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# A study on the effect of aspirin on clinical symptoms, laboratory indices, and outcomes in patients with COVID-19

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**ABSTRACT**

**Introduction:** Low-dose aspirin is one of the most widely used secondary prevention agents for cardiovascular disease and stroke. An unstable risk factor for chronic cardiovascular disease is a viral infection. Evidence suggests that the new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) could increase the risk of acute cardiovascular events by inducing systemic inflammatory responses and instability in coronary plaques.

**Objectives:** The present study aimed to examine the impact of aspirin on clinical symptoms, laboratory indices, and clinical outcomes in patients with COVID-19.

**Patients and Methods:** After reviewing the documents of hospitalized patients at the Dr. Shariati hospital in Isfahan, Iran, while case and control groups were selected using a cross-sectional method based on aspirin use and non-use. Following a random selection of the reference population (131 medical records of patients with COVID-19 who had aspirin use and 131 of the group of patients with COVID-19 without aspirin use). Medical records of patients with cardiovascular disease, diabetes, cardiovascular disease with diabetes, and patients without underlying disease were evaluated. After matching the two groups based on age, gender, and medical history, the examination and results were recorded in a questionnaire.

**Results:** The results showed that during treatment, no significant difference between the case and control groups regarding clinical symptoms, laboratory results, the need for bilevel positive airway pressure (BiPAP), and mechanical ventilation ($P=0.0111$ and $P=0.089$, respectively) were observed. Moreover, no significant difference in the outcome, including improvement and death was detected ($P=0.962$). Likewise, no significant difference in hospitalization duration between the aspirin and control groups was seen ($P=0.289$).

**Conclusion:** Our study on a group of COVID-19 patients showed, aspirin is ineffective on clinical symptoms, laboratory indices, and outcomes, however our results further investigation by multi-centric investigations.

*Implication for health policy/practice/research/medical education:*
In a cross-sectional and observational study, the case and control groups were selected based on aspirin use, with non-users divided into two groups (131 medical records of patients with COVID-19 who administered aspirin and 131 of the group of patients with COVID-19 without aspirin administration). Aspirin was found to be ineffective in treating clinical symptoms, laboratory indices, and outcomes in COVID-19 patients.

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## Introduction

Coronavirus disease 2019 (COVID-19) is caused by infection of a new coronavirus, officially known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), first identified in Wuhan, Hubei province, China, in December 2019 (1).

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Current data suggest that a high percentage of severe COVID-19 patients have coronary artery disease (CAD), since CAD may be associated with an elevated risk of COVID-19-related mortality in hospitalized patients (2).

According to a previous study, aspirin consumption is associated with decreased mechanical ventilation, intensive care unit (ICU) admission, in-hospital mortality, and decreased clinical symptoms in COVID-19 patients admitted to the hospital. COVID-19 infection manifests in patients with acute conditions associated with elevated coagulation risks (3). Few studies have been conducted to examine the relationship between aspirin administration and the risk of reduced mechanical ventilation, ICU admission, clinical symptoms, and hospital mortality.

Previous experiments suggest that the adimistration of aspirin is associated with improvements in the conditions of hospitalized COVID-19 patients. Low-dose aspirin is one of the most commonly used agents for secondary prevention of cardiovascular disease, and it has been demonstrated that it effectively reduces the risk of heart attack and stroke (4-6).

Viral infections are an unstable risk factor for chronic cardiovascular disease and a reduction in the heart's intrinsic reserve due to chronic cardiovascular disease and increased metabolic demands resulting from viral infection. Viral infections also induce systemic inflammatory responses and coronary plaque instability. Meanwhile, the new SARS-CoV-2 may increase the risk of acute cardiovascular events, according to the available evidence. Moreover, pneumonia may affect the cardiovascular system either directly or indirectly. In addition, thrombocytopenia causes lung and capillary tissue damage in 5 to 41% of patients with COVID-19 due to decreased bone marrow production and increasing DIC (disseminated intravascular coagulation) (3-5). Aspirin reduces the production of interleukin-6 and macrophage colony-stimulating factors in COVID-19 patients with cardiovascular disease. Moreover, aspirin irreversibly inhibits platelet cyclooxygenase (COX), and its effect can persist for the circulating platelets' lifespan (7,8).

