Original Article

Cardiology Discovery 心血管病探索（英文）

OPEN

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

Hesong Zeng[1,*], Xingwei He[1], Wanjun Liu[1], Jing Kan[2], Liqun He[3], Jinhe Zhao[4], Cynthia Chen[5], Junjie Zhang[2], Shaoliang Chen[1,2,6,*]

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% confident interval (CI): 1.980–3.440), all seen in severe and critical patients. After PSM, the in-hospital death was 13.6% in Abidol 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; Coronavirus induced disease; Inflammation; In-hospital death

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-

CLINICAL PERSPECTIVE

WHAT IS NEW?

- This report provides the treatment effect of antiviral Abidol among patients with COVID-19 in China.
- Abidol treatment is associated with the reduction of in-hospital death for patients with COVID-19 before and after propensity score matching.
- In patients who died during hospitalization, the mean duration from admission to death was 3 days delayed in Abidol treated patients.

WHAT ARE THE CLINICAL IMPLICATIONS?

- Abidol treatment is associated with the reduction of in-hospital death for patients with COVID-19, particularly for severe and critical patients.
- Abidol has potential therapeutic effects on patients infected with SARS-CoV-2, including antiviral, immunomodulatory, and prevention of the aggravation of bronchial asthma and chronic obstructive pulmonary disease caused by the virus.

Editor: Tianyu Xu and Xiaoxia Fu.

Hesong Zeng, Xingwei He and Wanjun Liu contributed equally to the work.

Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website, www.cardio-discovery.org.

[1] Department of Cardiology, Tongji Hospital, Tongji Medical College, Huazhong University of Science & Technology, Wuhan 430030, China; [2] Department of Cardiology, Nanjing First Hospital, Nanjing Medical University, Nanjing 210006, China; [3] Department of Cardiology, Wuhan First Hospital, Wuhan 430022, China; [4] Department of Cardiology, Tianyou Hospital Affiliated to Wuhan University of Science & Technology, Wuhan 430064, China; [5] Mailman School of Public Health, Columbia University, NewYork, New York 10027, USA; [6] College of Pharmacy, Nanjing Medical University, Nanjing 210002, China.

[*] Corresponding author: Hesong Zeng, E-mail: zenghs@tjh.tjmu.edu.cn; Shaoliang Chen, E-mail: chmengx@126.com.

Received: 12 October 2020; Accepted: 15 January 2021

http://dx.doi.org/10.1097/CD9.0000000000000014

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.[5] Neuraminidase inhibitors, such as Remdesivir,[6] peptide,[7] Abidol,[8] RNA synthesis inhibitors,[5] and anti-inflammatory drugs,[5,8] 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)[9] 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 confirmed by PCR. 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.[9] 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 sending 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.[3–5] 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.[10] Hypoproteinemia was defined as blood albumin level <25 g/L.[3] 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.[11] Mechanical ventilation was used for patients with acute respiratory distress syndrome according to the Berlin definition.[12] Antibiotic use was recommended for patients with evidence of secondary bacterial infections[3] and ventilator-associated pneumonia.[13] Extracorporeal membrane oxygenation (ECMO) was recommended if oxygen saturation could not be improved by mechanical ventilation.[14] 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.[15,16]

Use of Abidol

Abidol (Shiyao Company, Shijiazhuang, Hebei province, China) was prescribed according to physician's discretion, at 200 mg, 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 χ^2 test or Fisher's exact test. Continuous variables were presented as the mean $\pm$ 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, except for the time interval from the onset of symptoms to admission ((12.1±7.9) d *vs.* (14.3±10.2) d, $P<0.001$), renal dysfunction (1.5% *vs.* 4.3%, $P=0.017$), and disease severity ($P<0.001$).

