with COVID-19, particularly for severe and critical patients. Long-term follow-up is urgent to identify the clinical outcome in survivors after Abidol treatment. Furthermore, RCT with a large sample size is warranted to confirm the efficacy of Abidol for COVID-19 patients.

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Author Contributions
Shaoliang Chen and Hesong Zeng had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Conflicts of Interest
None.

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