Effect of low-dose aspirin on mortality and viral duration of the hospitalized adults with COVID-19

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Abstract
To clarify the effect of aspirin on mortality and viral duration in adults infected with respiratory syndrome coronavirus 2 (SARS-CoV-2).
After propensity score-matched (PSM) case-control analyses 24 pairs of patients were enrolled and followed up for 2 months. Both 30-day and 60-day mortality in the aspirin group were significantly lower than that in the non-aspirin group (P = .021 and P = .030, respectively). The viral duration time between the 2 groups was not significantly different (P = .942).

Among adults (with hypertension, cardiovascular diseases) infected with SARS-CoV-2, low-dose aspirin medication (100 mg/day) was associated with lower risk of mortality compared with non-aspirin users.

Abbreviations: AIDS = acquired immune deficiency syndrome, ALT = Alanine aminotransferase, CK = creatine kinase, COVID-19 = Coronavirus Disease 2019, CRP = C-reactive protein, ECMO = extracorporeal membrane oxygenation, IQR = interquartile range, LDH = lactate dehydrogenase, NSAID = non-steroidal anti-inflammatory drug, PSM = propensity score-matched, RT-PCR = reverse transcriptase-polymerase chain reactions, SARS-CoV-2 = respiratory syndrome coronavirus 2.

Keywords: aspirin, COVID-19, infections, prognosis, SARS-CoV-2

1. Introduction
Since December 2019, an outbreak of pneumonia caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused a serious epidemic worldwide.[1][1] Several non-steroidal anti-inflammatory drugs (NSAIDs) have been used in patients with SARS-CoV-2 infection, but many remained controversial effects on the disease.[2] Aspirin (acetylsalicylic acid), a popular medicine, exhibits a variety of effects including alleviating inflammatory response, reducing fever and pain, inhibiting platelet activation and aggregation, and blocking viral propagation of RNA viruses (e.g., influenza virus and hepatic C virus).[3,4] The low-dose aspirin to prevent embolic events has been used among patients hospitalized with Coronavirus Disease 2019 (COVID-19). Therefore, this study was performed for the effect of aspirin on mortality and viral duration of the COVID-19 patients.

2. Methods
2.1. Study populations
This study included patients with COVID-19 admitted to Yichang Central People’s Hospital between January 30 and March 20, 2020. The final date was followed up at May 27, 2020. The exclusion criteria included incomplete medical records, acute lethal organ injury (e.g., acute pulmonary embolism, acute renal failure and liver failure), decompensated chronic organ dysfunction (e.g., heart failure, hepatic cirrhosis, and renal dysfunction), leukemia, pregnancy, end stage of malignancy, sustained by extracorporeal membrane oxygenation (ECMO) and acquired immune deficiency syndrome (AIDS) on admission. Patients used 100 mg/day aspirin to prevent embolic events for at least 5 days were classified in to aspirin group, patients who did not use aspirin were in non-aspirin group.

2.2. Ethical considerations
The study protocols were approved by ethics committee of Yichang central people’s hospital. Patient informed consent was waived by ethics committee. Patients were diagnosed and
received treatment based on the 5th edition of the National Guideline on Prevention and Control of the Novel Coronavirus Pneumonia published by the National Health Commission of China on February 8, 2020.\[5\]

2.3. Specimen collection and testing
The throat swab specimen was collected from each eligible patient after admission. The reverse transcriptase–polymerase chain reactions (RT-PCR) from swabs for SARS-CoV-2 were noted and analyzed.\[7\] Respiratory samples were collected every 1 to 2 days until 2 sequential negative results were obtained. The viral duration defined as the interval from the first day of positive nucleic acid tests to the first day of continuous negative tests.

2.4. Data collection
Following data were collected from patients including demographic information, medical history, history of comorbidities, clinical characteristics, laboratory results, history of medication, and clinical outcomes. Personal information of patient (e.g., name and ID) was separately stored and a study ID was used to preserve patient privacy before data extraction. The accuracy of data was double-checked by 2 independent researchers.