Laboratory findings

Routine blood count tests demonstrated a less white blood cell count and percentage of lymphocytes <0.8, lower cTnI 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

Table 1

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

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 (−4.2–0.4)	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	11.1 (7.4–14.7)	<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)	28 (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)	0.890
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* (%)				
Fever	642 (81.5)	184 (79.7)	1.1 (0.7–1.6)	0.700
Cough	588 (74.6)	157 (67.9)	1.4 (0.9–1.9)	0.074
Dyspnea	234 (29.7)	61 (26.4)	1.2 (0.8–1.6)	0.408
Muscular soreness	121 (15.4)	28 (12.1)	1.3 (0.8–2.0)	0.288
Diarrhea	120 (15.2)	36 (15.6)	0.9 (0.6–1.5)	0.836
Chest pain	32 (4.4)	5 (2.2)	1.9 (0.7–4.9)	0.230
Disease severity, *n* (%)			0.05 (0.04–0.07)	<0.001
General	356 (45.2)	107 (47.2)		
Severe	274 (34.8)	38 (16.5)		
Critical	158 (20.1)	86 (37.3)		

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

Table 2

Laboratory measurements and CT findings of Abidol and No-Abidol group before PSM

Variable	Abidol (n=788)	No-Abidol (n=231)	Unadjusted OR (95% CI)	P
White blood cells ($\times 10^9$/L), mean ± SD	6.46±3.23	8.38±5.31	1.2 (1.0–3.3)	<0.001
White blood cells classification, *n* (%)				
$<4\times10^9$/L	150 (19.0)	30 (12.9)	1.6 (1.0–2.4)	0.039
$(4–10)\times10^9$/L	549 (69.7)	141 (61.0)	1.4 (1.1–1.9)	0.024
$>10\times10^9$/L	89 (11.3)	60 (25.9)	0.4 (0.3–0.6)	<0.001
Lymphocytes ($\times 10^9$/L), mean ± SD	1.16±1.02	1.11±0.67	0.7 (0.4–2.5)	0.497
Lymphocytes $<0.8\times10^9$/L, *n* (%)	266 (33.8)	98 (42.4)	0.7 (0.5–0.9)	0.015
Platelet ($\times 10^9$/L), mean ± SD	232.8±100.8	208.1±89.5	24.6 (7.1–35.6)	0.121
Platelet $<100\times10^9$/L, *n* (%)	38 (4.8)	19 (8.2)	0.6 (0.4–1.3)	0.051
Scr (mmol/L), median (Q1, Q3)	71.0 (57.0, 88.3)	72.0 (55.0, 95.0)	23.9 (1.9–91.1)	0.057
eGFR mL/(min·m^2), mean ± SD	72.9±35.1	92.4±51.8	6.4 (3.6–21.9)	0.703
eGFR Classification, *n* (%)			0.11 (0.10–0.14)	0.109
>60 mL/(min·m^2)	670 (85.0)	192 (83.1)		
30–60 mL/(min·m^2)	97 (12.3)	25 (10.8)		
<30 mL/(min·m^2)	21 (2.7)	14 (6.1)		
ALT (U/L), median (Q1, Q3)	24.0 (16.0, 38.0)	25.0 (13.3, 32.3)	11.3 (4.2–40.8)	0.931
ALT >40 U/L, *n* (%)	174 (22.1)	56 (24.2)	1.1 (0.5–1.5)	0.475
AST (U/L), median (Q1, Q3)	24.0 (15.8, 37.3)	24.5 (18.0, 39.3)	14.5 (1.2–56.5)	0.080
AST >40 U/L, *n* (%)	193 (18.9)	56 (24.2)	1.0 (0.7–1.4)	1.000
Albumin (g/L), mean ± SD	31.5±4.6	36.8±6.1	1.7 (0.4–6.3)	0.190
Albumin <25 g/L, *n* (%)	14 (1.8)	8 (3.5)	0.5 (0.2–1.2)	0.125
NT-proBNP (pg/mL), median (Q1, Q3)	118.0 (53.0, 301.8)	50.0 (27.1, 185.3)	12.3 (6.3–45.0)	0.196
cTnI (pg/mL), median (Q1, Q3)	3.40 (1.90, 9.65)	3.55 (1.90, 21.65)	2.4 (1.2–6.6)	<0.001
Myocardial injury, *n* (%)	94 (11.9)	66 (28.6)	3.3 (1.9–5.6)	<0.001
CRP (mg/L), median (Q1, Q3)	23.5 (4.0, 72.5)	30.6 (4.3, 86.7)	18.6 (4.8–23.9)	0.128
CRP >3 mg/dL, *n* (%)	586 (74.4)	166 (71.9)	1.2 (0.8–2.0)	0.153
ESR (mm/s), mean ± SD	35.9±26.9	41.3±28.4	5.0 (2.9–9.1)	0.008
IL-6 (pg/mL), median (Q1, Q3)	2.95 (1.50, 5.22)	4.36 (1.88, 14.26)	5.7 (2.5–9.0)	0.004
IL-6 >7 pg/mL, *n* (%)	205 (26.0)	77 (33.3)	1.8 (1.1–3.0)	0.033
IgG (mg/L), median (Q1, Q3)	168 (138, 223)	168 (98, 224)	6.5 (4.4–9.2)	0.004
IgM (mg/L), median (Q1, Q3)	44.2 (16.0, 145.1)	48.9 (10.1, 163.3)	0.9 (0.16–2.4)	0.568
Saturation of oxygen (%), mean ± SD	95.4±11.3	84.4±12.9	2.0 (1.9–2.3)	0.002
Saturation of oxygen <90%, *n* (%)	348 (44.2)	100 (43.3)	1.0 (0.8–1.4)	0.940
CT findings, *n* (%)				
Ground glass opacity	466 (59.2)	123 (53.2)	1.3 (0.9–1.7)	0.149
Consolidation	203 (25.8)	55 (23.8)	2.4 (0.9–6.2)	0.765
Bilateral infiltration	377 (47.8)	120 (51.9)	0.8 (0.6–1.1)	0.260

