Decreased in-hospital mortality associated with aspirin administration in hospitalized patients due to severe COVID-19

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Abstract
Hypercoagulability and thrombosis caused by coronavirus disease 2019 (COVID-19) are related to the higher mortality rate. Because of limited data on the antiplatelet effect, we aimed to evaluate the impact of aspirin add-on therapy on the outcome of the patients hospitalized due to severe COVID-19. In this cohort study, patients with a confirmed diagnosis of severe COVID-19 admitted to Imam Hossein Medical Center, Tehran, Iran from March 2019 to July 2020 were included. Demographics and related clinical data during their hospitalization were recorded. The mortality rate of the patients was considered as the primary outcome and its association with aspirin use was assessed. Nine hundred and ninety-one patients were included, of that 336 patients (34%) received aspirin during their hospitalization and 655 ones (66%) did not. Comorbidities were more prevalent in the patients who were receiving aspirin. Results from the multivariate COX proportional model demonstrated a significant independent association between aspirin use and reduction in the risk of in-hospital mortality (0.746 [0.560–0.994], \(p = 0.046\)). Aspirin use in hospitalized patients with COVID-19 is associated with a significant decrease in mortality rate. Further prospective randomized controlled trials are needed to assess the efficacy and adverse effects of aspirin administration in this population.

Keywords
aspirin, cohort study, COVID-19, mortality, SARS coronaviruses, thromboembolism

1 | INTRODUCTION

From the beginning of the coronavirus disease 2019 (COVID-19) pandemic, different aspects of the disease pathology have been reported. Studies showed the significant effect of COVID-19 on increasing the risk of hypercoagulability and thrombosis that are associated with increased mortality.\(^1,4\) Although the incidence rate of thrombotic complications of COVID-19 was initially reported 25%–42%, recent studies showed a higher prevalence of up to 85% despite using pharmacological thromboprophylaxis.\(^1,2,5\) The benefit of using the anticoagulant to decrease the risk of these complications and improve the survival of the patients with COVID-19 was confirmed by many studies,\(^3,6,7\) but data about the effect of antiplatelet agents on these complications are limited.\(^2,7\) Aspirin has been commonly recommended for the primary prevention of atherosclerotic cardiovascular diseases in high-risk patients.\(^2,8\) As the thromboinflammatory syndrome is one of the suggested pathophysiological hypotheses in COVID-19,\(^5,7\) the anti-inflammatory effect of aspirin...
by the inhibition of cyclooxygenase-1 should also be considered as the potential benefit in the prevention of thrombotic complications of COVID-19 in addition to its antiplatelet effect.\textsuperscript{2,5} In this study, we aimed to evaluate the impact of aspirin add-on therapy on the outcome of the patients hospitalized due to severe COVID-19.

2 | MATERIALS AND METHODS

2.1 | Setting and study population

This retrospective cohort study was conducted at Imam Hossein Medical Center, a tertiary teaching hospital, affiliated with Shahid Beheshti University of Medical Sciences in Tehran, Iran. Patients with confirmed severe to critical COVID-19, based on reverse transcriptase-polymerase chain reaction (rt-PCR), who admitted to the hospital from March 2019 to July 2020 were evaluated.\textsuperscript{9} The study was performed following the declaration of Helsinki and the board of ethics committee approval. Age younger than 18 years old and diagnosis of COVID-19 based on clinical criteria without positive rt-PCR results were considered as exclusion criteria. Included patients in the study were divided into two groups, patients who received aspirin at the dose of 80 mg per day from the first day of admission during their hospitalization period, and subjects who did not.

2.2 | Study data

Baseline characteristics of enrolled patients including age, sex, body mass index (BMI), past medical and habitual history, and other related clinical data were recorded. Laboratory data regarding complete blood cell count, inflammatory markers such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and ferritin were extracted from the records. Besides agents used for the treatment of COVID-19, administration of beta-blockers, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs) during hospitalization were also recorded.

All patients in both groups received the standard of care in the intensive care unit including oxygen supplementation and ventilation support, rehydration and electrolyte correction, vasoactive agents and antibiotic administration, and renal replacement support as needed. All support was provided by the attending intensive care unit specialists for all patients. Also, they received nutrition support provided by the center nutritionist to optimize their feed and nutrition plan based on their clinical status.

2.3 | Outcome

The mortality rate of patients was assessed as the primary outcome. The need for mechanical ventilation and duration of hospitalization were also considered as secondary outcomes.