In contrast to individuals without diabetes, COVID-19 infection in diabetics is associated with an increased risk of severe diseases, pneumonia, hospitalization in the ICU, the need for ventilation, and death. However, it is unclear how much of this increased risk could be attributed to high blood glucose because individuals with diabetes (particularly type 2) have other risk factors for severe COVID-19 (such as older age, obesity, and cardiovascular disease) compared to those without diabetes (9).

## Objectives

This study aims to examine the effect of aspirin consumption on the severity of clinical symptoms, laboratory indices, deaths, and recovery in four categories as the following groups; (1) COVID-19 patients with diabetes, (2) COVID-19 patients with cardiovascular disease and diabetes, (3) COVID-19 patients with cardiovascular disease, (4) COVID-19 infected patients without underlying medical conditions, they were divided into aspirin users and non-users.

## Patients and Methods

### *Study design*

This study examined 5000 files of COVID-19 patients hospitalized at the Dr. Shariati hospital in Isfahan between January 1, 2021, and May 10, 2021. The patients were divided into two groups: those administered 80 mg of aspirin (population A) and those without (population B).

Case group selection from population A and control group selection from population B were initially made by non-random selection (at this stage, only documents of COVID-19-infected patients accompanied by patients who had an underlying cardiovascular disease, diabetes, cardiovascular with diabetes, and no underlying diseases were divided, and the population of two groups of A and B were subsequently designated. At this stage, a sample of 170 documents was selected randomly from the case group. Then, after examining the documents, 39 files were deleted due to errors in the clinical or laboratory data, and 131 documents representing the population of cases were added to the study. Following matching (according to age-gender and underlying disease), the control group (131 documents) was included in the study alongside the case group.

This study was observational and cross-sectional; information on both groups was gathered from documents and questionnaires. After selecting the case group and the control group (matching in terms of age, gender, and underlying disease) based on the available data in the files, information was recorded equitably based on the variables table, and their significance was analyzed.

Records for individuals under 40 years old were excluded from the study group, and each document in the study group was divided into two age groups; 40 to 60 years and over 60 (aspirin consumption is typically prescribed for individuals over 40 years). Consequently, by analyzing the characteristics above, we were able to compare the two individual groups (each comprising 131 records).

The indices recorded by nurses and physicians at the files on the first day of admission to the hospital emergency department were noted and compared to examine the effect of aspirin use on the clinical and laboratory indices for study groups (Figure 1).

This study evaluates the effect of aspirin throughout clinical symptoms and laboratory indices in patients with COVID-19. Finally, this research will provide physicians, nurses, and hospital staff, as well as the entire community, with a general understanding of this disease.

The study indices were divided into two categories; matched indices and examined indices.

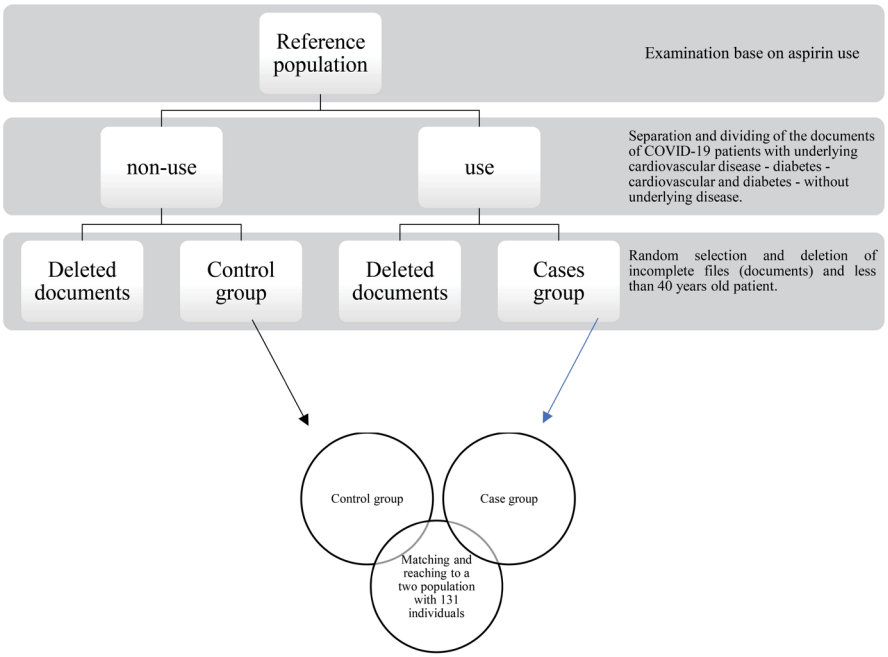


**Figure 1.** Diagram of study design.

*A) Matched indicators:*

1- Age (40-60 years old, >60)

2- Gender

3- Underlying disease (cardiovascular diseases, diabetes, cardiovascular diseases with diabetes, and no underlying disease).