ALT: Glutamic-pyruvic transaminase; AST: Glutamic oxalacetic transaminase; CRP: C reactive protein; cTnI: Cardiac troponin I; ESR: Erythrocyte sending rate; eGFR: Estimated glomerular filter rate; IL: Interleukin; NT-proBNP: N-terminal pro brain natriuretic peptide; PMS: Propensity score matching; Scr: Serum creatinine; SD: Standard deviation.

also much more commonly administered to patients in the No-Abidol 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 Abidolr 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: 1.238–5.669; $P<0.001$), 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.

Table 3

Treatments and in-hospital mortality of Abidol and No-Abidol group

Variable	Abidol (n=788)	No-Abidol (n=231)	Unadjusted OR (95% CI)	P
Antibiotics, n (%)	662 (84.0)	158 (68.4)	2.4 (1.7–3.3)	<0.001
4-quinolones	605 (76.8)	115 (49.8)	3.3 (2.4–4.5)	<0.001
Cephalosporin	188 (23.9)	87 (37.7)	0.5 (0.4–0.7)	<0.001
Azithromycin	13 (1.6)	7 (3.0)	0.5 (0.2–1.4)	0.181
Carbapenems antibiotics	34 (4.3)	29 (12.6)	0.3 (0.2–0.5)	<0.001
Glucocorticoid, n (%)	303 (38.5)	108 (46.8)	0.7 (0.5–0.9)	0.022
ACEI, n (%)	4 (0.5)	2 (0.9)	0.6 (0.1–3.2)	0.622
Angiotensin receptor blocker, n (%)	51 (6.5)	9 (3.9)	0.04 (0.03–0.05)	0.043
Traditional Chinese medicine, n (%)	576 (73.1)	130 (56.3)	2.1 (1.5–2.8)	<0.001
Injection of gamma globulin, n (%)	257 (32.6)	79 (34.2)	0.9 (0.7–1.3)	0.632
Mechanical ventilation, n (%)	157 (19.9)	87 (37.7)	0.4 (0.3–0.6)	<0.001
Invasive	13 (1.6)	7 (3.0)	0.5 (0.2–1.4)	0.278
Non-invasive	144 (18.3)	80 (34.6)	0.4 (0.3–0.6)	<0.001
ECMO, n (%)	3 (0.4)	4 (1.7)	0.2 (0.05–0.90)	0.049
CRRT, n (%)	32 (4.1)	9 (3.9)	1.0 (0.5–2.2)	1.000
In-hospital death*				
Before PSM, n (%)	141 (17.9)	80 (34.6)	0.4 (0.3–0.6)	<0.001
Days from admission to death† (d), mean ± SD	13.3±7.7	10.3±8.6	0.7 (0.5–1.1)	0.828
After PSM, n (%)	20 (13.6)	42 (28.6)	2.6 (1.4–4.9)	<0.001
Days from admission to death‡ (d), mean ± SD	12.3±7.6	10.3±6.1	0.6 (0.3–0.9)	0.280