2.4 | Statistical analysis

All patients were stratified based on their recorded data on aspirin use during their hospitalization. Quantitative data were analyzed for nonparametric distribution by the Kolmogorov–Smirnov test. Variables with parametric distribution were reported by means ± standard deviation and nonparametric distributed variables by median (interquartile range [IQR]). Data description for qualitative variables conducted using frequency (percentage). Independent \( t \)-test or Mann–Whitney test considered for bivariable analysis of parametric and nonparametric continuous variables, respectively. \( \chi^2 \) test considered for analysis of categorical variables. The \( p \)-value of less than 0.05 was considered significant.

COX proportional hazard regression model was performed for the assessment of survival. The crude analysis of the association of variables and survival for the selection of predictors performed by univariable analysis. The selection of the best predictors was based on a \( p \)-value of less than 0.2 in univariable analysis. A multivariable stepwise COX regression model consisting of the selected variables was performed to assess the effect of aspirin add-on therapy on in-hospital mortality. Confounder factors selected based on previously published data on epidemiologic and clinical factors associated with death from COVID-19.\textsuperscript{10} Adjustment of the model for two medications classes including ACEIs/ARB and beta-blockers and medications used to treat COVID-19, that is, antiviral agents and corticosteroids were considered.\textsuperscript{11,12} Scaled Schoenfeld residual test with the significance of \( p \)-value of less than 0.05 is considered to assess the proportional hazard assumption in COX analysis. The proportional hazard with the 95% confidence interval was reported. A \( p \)-value of less than 0.05 was considered significant.