*(B) Examined indicators*

1- Outcome measurement indicators: death, improvement, the number of days hospitalized, the need for a ventilator, the need for bilevel positive airway pressure (BiPAP).

2- Clinical indices; cough, dyspnea, fever, body aches, nausea, and sore throat.

3- Laboratory indicators: creatinine, white blood cell (WBC) count, alanine aminotransferase (ALT), aspartate aminotransferase (AST), D-dimer-lactate dehydrogenase, erythrocyte sedimentation rate, C-reactive protein, $O_2$saturation, $PCO_2$, PH-$HCO_3$.

4- Other indicators: history of smoking, warfarin, and the consumption of remdesivir, interferon, antibiotics, and corticosteroids during hospitalization.

### *Statistical analysis*

The data were organized in frequency tables, and the results were presented as percentages. The chi-square test and the *P* value were utilized to compare percentages. Statistical analysis was performed using SPSS (version 18, Chicago, IL, USA). A $P<0.05$ was considered statistically significant.

## Results

This study examined 131 patients assigned to the aspirin group and 131 patients assigned to the control group. Age and gender were matched between two groups of patients; 22 in the aspirin group and 23 in the control group, aged 40 to 60 years ($P=0.826$). Regarding gender, 77 individuals were present in both groups ($P=0.884$). In the two groups of patients, both cardiovascular disease and diabetes histories were prevalent ($P=0.959$). There was no significant difference in blood oxygen saturation ($O_2$Sat) between the two groups ($P=0.240$). There was no significant difference between the two groups in terms of prescription drugs, including warfarin, remdesivir, corticosteroids, and antibiotics, however interferon prescriptions were higher in the aspirin group ($P=0.005$; Table 1).

The most prevalent symptoms in both groups were dyspnea ($P=0.210$) and cough ($P=0.266$), whereas body aches ($P=0.001$), nausea ($P=0.094$), and sore throat ($P=0.001$) were more prevalent in the control group, and fever ($P=0.172$) was more prevalent in the aspirin group (Figure 2).

The results of laboratory variables between the aspirin and control groups indicate that, in almost all instances, there was no statistically significant difference between the two groups, except for the WBC mean, which was significantly higher in the aspirin group than in the control group ($P=0.009$; Table 2).

The examination of the difference between treatment needs and outcomes of COVID-19 patients in the two groups of aspirin and intervention revealed no statistically significant difference ($P=0.962$) between the two groups regarding the need for BiPAP and ventilator ($P=0.0111$ and $P=0.089$, respectively) during the treatment process

**Table 1.** Frequency distribution of demographic variables, contextual factors, and prescription drugs in COVID-19-infected patients treated with aspirin and control group

| Variables | Control group | | Aspirin | | *P* value |
|---|---|---|---|---|---|
| | Number | Percent | Number | Percent | |
| Age group | | | | | 0.826 |
| 40-60 years | 22 | 16.5 | 23 | 17.6 | |
| Over 60 | 111 | 83.5 | 108 | 82.4 | |
| Gender | | | | | 0.884 |
| Male | 77 | 57.9 | 77 | 58.8 | |
| Female | 56 | 42.1 | 54 | 41.2 | |
| Underlying disease | | | | | 0.959 |
| Cardiovascular | 40 | 30.1 | 40 | 30.5 | |
| Diabetes | 9 | 6.8 | 9 | 6.9 | |
| Cardiovascular and diabetes | 64 | 48.1 | 62 | 47.3 | |
| No underlying disease | 20 | 15.0 | 20 | 15.3 | |
| Smoking | | | | | 0.114 |
| No | 128 | 96.2 | 120 | 91.6 | |
| Yes | 5 | 3.8 | 11 | 8.4 | |
| Warfarin | | | | | 0.717 |
| No | 129 | 97.0 | 128 | 97.7 | |
| Yes | 4 | 3.0 | 3 | 2.3 | |
| Remdesivir | | | | | 0.649 |
| No | 91 | 68.4 | 93 | 71.0 | |
| Yes | 42 | 31.6 | 38 | 29.0 | |
| Corticosteroids | | | | | 0.089 |
| No | 6 | 4.5 | 13 | 9.9 | |
| Yes | 127 | 95.5 | 118 | 90.1 | |
| Antibiotics | | | | | 0.777 |
| No | 52 | 39.1 | 49 | 37.4 | |
| Yes | 81 | 60.9 | 82 | 62.6 | |
| Interferon | | | | | 0.005 |
| No | 104 | 78.2 | 119 | 90.8 | |
| Yes | 29 | 21.8 | 12 | 9.2 | |
| Blood oxygen saturation (So2) | | | | | 0.240 |
| Less than 85 | 46 | 34.6 | 33 | 25.2 | |
| 85-92 | 66 | 49.6 | 76 | 58.0 | |
| Over 92 | 21 | 15.8 | 22 | 16.8 | |