* Calculated from patients who died during hospitalization.
† Calculated from the patient number in Table 1.
‡ Calculated from the patient number in Supplemental Table 1, http://links.lww.com/CD9/A3.
ACEI: Angiotensin converting enzyme inhibitor; CRRT: Continuous renal replacement therapy; ECMO: Extracorporeal membrane oxygenation; PSM: Propensity score matching.

Discussion

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

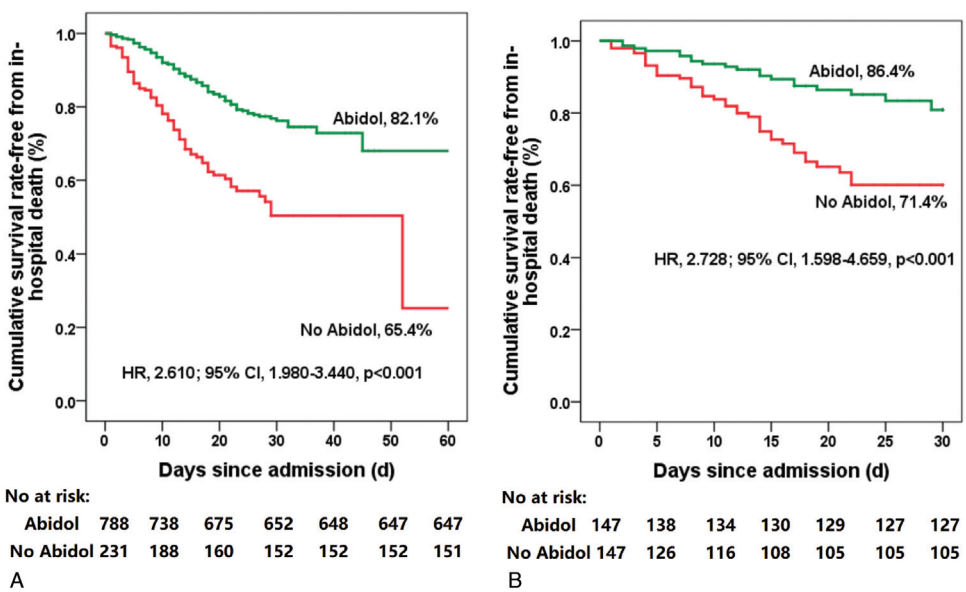

Figure 1: Kaplan-Meier survival rate between Abidol and No-Abidol groups. (A) Before propensity score matching (n=1019 pairs). (B) After propensity score matching (n=147 pairs).

Table 4

Independent factors of all-cause death by Cox regression analysis of 1019 patients

	Univariate analysis			Multivariate analysis		
Variable	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***
Male	2.301	1.657–3.178	<0.001	NA	NA	NA
Age	2.335	1.709–3.266	<0.001	NA	NA	NA
Preexisting CVD	2.831	1.255–5.310	0.001	NA	NA	NA
Current smoking	2.044	1.739–3.110	<0.001	NA	NA	NA
COPD	3.107	1.925–5.726	0.001	NA	NA	NA
Renal failure	3.502	1.621–6.004	0.001	NA	NA	NA
Critical illness	6.278	2.353–11.820	<0.001	3.042	1.238–5.669	<0.001
Myocardial injury	5.362	2.109–8.803	<0.001	2.561	1.849–4.548	<0.001
WBC $>10\times10^9$/L	2.621	1.159–5.137	<0.001	NA	NA	NA
LYM $<0.8\times10^9$/L	2.046	1.827–5.546	<0.001	NA	NA	NA
Platelet $<100\times10^9$/L	4.534	3.087–6.659	<0.001	NA	NA	NA
CRP >3 mg/L	2.364	1.691–3.304	<0.001	NA	NA	NA
IL-6	1.001	1.001–1.001	<0.001	NA	NA	NA
SpO_2 <95%	8.731	5.893–12.935	<0.001	NA	NA	NA
Arbidol	0.383	0.291–0.505	<0.001	0.268	0.176–0.407	<0.001
Antibiotics	7.549	2.799–20.356	<0.001	NA	NA	NA
Mechanical ventilation	21.659	13.625–64.188	<0.001	13.104	7.221–20.044	<0.001