3 | RESULTS

In a duration of 5 months, 991 patients were included in the study, of that 544 patients (54.89%) were males and 447 ones (45.10%) were females. The mean age of patients was 61.640 ± 17.003 years. Baseline demographics and clinical characteristics of the patients are demonstrated in Table 1. Three hundred and thirty-six patients (34%) received aspirin during their hospitalization whereas 655 (66%) did not. Of those who received aspirin, 202 patients (60%) were taking the medication before hospital admission, and aspirin was initiated for the rest of them on the first day of hospital admission. Patients received aspirin during their hospitalization period for the median duration of 7 days. Regarding demographics, patients who received aspirin were older (\( p < 0.001 \)) but no significant differences were observed in gender distribution and obesity between the two groups. We also did not detect any significant differences in initial vital signs between the two groups except for systolic blood pressure which was significantly higher in the group receiving aspirin (\( p = 0.011 \)). Hypertension, diabetes, chronic kidney disease, and coronary artery disease were more prevalent in patients who received aspirin (\( p < 0.001 \)), but there was no significant difference.
| Characteristics               | Total (n = 991) | Received aspirin (n = 336) | Not-received aspirin (n = 655) | p value |
|------------------------------|----------------|----------------------------|-------------------------------|---------|
| Age (years)                  | 61.64 ± 17.003 | 65.75 ± 14.33              | 58.50 ± 17.41                 | <0.001  |
| Sex                          |                |                            |                               |         |
| Male (%)                     | 544 (54.89)    | 189 (56)                   | 355 (54)                      | 0.539   |
| Female (%)                   | 447 (45.11)    | 147 (44)                   | 300 (46)                      |         |
| Body mass index (kg/m²)      | 27.051 ± 4.854 | 27.13 ± 5.13               | 27.01 ± 4.71                  | 0.717   |
| Vital signs                  |                |                            |                               |         |
| Systolic blood pressure (mmHg) | 117.59 ± 20.71 | 120.04 ± 19.04             | 116.3 ± 21.43                 | 0.011   |
| Diastolic blood pressure (mmHg) | 74.69 ± 27.19  | 73.28 ± 10.46              | 77.38 ± 43.96                 | 0.112   |
| Pulse rate (beats/min)       | 89.55 ± 15.71  | 89.25 ± 17.01              | 89.7 ± 14.98                  | 0.685   |
| Respiratory rate (breath/min) | 20.64 ± 7.92   | 20.3 ± 6/17                | 20.82 ± 8.7                   | 0.355   |
| O₂ saturation (%)            | 88.29 ± 7.82   | 88.48 ± 6.84               | 88.19 ± 8.3                   | 0.598   |
| Comorbidities                |                |                            |                               |         |
| Hypertension (%)             | 407 (41.07)    | 210 (62.5)                 | 197 (30)                      | <0.001  |
| Diabetes (%)                 | 303 (30.58)    | 160 (47.61)                | 143 (21.83)                   | <0.001  |
| Coronary artery disease (%)  | 194 (19.58)    | 137 (40.77)                | 57 (8.7)                      | <0.001  |
| Chronic kidney disease (%)   | 102 (10.29)    | 40 (11.9)                  | 23 (3.51)                     | <0.001  |
| Malignancy (%)               | 42 (4.24)      | 9 (2.67)                   | 33 (5.03)                     | 0.081   |
| COPD/Asthma (%)              | 87 (8.78)      | 34 (10.11)                 | 39 (5.95)                     | 0.114   |
| Baseline laboratory data     |                |                            |                               |         |
| WBC (cell/µl)                | 6.90 (4.63)    | 8 (3.62)                   | 7.95 (6.30)                   | 0.572   |
| Lymphocyte (cell/µl)         | 821.75 (1588.10) | 886.90 (1578.55)          | 780.00 (1587.20)              | 0.054   |
| Hemoglobin (g/dl)            | 12.41 ± 2.08   | 12.23 ± 2.21               | 12.49 ± 2.00                  | 0.068   |
| Platelet (×10³ cells/µl)     | 199.35 ± 92.22 | 194.44 ± 88.66            | 201.91 ± 93.99               | 0.231   |
| INR                          | 1.20 ± 0.48    | 1.24 ± 0.55                | 1.17 ± 0.43                   | 0.091   |
| PT                           | 13.09 ± 5.09   | 13.47 ± 5.62               | 12.85 ± 4.72                  | 0.116   |
| PTT                          | 28.25 ± 12.79  | 28.67 ± 14.8               | 27.99 ± 11.45                 | 0.475   |
| Lactate dehydrogenase        | 645.00 (403.00) | 653.00 (421.25)           | 647.00 (446.00)               | 0.253   |
| Ferritin                     | 621.30 (964.00) | 609.65 (1169.33)         | 637.05 (737.13)              | 0.937   |
| C-reactive protein           | 54.00 (53.10)  | 50.50 (57.30)              | 59.60 (44.53)                 | 0.065   |
| Erythrocyte sedimentation rate| 52.74 ± 28.41  | 48.88 ± 27.25             | 62.98 ± 25.59                 | 0.043   |
| Creatine phosphokinase       | 130.00 (211.00) | 124.00 (148.75)           | 110.50 (269.75)              | 0.533   |
| Serum creatinine             | 1.40 (1.20)    | 1.70 (1.00)                | 1.20 (1.05)                   | <0.001  |
| Serum urea                   | 50.00 (45.00)  | 66.30 (58.28)              | 41.50 (35.30)                 | <0.001  |
| Procalcitonin                | 0.73 (1.85)    | 0.87 (2.46)                | 0.77 (1.55)                   | 0.616   |
between the two arms of the study concerning malignancy ($p = 0.081$) and chronic pulmonary diseases ($p = 0.114$). The three most frequently reported signs and symptoms were dyspnea (63.1%), cough (53.0%), and fever (49.8%). Fever was reported in 156 (46.4%) of the patients who received aspirin and in 338 (51.6%) of them who did not ($p = 0.123$). Furthermore, fever was not significantly less prevalent in the patients who were receiving aspirin before hospital admission ($p = 0.369$). Fever was reported in 95 (47.1%) of patients who were receiving aspirin before hospitalization compared with 107 (53.0%) of patients who did not receive aspirin. Baseline laboratory data did not show any significant difference between the two groups except in ESR, serum urea, and creatinine levels (Table 1).

Patients received hydroxychloroquine, lopinavir/ritonavir, corticosteroids, interferon beta 1a, remdesivir, and favipiravir for treatment of COVID-19. No significant differences were observed in the distribution of used medication between the two groups of the study.

In the comparison of the outcomes between patients who received aspirin and those who did not, the need for mechanical ventilation was in 54 (16.07%) and 90 (13.74%) patients, respectively ($p = 0.324$). The length of hospital stay was significantly longer in patients who received aspirin ($p < 0.001$) and the mortality occurred in 109 (32.4%) and 147 (22.44%) patients, respectively ($p = 0.001$).