2.5. Statistical analyses
Continuous variables were summarized as medians (interquartile ranges, IQR). For categorical variables, the incidence for each category was calculated. Clinical characteristics were compared between patients who received aspirin and those not, using the Mann–Whitney U test or Chi-Squared test.

We further performed one-to-one matching to minimize the effect of selective bias, based on propensity score analysis between patients with aspirin and those not. The propensity scores were determined by multiple logistic regressions disregarding to the outcomes. PSM cohorts were created by variables which were potential confounders to the propensity for mortality or viral durations of COVID-19 patients, including age, gender, comorbidities (e.g., cerebrovascular disease, coronary disease, hypertension, diabetes, chronic renal disease, and chronic obstructive pulmonary disease), symptoms on admission (e.g., fever, cough, dyspnea, sore throat, and fatigue), main laboratory findings on admission (e.g., incidence of increased creatine kinase (CK), lactate dehydrogenase (LDH), Alanine aminotransferase (ALT), C-reactive protein (CRP), and creatinine; incidence of leukocytopenia, lymphocytopenia, low-hemoglobin, hypoproteinemia, and thrombocytopenia), and incidence of systemic corticosteroids medication. Nagelkerke R

\[\text{Figure 1. The flowchart of adults enrolled in this study.}\]
3. Results

This study cohort included 246 patients with COVID-19 pneumonia who were admitted to the Yichang Central People's Hospital in Hubei, China. After excluding 14 participants following our exclusion criteria, 232 participants were included for subsequent analysis (Fig. 1). Among these participants, 204 were classified as non-aspirin group (median age 54 [IQR 42–65] years; 53.4% men) and 28 were classified as aspirin group (median age 69.5 [IQR 61–77]; 64.3% men) (Table 1). All of the participants received antivirals and 94.0% received Traditional Chinese Medicine. 133 (57.3%) participants received corticosteroid treatment. Compared to the non-aspirin group, the aspirin group had higher prevalence of hypertension, cerebrovascular disease, coronary disease, fatigue, and hypohemoglobinemia at presentation (Table 1). There are no participants with missing data for each variable of interest. The 30d mortality and 60d mortality of the COVID-19 patients in cohort were 4.3% and 5.6%, respectively (Table 1).

Propensity scores were calculated using a multivariate logistic regression model that included all the factors listed in Table 1. We successfully matched 24 patients in the aspirin group to non-aspirin group at a ratio of 1:1, and Nagelkerke R square was 0.432, indicating moderate model discrimination. The baseline characteristics and medications (except for aspirin medication, incidence of coronary disease and hypohemoglobinemia) were well balanced between the patients in the PSM non-aspirin and aspirin group (Table 2).

Kaplan–Meier survival curves (Fig. 2) for the PSM non-aspirin group and aspirin group showed that both 30-day and 60-day mortality in the aspirin group were significantly lower than that in the non-aspirin group (log-rank Chi-Squared = 5.475, *P* = .021)

| Table 1 |

Characteristics of patients hospitalized with COVID-19 pneumonia stratified according to the patients’ aspirin status.