COPD: Chronic obstructive pulmonary disease; CRP: C reactive protein; CVD: Cardiovascular disease; IL: Interlukin; LYM: Lymphocyte; NA: Not available; SpO_2: Oxygen saturation; WBC: White blood cells.

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.[24] In total, antiviral effect, immunomodulation, as well as preventing virus-induced exacerbations 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,[9] 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.

Acknowledgments

We deeply acknowledge the Cooperative Innovational Center of Nanjing Medical University for data analysis.

Funding

None.

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.
Concept and design: Shaoliang Chen, Hesong Zeng.
Acquisition, analysis, or interpretation of data: Shaoliang Chen, Jing Kan, Cynthia Chen.
Drafting of the manuscript: Shaoliang Chen, Cynthia Chen.
Critical revision of the manuscript for important intellectual content: Shaoliang Chen, Hesong Zeng, Xingwei He, Wanjun Liu, Jing Kan, Liqun He, Jinhe Zhao, Cynthia Chen, Junjie Zhang.
Statistical analysis: Jing Kan, Cynthia Chen.
Administrative, technical, or material support: Xingwei He, Liqun He, Jinhe Zhao, Junjie Zhang.
Supervision: Shaoliang Chen, Hesong Zeng.

Conflicts of Interest

None.

References

[1] Phelan AL, Katz R, Gostin LO. The novel coronavirus originating in Wuhan, China: challenges for global health governance. JAMA 2020;323(8):709–710. doi: 10.1001/jama.2020.1097.
[2] Chan JW, Ng CK, Chan YH, et al. Short term outcome and risk factors for adverse clinical outcomes in adults with severe acute respiratory syndrome (SARS). Thorax 2003;58(8):686–689. doi: 10.1136/thorax.58.8.686.
[3] Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395 (10223):497–506. doi: 10.1016/S0140-6736(20)30183-5.
[4] 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(11):1061–1069. doi: 10.1001/jama.2020.1585.
[5] Lu H. Drug treatment options for the 2019-new coronavirus (2019-nCoV). Biosci Trends 2020;14(1):69–71. doi: 10.5582/bst.2020.01020.
[6] Reina J. [Remdesivir, the antiviral hope against SARS-CoV-2]. Rev Esp Quimioter 2020;33(3):176–179. doi: 10.37201/req/098.2020.
[7] Sun P, Lu X, Xu C, et al. CD-sACE2 inclusion compounds: an effective treatment for coronavirus disease 2019 (COVID-19). J Med Virol 2020;92(10):1721–1723. doi: 10.1002/jmv.25804.
[8] Li G, De Clercq E. Therapeutic options for the 2019 novel coronavirus (2019-nCoV). Nat Rev Drug Discov 2020;19(3):149–150. doi: 10.1038/d41573-020-00016-0.
[9] National Health Commission of the People's Republic of China. Beijing, China. Chinese management guideline for COVID-19 (version 6.0). Available from: http://www.nhc.gov.cn/yzygj/s7653p/202002/8334a8326dd94d329df351d7da8aefc2/files/b218cfeb1bc54639af227f922bf6b817.pdf. Accessed February 19, 2020.
[10] Thygesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction (2018). J Am Coll Cardiol 2018;72(18):2231–2264. doi: 10.1016/j.jacc.2018.08.1038.
[11] Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. Nephron Clin Pract 2012;120(4):c179–c184. doi: 10.1159/000339789.
[12] Ranieri VM, Rubenfeld GD, Thompson BT, et al. Acute respiratory distress syndrome: the Berlin Definition. JAMA 2012;307(23):2526–2533. doi: 10.1001/jama.2012.5669.