Based on univariate Cox proportional regression for analysis of related variable to in-hospital mortality, aspirin use ($0.753 \ [0.573–0.991]$), hypertension ($0.814 \ [0.634–1.044]$), and hydroxychloroquine ($0.648 \ [0.248–1.674]$) were collected to be assessed by the multivariate Cox regression model. Results from the stepwise multivariate Cox proportional model demonstrated that aspirin ($0.753 \ [0.573–0.991]$) and hydroxychloroquine ($0.814 \ [0.634–1.044]$) were associated with decreased risk of in-hospital mortality. In contrast to aspirin, older age ($1.035 \ [1.026–1.044]$, $p < 0.001$) was associated with the increased risk of in-hospital mortality. The association of different factors with mortality in the total population is represented in Table 2. In the assessment of the need for mechanical ventilation in the Cox regression model as the dependent variable, the Schoenfeld residual test for the proportionality evaluation of the model showed that the model does not fit the data ($p = 0.002$).

### Discussion

In this cohort study, based on results from the bivariable analysis, the mortality and hospital length of stay were higher in the group of patients who received aspirin. By considering the higher prevalence of underlying conditions and older age in the aspirin group, it could be expected that these patients may experience a more severe course of the disease and a higher rate of mortality. By adjustment of the effect of underlying conditions and demographics, which could be related to the higher rate of mortality and severity of the disease course, the analysis revealed that aspirin has a protective effect on mortality.

Vascular and thrombotic events are relatively common in severe COVID-19. Some studies reported the association between severe COVID-19 and increased risk of endothelial damage, coagulation disorders, thromboembolic events, and severe pulmonary parenchymal

### Table 2

| Characteristics | Total ($n = 991$) | Received aspirin ($n = 336$) | Not-received aspirin ($n = 655$) | $p$ value |
|-----------------|------------------|-----------------------------|-------------------------------|----------|
| d-dimer         | 799.20 (2434.00) | 1171.00 (2200.25)           | 715.800 (2529.00)             | 0.648    |
| Aspartate aminotransferase | 26.00 (27.00) | 36.20 (22.50) | 33.00 (34.75) | 0.107 |
| Alanine aminotransferase | 37.00 (29.50) | 21.60 (29.25) | 26.00 (24.35) | 0.203 |

| Medication used to treat COVID-19 | Total ($n = 991$) | Received aspirin ($n = 336$) | Not-received aspirin ($n = 655$) | $p$ value |
|----------------------------------|------------------|-----------------------------|-------------------------------|----------|
| Hydroxychloroquine               | 553 (55.80)      | 174 (51.78)                 | 379 (57.86)                  | 0.068    |
| Sofosbuvir                       | 24 (2.42)        | 19 (5.65)                   | 5 (0.76)                     | 0.171    |
| Lopinavir/ritonavir              | 557 (56.21)      | 180 (53.57)                 | 377 (57.55)                  | 0.231    |
| Corticosteroid                   | 287 (28.96)      | 101 (30.05)                 | 186 (28.39)                  | 0.585    |
| Interferon Beta 1a               | 372 (37.54)      | 133 (39.58)                 | 239 (36.48)                  | 0.341    |
| Remdesivir                       | 46 (4.64)        | 18 (5.35)                   | 28 (4.27)                    | 0.443    |
| Favipiravir                      | 40 (4.04)        | 18 (5.35)                   | 22 (3.35)                    | 0.130    |

Abbreviations: COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; INR, international normalized ratio; PT, prothrombin time; PTT, Partial thromboplastin time; WBC, white blood cells.
damage due to the conformation of micro thrombosis, and the autopsy showed megakaryocytes platelet-rich thrombi in the heart, lung, and kidneys of these patients. Also, these patients are prone to dehydration and accurate examination should be performed to diagnose the possible dehydration as a possible cause of hypercoagulopathy. Therefore, inhibition of platelet aggregation by aspirin could be helpful.

Different mechanisms for the protective role of aspirin in COVID-19 could be proposed but further studies are needed to explore this effect.