| Characteristic                                      | Patients (N = 232) | Non-Aspirin (N = 204) | Aspirin (N = 28) | P value |
|---------------------------------------------------|--------------------|-----------------------|-----------------|---------|
| Clinical characteristics on admission             |                    |                       |                 |         |
| Age -median (IQR)†                                 | 56 (44–67)         | 54 (42–65)            | 69.5 (61–77)    | < .001  |
| Male gender - no. (%)                             | 117 (50.4)         | 109 (53.4)            | 18 (64.3)       | .279    |
| Comorbidities on admission -no. (%)               |                    |                       |                 |         |
| Chronic obstructive pulmonary disease             | 6 (2.6)            | 5 (2.5)               | 1 (3.6)         | .726    |
| Chronic kidney disease                            | 4 (1.7)            | 4 (2.0)               | 0 (0)           | .465    |
| Diabetes                                          | 28 (12.1)          | 23 (11.3)             | 5 (17.9)        | .316    |
| Hypertension                                      | 60 (25.9)          | 40 (19.6)             | 20 (71.4)       | < .001  |
| Cerebrovascular disease                           | 11 (4.7)           | 5 (2.5)               | 6 (21.4)        | < .001  |
| Coronary disease                                  | 18 (7.8)           | 3 (1.5)               | 15 (53.6)       | < .001  |
| Symptoms on admission -no. (%)                    |                    |                       |                 |         |
| Cough                                             | 116 (50.0)         | 104 (51.0)            | 12 (42.9)       | .420    |
| Shortness of breath                               | 12 (5.2)           | 9 (4.4)               | 3 (10.7)        | .158    |
| Sore throat                                       | 26 (11.2)          | 24 (11.8)             | 2 (7.1)         | .467    |
| Fever                                             | 174 (75.0)         | 154 (75.5)            | 20 (71.4)       | .642    |
| Fatigue                                           | 80 (34.4)          | 74 (36.3)             | 15 (53.6)       | .078    |
| Main laboratory findings on admission             |                    |                       |                 |         |
| Leukocytopenia -no. (%)                           | 51 (22.0)          | 45 (22.1)             | 6 (21.4)        | .940    |
| Lymphocytopenia -no. (%)                          | 150 (64.7)         | 129 (63.2)            | 21 (75.0)       | .222    |
| Hemoglobin (< ULN) - no. (%)                      | 51 (22.0)          | 40 (19.6)             | 11 (39.3)       | .018    |
| Platelet count (<ULN) - no. (%)                   | 53 (22.8)          | 48 (23.5)             | 5 (17.9)        | .503    |
| C-reactive protein (>=ULN) - no. (%)              | 152 (65.5)         | 133 (65.2)            | 19 (67.9)       | .781    |
| Alanine aminotransferase (>=ULN) - no. (%)        | 41 (17.7)          | 35 (17.2)             | 6 (21.4)        | .578    |
| Albumin (<ULN) - no. (%)                          | 150 (64.7)         | 130 (63.7)            | 20 (71.4)       | .424    |
| Creatine kinase (>=ULN) - no. (%)                 | 42 (18.1)          | 33 (16.2)             | 9 (32.1)        | .040    |
| Creatinine (>=ULN) - no. (%)                      | 70 (30.2)          | 57 (27.9)             | 13 (46.4)       | .046    |
| Lactate dehydrogenase (>=ULN) - no. (%)           | 81 (34.9)          | 70 (34.3)             | 11 (39.3)       | .605    |
| Treatment - no. (%)                               |                    |                       |                 |         |
| Traditional Chinese medicine                      | 218 (94.0)         | 192 (94.1)            | 26 (92.8)       | .793    |
| Antivirals                                        | 232 (100.0)        | 204 (100.0)           | 28 (100.0)      | .230    |
| Systemic corticosteroids                          | 133 (57.3)         | 114 (55.9)            | 19 (67.9)       | .230    |
| Outcomes                                          |                    |                       |                 |         |
| Viral duration-median (IQR)- day                  | 25 (19–30)         | 25 (18–30)†           | 27 (20–31)†     | .310    |
| 30d-Mortality - no. (%)                           | 10 (4.3)           | 9 (4.4)               | 1 (3.6)         | .837    |
| 60d-Mortality - no. (%)                           | 13 (5.6)           | 11 (5.4)              | 2 (7.1)         | .706    |

† IQR = interquartile range, ULN = upper limit of normal.