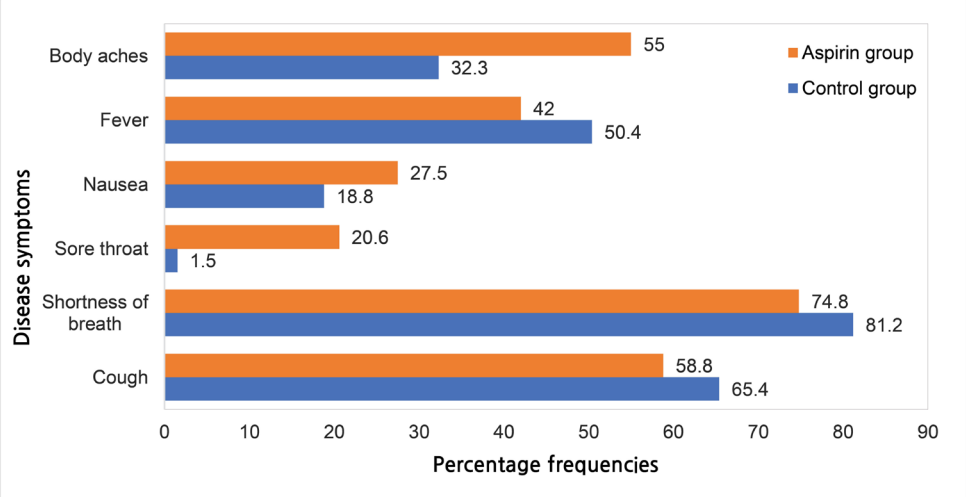


**Figure 2.** Frequency distribution of patients' symptoms in two aspirin and control groups among COVID-19 infected patients.

**Table 2.** Mean values of laboratory variables between aspirin and control groups

| Variables | Control group | Aspirin | *P* value |
|---|---|---|---|
| | Mean ± standard deviation | Mean ± standard deviation | |
| Cr (mg/dL) | 1.12 ± 0.41 | 1.12 ± 0.37 | 0.970 |
| ALT (unit/L) | 45.73 ± 28.30 | 43.57 ± 29.94 | 0.548 |
| AST (unit/L) | 51.69 ± 28.21 | 49.33 ± 33.79 | 0.538 |
| LDH (unit/L) | 672.25 ± 333.08 | 618.14 ± 301.31 | 0.196 |
| WBC ($10^3$/µL) | 7082.78 ± 3456.66 | 8469.89 ± 4992.02 | 0.009 |
| CRP (mg/L) | 56.68 ± 37.38 | 57.38 ± 41.11 | 0.887 |
| ESR (mm/h) | 53.53 ± 27.25 | 51.47 ± 23.63 | 0.599 |
| D-dimer (ng/mL) | 1013.77 ± 704.91 | 1114.24 ± 1180.39 | 0.493 |
| PCO2 (mm Hg) | 38.31 ± 9.28 | 38.32 ± 7.88 | 0.996 |
| HcO3 (mmol/L) | 23.77 ± 4.99 | 23.83 ± 4.24 | 0.917 |
| pH log[H+] | 7.39 ± 0.06 | 7.40 ± 0.08 | 0.209 |

Cr, Creatinine; ALT, Alanine aminotransferase; Aspartate aminotransferase; LDH, Lactate dehydrogenase; WBC, White blood cell count; CRP, C-reactive protein; ESR, Erythrocyte sedimentation rate; PCO2, Partial pressure of carbon dioxide; HcO3, Bicarbonate; pH, Potential of hydrogen.

and outcome occurrence, including improvement and death. There was no significant difference in hospitalization duration between the aspirin and control groups ($P=0.289$; Table 3).