The clinical benefits of aspirin use in the COVID-19 patients have been reported in few previous studies. In a retrospective cohort study of adult patients with COVID-19, the outcome of 98 patients who received aspirin was compared with those who did not. Aspirin use was defined as administration within 24 h of hospital admission or in the 7 days before it. The median treatment duration was 6 days. Aspirin use was associated with a significant decrease in the mortality rate (HR = 0.53). Also, these patients received less mechanical ventilation (35.7% vs. 48.4%) and had a lower ICU admission rate (38.8% vs. 51%). These results corroborate the findings of ours about mortality (HR = 0.746), but we could not evaluate the effect of aspirin on mechanical ventilation and the rate of ICU admission. In another retrospective cohort study on 183 patients with coronary artery disease who were hospitalized due to COVID-19 disease, 52 patients used low-dose aspirin. There was no significant difference in mortality between those who take aspirin and those who did not (21.2% vs. 22.1%, respectively, p = 0.885). Aspirin use also could not significantly decrease the mortality rate in critically ill patients (44% vs. 45.9%, respectively, p = 0.872). Although it should be noted that the nonsignificant (p = 0.893) association of low-dose aspirin usage and mortality reported by the authors was according to a multivariate logistic regression model that was not adjusted for all confounders.

To the best of our knowledge, our study is the largest study for the evaluation of aspirin effect in outcomes of the patients with severe to critical COVID-19, based on a multivariable model. We revealed that aspirin use was associated with a decrease in mortality.

### TABLE 2

| Variable                  | Crude HR*, 95% CI | p value | Adjusted HR, 95% CI | p value |
|---------------------------|-------------------|---------|---------------------|---------|
| In hospital mortality     |                   |         |                     |         |
| Age                       | 1.033 [1.025-1.042] | <0.001  | 1.035 [1.026-1.044] | <0.001  |
| Sex                       | 1.197 [0.930-1.540] | 0.162   |                     |         |
| BMI > 30                  | 0.999 [0.742-1.344] | 0.996   |                     |         |
| Smoking                   | 0.931 [0.666-1.302] | 0.679   |                     |         |
| HTN                       | 1.534 [1.198-1.964] | 0.001   |                     |         |
| DM                        | 0.981 [0.754-1.277] | 0.890   |                     |         |
| CKD                       | 0.859 [0.702-1.052] | 0.143   |                     |         |
| Cancer                    | 1.370 [0.783-2.395] | 0.269   |                     |         |
| Respiratory disorder      | 1.194 [0.962-1.482] | 0.107   |                     |         |
| Immunosuppressive disorder| 1.204 [0.674-2.152] | 0.530   |                     |         |
| CAD                       | 1.330 [1.003-1.764] | 0.047   |                     |         |
| ACEI or ARB               | 1.006 [0.808-1.407] | 0.647   |                     |         |
| Beta blocker              | 1.373 [1.051-1.793] | 0.020   | 1.273 [0.953-1.701] | 0.102   |
| Remdesivir                | 0.814 [0.455-1.455] | 0.489   |                     |         |
| Favipiravir               | 0.739 [0.429-1.272] | 0.276   |                     |         |
| Lopinavir/ritonavir       | 1.219 [0.944-1.574] | 0.128   | 1.313 [1.015-1.698] | 0.038   |
| Hydroxychloroquine        | 0.814 [0.563-1.044] | 0.106   | 0.805 [0.625-1.032] | 0.087   |
| Corticosteroid            | 1.204 [0.929-1.560] | 0.159   |                     |         |
| Interferon                | 1.149 [0.895-1.475] | 0.273   |                     |         |
| Heparin/Enoxaparin        | 0.832 [0.607-1.139] | 0.251   |                     |         |
| Aspirin                   | 1.021 [0.791-1.316] | 0.873   | 0.753 [0.573-0.991] | 0.043   |

Note: The model was fitted based on the Schoenfeld residual test for the evaluation of proportional hazard assumption with p = 0.267.

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CAD, coronary artery disease; CKD, chronic kidney disease; DM, diabetes mellitus; HTN, hypertension.

*Hazard ratio.
The main limitations of our study were the retrospective pattern of the study and lack of data about the probable adverse effect of aspirin, such as bleeding components.

In conclusion, based on the result of our study, in patients who received aspirin, a relevant underlying condition such as hypertension, diabetes, and coronary artery disease was more prevalent. These patients had a more severe course of the disease and a longer duration of hospitalization. By adjustment of the effect of underlying conditions and confounding factors, aspirin use in severe hospitalized COVID-19 patients is independently associated with a 25% decrease in mortality rate. So, by considering all the probable described mechanisms and the results of other studies in this regard, we recommend using aspirin during the hospital stay for all patients with the diagnosis of severe COVID-19.

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CONFLICT OF INTERESTS
The authors declare that there are no conflicts of interest.