1 194 valid data for non-aspirin group and 27 valid data for aspirin group.
Table 2

Characteristics of patients hospitalized with COVID-19 pneumonia stratified according to the patients’ aspirin status after propensity score matching.

| Characteristic                          | Non-Aspirin (N=180) | Aspirin (N=4) | Unmatched P value | Matched (1:1) P value |
|----------------------------------------|---------------------|---------------|-------------------|-----------------------|
| Clinical characteristics on admission  |                     |               |                   |                       |
| Age -median (IQR)†                     | 52 (40–62)          | 76 (60–84)    | .008              | 74 (65–79.5)          |
| Male gender - no. (%)                  | 91 (50.6)           | 4 (100.0)     | .050              | 18 (70.8)             |
| Comorbidities on admission - no. (%)   |                     |               |                   |                       |
| Chronic obstructive pulmonary disease  | 2 (1.1)             | 1 (25.0)      | <.001             | 3 (12.5)              |
| Chronic kidney disease                 | 2 (1.1)             | 0 (0.0)       | .832              | 2 (8.3)               |
| Diabetes                               | 19 (10.6)           | 1 (25.0)      | .359              | 4 (16.7)              |
| Hypertension                           | 28 (15.6)           | 4 (100.0)     | <.001             | 12 (50.0)             |
| Coronary disease                       | 2 (1.1)             | 4 (100.0)     | <.001             | 1 (4.2)               |
| Symptoms on admission - no. (%)        |                     |               |                   |                       |
| Cough                                  | 89 (49.4)           | 0 (0.0)       | .050              | 15 (62.5)             |
| Dyspnea                                | 5 (27.8)            | 0 (0.0)       | .735              | 4 (16.7)              |
| Sore throat                            | 21 (11.7)           | 1 (25.0)      | .416              | 3 (12.5)              |
| Fever                                  | 139 (77.2)          | 4 (100.0)     | .279              | 15 (62.5)             |
| Fatigue                                | 59 (32.8)           | 1 (25.0)      | .743              | 15 (62.5)             |
| Main laboratory findings on admission  |                     |               |                   |                       |
| Leukocytopenia - no. (%)               | 41 (22.8)           | 0 (0.0)       | .279              | 4 (16.7)              |
| Lymphocytopenia - no. (%)              | 109 (60.6)          | 3 (75.0)      | .558              | 20 (83.3)             |
| Hemoglobin (<ULN) - no. (%)            | 22 (12.2)           | 1 (25.0)      | .445              | 18 (75.0)             |
| Platelet count (<ULN) - no. (%)        | 43 (23.9)           | 0 (0.0)       | .264              | 5 (20.8)              |
| C-reactive protein (>ULN) - no. (%)    | 134 (74.4)          | 2 (50.0)      | .271              | 18 (75.0)             |
| Alanine aminotransferase (>ULN) - no. (%) | 30 (16.7)         | 0 (0.0)       | .372              | 5 (20.8)              |
| Albumin (>ULN) - no. (%)               | 118 (65.6)          | 3 (75.0)      | .694              | 12 (50.0)             |
| Creatine kinase (>ULN) - no. (%)       | 26 (14.4)           | 3 (75.0)      | .001              | 9 (37.5)              |
| Creatinine (>ULN) - no. (%)            | 44 (24.4)           | 3 (75.0)      | .022              | 13 (54.2)             |
| Lactate dehydrogenase (>ULN) - no. (%) | 57 (31.7)           | 1 (25.0)      | .777              | 13 (54.2)             |
| Treatment - no. (%)                    |                     |               |                   |                       |
| Traditional Chinese medicine           | 172 (95.6)          | 4 (100.0)     | .666              | 20 (83.3)             |
| Antivirals                             | 180 (100.0)         | 4 (100.0)     | .24              | 24 (100.0)            |
| Systemic corticosteroids               | 96 (53.3)           | 2 (50.0)      | .895              | 18 (75.0)             |
| Outcomes                               |                     |               |                   |                       |
| viral duration -median (IQR) -day      | 25 (18–30)†         | 24.5 (18–30)† | .981              | 26.5 (20–31)‡         |