## Discussion

In most cases, coronavirus 2019 (COVID-19) is mild, but fatality has been reported in 6% to 19% of cases. Although pneumonia and acute respiratory distress syndrome (ARDS) are the most common symptoms, thrombotic complications have been reported in 25%-42% of patients and are associated with increased mortality risk. Coagulation tests have revealed hypercoagulopathy, and D-dimer and fibrinogen concentrations are frequently elevated in COVID-19 patients. Moreover, alveolar capillary micro thrombosis, arterial thrombosis, and platelet thrombosis are observed in the heart, lung, and kidney of COVID-19 patients (3).

According to one study, aspirin may have lung protective effects, reducing the need for mechanical ventilation, ICU hospitalization, and in-hospital mortality in COVID-19 patients. According to studies, there has not been a significant increase in major bleeding in aspirin patients. This disparity may be explained by the fact that COVID-19 patients are excessively hypercoagulable. Thrombocytopenia is uncommon in COVID-19 patients, and the risk of bleeding appears low even when heparin is used (4).

A previous study demonstrated that systemic anticoagulants decrease mortality in COVID-19 patients receiving mechanical ventilation. Low-dose aspirin has been used to prevent brain and heart stroke in high-risk patients, and the US Preventive Services Task Force mandated its use for adults at risk of heart attack (6).

The anti-inflammatory properties of Aspirin may contribute to COVID-19 disease's pulmonary protective effects. It has been demonstrated that aspirin reduces the production of interleukin-6, C-reactive protein, and

**Table 3.** Examination of the difference between treatment needs and outcomes of infected COVID-19 patients between two groups of aspirin and intervention

| Variables | Control group | | Aspirin | | *P* value |
|---|---|---|---|---|---|
| | Number | Percent | Number | Percent | |
| The need for BiPAP | | | | | 0.111 |
| No | 122 | 91.7 | 112 | 85.5 | |
| Yes | 11 | 8.3 | 19 | 14.5 | |
| The need for ventilator | | | | | 0.089 |
| No | 127 | 95.5 | 118 | 90.1 | |
| Yes | 6 | 4.5 | 13 | 9.9 | |
| The period of hospitalization | | | | | 0.289 |
| Less than 7 days | 88 | 66.2 | 80 | 61.1 | |
| 7 to 14 days | 33 | 24.8 | 43 | 32.8 | |
| 14 to 21 days | 12 | 9.0 | 8 | 6.1 | |
| Outcomes | | | | | 0.962 |
| Recovery | 116 | 87.2 | 114 | 87.0 | |
| Death | 17 | 12.8 | 17 | 13.0 | |

macrophage colony-stimulating factors in COVID-19-positive cardiovascular disease patients. ARDS has been the subject of multiple studies examining the potential benefits of aspirin. Overall, aspirin may reduce the incidence of ARDS (7).

## Conclusion

Aspirin is ineffective throughout clinical symptoms, laboratory indices, and outcomes in patients with COVID-19.

## Limitations of the study

- 1- It is evident that recorded information in studies is retrospective, and if the study was based on an interview, the most significant bias is the reminder bias. In order to reduce this bias during the study, the examination of this indicator, the history of aspirin use in patients who still consume aspirin (case group) however have no history of consumption (control group) was considered for inclusion in the study (while the reminder bias of cigarette and warfarin use could influence the outcome).
- Selection bias occurs in some studies based on hospital information (using archived files) because the information was not completely and equally recorded in hospital files (documents) and was not recorded for specific research use. Furthermore, the study's eligible population may not represent the reference population.
- The documents were chosen randomly from all files to lessen this type of bias. Since only one hospital was examined in this study, selection bias may have influenced the results.

## Authors' contribution

The principal investigators of the present study were RA and MDM. AM contributed to the conception and design of the study and revised and revaluated the manuscript. RG conducted data analysis. MNA and SMR collected data. In addition, all authors contributed to the final manuscript, read it, approved it, and attested to its accuracy and validity.

## Conflicts of interest

The authors declare that they have no competing interests.

## Ethical issues

The research adhered to the principles of the Helsinki Declaration. Patients' consent was obtained with their knowledge. The permission number of 154/99/30362 was granted by the Ethics Committee in Deputy of Treatment of Social Security Organization. Moreover, the authors have identified ethical concerns (including plagiarism, data fabrication, and double publication).

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