[13] Kalil AC, Metersky ML, Klompas M, et al. Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society. Clin Infect Dis 2016;63(5):e61–e111. doi: 10.1093/cid/ciw353.
[14] Hardin CC, Hibbert K. ECMO for severe ARDS. N Engl J Med 2018;378(21):2032–2034. doi: 10.1056/NEJMe1802676.
[15] Ye Z, Zhang Y, Wang Y, et al. Chest CT manifestations of new coronavirus disease 2019 (COVID-19): a pictorial review. Eur Radiol 2020;30(8):4381–4389. doi: 10.1007/s00330-020-06801-0.
[16] Lian J, Jin X, Hao S, et al. Analysis of epidemiological and clinical features in older patients with coronavirus disease 2019 (COVID-19) outside Wuhan. Clin Infect Dis 2020;71(15):740–747. doi: 10.1093/cid/ciaa242.
[17] Gagarinova VM, Ignat'eva GS, et al. The new chemical preparation arbidol: its prophylactic efficacy during influenza epidemics. Zh Mikrobiol Epidemiol Immunobiol 1993;(5):40–43.
[18] Boriskin YS, Leneva IA, Pécheur EI, et al. Arbidol: a broad-spectrum antiviral compound that blocks viral fusion. Curr Med Chem 2008;15 (10):997–1005. doi: 10.2174/092986708784049658.
[19] Leneva IA, Russell RJ, Boriskin YS, et al. Characteristics of arbidol-resistant mutants of influenza virus: implications for the mechanism of anti-influenza action of arbidol. Antiviral Res 2009;81(2):132–140. doi: 10.1016/j.antiviral.2008.10.009.
[20] Pshenichnaya NY, Bulgakova VA, Lvov NI, et al. Clinical efficacy of umifenovir in influenza and ARVI (study ARBITR). Ter Arkh 2019;91 (3):56–63. doi: 10.26442/00403660.2019.03.000127.
[21] Pécheur EI, Lavillette D, Alcaras F, et al. Biochemical mechanism of hepatitis C virus inhibition by the broad-spectrum antiviral arbidol. Biochemistry 2007;46(20):6050–6059. doi: 10.1021/bi700181j.
[22] Fink SL, Vojtech L, Wagoner J, et al. The antiviral drug arbidol inhibits Zika virus. Sci Rep 2018;8(1):8989. doi: 10.1038/s41598-018-27224-4.
[23] Hulseberg CE, Fénéant L, Szymańska-de Wijs KM, et al. Arbidol and other low-molecular-weight drugs that inhibit lassa and ebola viruses. J Virol 2019;93(8):e02185-18. doi: 10.1128/JVI.02185-18.
[24] Proskurnina EV, Izmailov DY, Sozarukova MM, et al. Antioxidant potential of antiviral drug umifenovir. Molecules 2020;25(7):1577. doi: 10.3390/molecules25071577.
[25] Titova ON, Petrova MA, Shklyarevich NA, et al. Efficacy of Arbidol in the prevention of virus-induced exacerbations of bronchial asthma and chronic obstructive pulmonary disease. Ter Arkh 2018;90(8):48–52. doi: 10.26442/terarkh201890848-52.
[26] Deng L, Li C, Zeng Q, et al. Arbidol combined with LPV/r versus LPV/r alone against corona virus disease 2019: a retrospective cohort study. J Infect 2020;81(1):e1–e5. doi: 10.1016/j.jinf.2020.03.002.
[27] Wang Z, Chen X, Lu Y, et al. Clinical characteristics and therapeutic procedure for four cases with 2019 novel coronavirus pneumonia receiving combined Chinese and Western medicine treatment. Biosci Trends 2020;14(1):64–68. doi: 10.5582/bst.2020.01030.
[28] Wang Z, Yang B, Li Q, et al. Clinical features of 69 cases with coronavirus disease 2019 in Wuhan, China. Clin Infect Dis 2020;71 (15):769–777. doi: 10.1093/cid/ciaa272.

How to cite this article: Zeng H, He X, Liu W, Kan J, He L, Zhao J, Chen C, Zhang J, Chen S. Antiviral Abidol is Associated with the Reduction of in-hospital Mortality in COVID-19 Patients. Cardiol Discov 2021;1(1):37–43. doi: 10.1097/CD9.0000000000000014