1 IQR = interquartile range, ULN = Upper limit of normal.
2 176 valid data for non-aspirin group and 4 valid data for aspirin group.
3 20 valid data for non-aspirin group and 27 valid data for aspirin group.

and log-rank Chi-Squared = 4.782, P = .030, respectively). The viral duration time of the patients in the PSM non-aspirin and aspirin group were 26.5 (IQR 20–31) and 27 (IQR 20–31) respectively, which was not significantly different (P = .942).

4. Discussion

In this study, aspirin medication among patients with COVID-19 was associated with low risk of mortality compared with those who did not. However, the viral duration of SARS-CoV-2 was not significantly different between the 2 groups. Although other confounding factors may also contribute to the effect of aspirin, our data suggest that low-dose of aspirin medication was not associated with increased mortality in COVID-19.

Although COVID-19 is an acute respiratory disease, emerging studies show that mortality are driven by disseminated intravascular coagulopathy. Aspirin is a popular used NSAID which has been widely used to prevent the embolic events. Its role in modulating the immune response to viral infections is complicated. Aspirin has an ability to directly inhibit the prostaglandin synthesis by irreversible inactivation of cyclooxygenase 1 and 2(COX-1/-2), whereas other NSAIDs are competitive inhibitors. Several studies suggest that aspirin may reduce the risk of deadly infections. But latest studies argued that the NSAIDs have powerful effects on the immune system and may have association with the poor prognosis after infection with COVID-19. Therefore, NSAIDs were not recommended for COVID-19 patients with fever by some guidelines. In our study, the Kaplan–Meier survival curves for the PSM groups showed that both the 30-day and 60-day mortality for the aspirin group were significantly lower than that in the non-aspirin group. Therefore, our findings provide evidence supporting the low-dose use of aspirin to prevent embolic events for patients infected with SARS-COV-2 was not associated with increased mortality of COVID-19 patients.

Despite the age and baseline disease of patients, the mortality rate in matched groups might just result from the age and more severe baseline condition of patients. We tried to
minimize the selection bias for aspirin use among different patients with PMS, however, only the known and measured confounders can be adjusted (Table 2).

Many reports suggest that aspirin can inhibit pathogens, especially viruses including adenovirus, herpes simplex virus, H1N1 influenza A, human respiratory syncytial virus, and Coxsackie virus. In our study the viral duration of SARS-Cov-2 has not significantly affected by the treatment of aspirin. A former study shown that the effective concentrations (EC50) of aspirin may too high to expect a potential antiviral effect in vivo. We speculate that low-dose aspirin may not reach the effective concentrations to inhibit SARS-Cov-2, and therefore viral duration is not affected.

This study has several limitations.

1. Although the incidence of aspirin medication to prevent embolic events may reflect the natural history of hospitalized patients with COVID-19, the sample size was small which may reduce the power of the study and increases the margin of error.
2. Some parameters (e.g., D-dimer, PCT, etc.) were not available in all patients which might induce confounding to conclusion.
3. This is a single-center-retrospective study which may have benefits for quality control but its validation in geographical diversity may need further confirmation.

Therefore, large-scale prospective and randomized controlled trials are needed to better understand the effect of aspirin on the survival of COVID-19 patients.

5. Conclusions

Medication with low-dose of aspirin to prevent the embolic events is not associated with increased mortality of COVID-19 patients.

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Author contributions

Q Liu and XL Zhou conceived the study and its design; N Huang and AN Li collected the data; YH Zhou, L Liang, and XY Song managed and analyzed the data; Q Liu and XL Zhou interpreted the results; Q Liu, N Huang, and AN Li written the manuscript. ZQ Yang gave the statistical consultation and revised the manuscript. All authors have read and approved the final manuscript.

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