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REFERENCES
1. Sivaloganathan H, Ladikou EE, Chevassut T. COVID-19 mortality in patients on anticoagulants and antiplatelet agents. Br J Haematol. 2020;190(4):e192-e195. https://doi.org/10.1111/bjh.16968
2. Chow JH, Khanna AK, Kethireddy S, et al. Aspirin use is associated with decreased mechanical ventilation, ICU admission, and hospital mortality in hospitalized patients with COVID-19 [published online ahead of print]. Anesth Analg. 2020https://doi.org/10.1213/ANE.00000000000005292
3. Carfora V, Spinello G, Ricciolino R, et al. Anticoagulant treatment in COVID-19: a narrative review. J Thromb Thrombolysis. 2021;51:642-648. https://doi.org/10.1007/s11239-020-02242-0
4. Abou-Ismail MY, Diamond A, Kapoor S, Arafah Y, Nayak L. The hypercoagulable state in COVID-19: incidence, pathophysiology, and management. Thromb Res. 2020;194:101-115. https://doi.org/10.1016/j.thromres.2020.06.029
5. Porfidia A, Valeriani E, Pola R, Porreca E, Rutjes AW, Di Nisio M. Venous thromboembolism in patients with COVID-19: systematic review and meta-analysis. Thromb Res. 2020;196:67-74. https://doi.org/10.1016/j.thromres.2020.08.020
6. Mulcahy CF, Ghulam-Smith M, Mamidi IS, et al. Oropharyngeal hemorrhage in patients with COVID-19: a multi-institutional case series. Am J Otolaryngol. 2020;41(6):102691. https://doi.org/10.1016/j.amjoto.2020.102691
7. Godino C, Scotti A, Maugeri N, et al. Antithrombotic therapy in patients with COVID-19: Rationale and evidence. Int J Cardiol. 2020;324:261-266. https://doi.org/10.1016/j.ijcard.2020.09.064
8. Cicci JD, Iyer P, Clarke MM, Mazzeila AJ. Aspirin for the primary prevention of cardiovascular disease: a review of the literature and considerations for clinical practice. Cardiol Rev. 2020;28(2):98-106. https://doi.org/10.1097/CRD.0000000000002979
9. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72314 cases from the Chinese Center for Disease Control and Prevention. JAMA. 2020;323(13):1239-1242. https://doi.org/10.1001/jama.2020.2648
10. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395(10229):1054-1062. https://doi.org/10.1016/S0140-6736(20)30566-3
11. Vasanthakumar N. Beta-adrenergic blockers as a potential treatment for COVID-19 patients. BioEssays. 2020;42(11):2000094. https://doi.org/10.1002/bies.20200094
12. Zhang P, Zhu L, Cai J, et al. Association of inpatient use of angiotensin converting enzyme inhibitors and angiotensin II receptor blockers with mortality among patients with hypertension hospitalized with COVID-19. Circ Res. 2020;126(12):1671-1681. https://doi.org/10.1161/CIRCRESAHA.120.317134
13. Levi M, Thachil J, Iba T, JHUTLH L. Coagulation abnormalities and thrombosis in patients with COVID-19. Lancet Hematol. 2020;7(6):e438. https://doi.org/10.1016/S2352-3026(20)30145-9
14. McFadyen JD, Stevens H, Peter K. The emerging threat of (Micro) thrombosis in COVID-19 and its therapeutic implications. Circ Res. 2020;127(4):571-587. https://doi.org/10.1161/CIRCRESAHA.120.317447
15. Rapkiewicz AV, Mai X, Carson SE, et al. Megakaryocytes and platelet-thrombi characterize multi-organ thrombosis at autopsy in COVID-19: a case series. EClinicalMedicine. 2020;24:100434. https://doi.org/10.1016/j.eclinm.2020.100434
16. Barrett CD, Moore HB, Yaffe MB, Moore EE. ISTH interim guidance on recognition and management of coagulopathy in COVID-19: a comment. J Thromb Haemost. 2020;18(8):2060-2063. https://doi.org/10.1111/jth.14860
17. Yuan S, Chen P, Li H, Chen C, Wang F, Wang DW. Mortality and pre-hospitalization use of low-dose aspirin in COVID-19 patients with coronary artery disease. J Cell Mol Med. 2020;24(2):1263-1273. https://doi.org/10.1111/jcmm.16198

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