Association between previous anticoagulant use and mortality among hospitalized patients with COVID-19

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Abstract

Although COVID-19 disease primarily affects the respiratory system, it has been seen in many studies that it causes thromboembolic (TE) events in many tissues and organs. So that, to prevent TE can reduce mortality and morbidity. In this context, this study aimed to investigate the relationship between the previous use of warfarin or other new direct oral anticoagulants (OAC) and mortality in patients hospitalized with a diagnosis of COVID-19 before hospitalization. A total of 5575 patients who were diagnosed with COVID-19 were hospitalized and started treatment between March 21 and November 30, 2020 were included in the study. The primary outcome was in-hospital all-cause mortality. A retrospective cohort study design was planned. Patients were followed up until death or censoring on November 30, 2020. The candidate predictors for primary outcome should be clinically and biologically plausible, and their relationships with all-cause death should be demonstrated in previous studies. We considered all candidate predictors included in the model in accordance with these principles. The main candidate predictor was previous OAC use. The primary analysis method was to compare the time to deaths of patients using and not using previous OAC by a multivariable Cox proportional hazard model (CPHM). In the CPHM, previous OAC use was found to be associated with a significantly lower mortality risk (adjusted hazard ratio 0.62, 95% CI 0.42–0.92, p = 0.030). In hospitalized COVID-19 patients, in patients who previously used anticoagulant was associated with lower risk of in-hospital death than in those who did not.

Keywords COVID-19 · Oral anticoagulant · Mortality · Thromboembolism

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Highlights

- COVID-19 primarily affects the respiratory system, it causes thrombo-embolic events in many tissues and organs. Coagulopathy occurs in many patients with Covid-19.
- We found that in hospitalized COVID-19 patients, in patients who previously used anticoagulants was associated with lower risk of in-hospital death than in those who did not.

Introduction

The COVID-19 disease caused by the SARS-CoV-2 virus was first seen in Wuhan, China, on December 1, 2019 and was recognized as a pandemic by the World Health Organization (WHO) on March 11, 2020 [1]. It immediately drew attention from all over the world with its rapid clinical progression and high mortality, especially in patients with advanced age and chronic diseases. Although COVID-19 primarily affects the respiratory system, many studies have shown that it causes thromboembolic (TE) events in many tissues and organs [2, 3].

The mechanisms considered to be primarily responsible for the development of TE events are hypercoagulopathy and endothelial damage due to hypoxia and excessive inflammation. COVID-19 infection causes the excessive release of cytokines as a result of increased viral load and creates a sepsis-like clinical presentation [4, 5]. In addition, over-activation in the coagulation cascade by the inflammatory mediators released induces thrombus development. The increase in sympathetic activity and neurohormonal irregularities occurring in the clinical course also causes hypercoagulability [6].

Anticoagulants are currently used in the prophylaxis and treatment of thromboembolism due to various diseases, especially atrial fibrillation (AF) [7]. Although oral forms, such as warfarin and new-generation anticoagulants, are widely used, parenteral forms are also used in daily practice.

As coagulopathy caused by COVID-19 is difficult to control, it is important to better understand what treatments have been studied so far and which ones show better results for hospitalized patients. In this context, this study aimed to investigate the relationship between the previous use of warfarin or other new direct oral anticoagulants (DOAC) and mortality in patients hospitalized with a diagnosis of COVID-19 before hospitalization.

Methods

A total of 5,575 patients who were diagnosed with COVID-19 by polymerase chain reaction (PCR) and/or computed tomography (CT), were hospitalized, and started treatment between March 21 and November 30, 2020 were included in the study. This work was performed in accordance with the Helsinki Declaration and with the approval of the local ethics committee. Patient complaints, previous medical history, history of drug use, clinical and demographic characteristics, and hematological and biochemical parameters were recorded. Patients whose PCR and CT were not compatible with COVID-19, who were found to have a different clinical diagnosis explaining their current clinical status, and who were recently hospitalized and received parenteral anticoagulation were excluded from the study.

Parenteral anticoagulation treatments were given at therapeutic doses to patients who had previously used DOAC. Parenteral anticoagulation was initiated at the time of the next dose in DOAC users and when INR < 2 for warfarin users. The parenteral anticoagulation treatment dose of patients who do not use OAC was arranged according to the Ministry of Health guidelines by estimated glomerular filtration rate (eGFR), weight, and clinical status of the disease.

Definitions

Hypertension (HT) was defined as a systolic blood pressure > 140 mmHg and/or a diastolic blood pressure > 90 mmHg or the use of an antihypertensive drug [8]. Diabetes mellitus (DM) was defined according to the current American Diabetes Association guidelines [9]. A history of coronary artery disease (CAD) was defined as patients who had invasive or non-invasive imaging studies showing evidence of coronary artery disease. Renal failure was defined as creatinine clearance below 60 ml/min. The Cockcroft–Gault equation was used to calculate the eGFR.

PCR test A combined swab sample was taken in accordance with the specified procedures in all patients admitted to the emergency room or infection outpatient clinics [10].

CT: In the COVID-19 guide published by the Ministry of Health, the findings are classified as typical, indeterminate, atypical, and negative in the table of CT findings and reporting recommendations [11].

The patients were diagnosed with COVID-19 based on their current complaints, contact histories, physical examination findings, blood parameters, imaging findings, and PCR test results. In light of the updated scientific data, the treatments of the patients were also updated, and their treatments were planned and started in accordance with the algorithms and guidelines of the Ministry of Health [12]. Drug doses
and durations were arranged by relevant clinicians according to the clinical characteristics and comorbid conditions of the patients [13, 14].

Analysis of blood samples

Blood samples were taken from the antecubital vein by creating a slight venous stasis in the upper arm. The samples were placed in tubes with potassium EDTA for complete blood count. Hemoglobin, hematocrit, platelet, and white blood cell counts were determined by the electrical impedance method with an automatic blood counting device (BeckmanCoulter LH 780). The biochemical parameters were measured by standard laboratory methods.

Statistics

For all statistical analyses, we used R-software version 3.5.1 (R statistical software, Institute for Statistics and Mathematics, Vienna, Austria). Numerical variables were presented as median and interquartile ranges. Categorical data were shown as percentages and n. The primary outcome was inhospital all-cause mortality. A retrospective cohort study design was planned. Patients were followed up until death or censoring on November 30, 2020.

The candidate predictors (main candidate predictor and adjustment variables) for primary outcome should be clinically and biologically plausible, and their relationships with all-cause death should be demonstrated in previous studies. We considered all candidate predictors included in the model in accordance with these principles. The main candidate predictor was previous OAC use. The primary analysis method was to compare the time to deaths of patients using and not using previous OAC by a multivariable Cox proportional hazard model. In addition to previous OAC use, age, gender, HT, DM, heart failure (HF), CAD, eGFR, albumin, CRP, D-dimer, hemoglobin, platelet count, LDH, and oxygen saturation variables were also included in the model. We retained all candidate predictors in the model and did not remove any of these predictors based on statistical significance. The associations between candidate predictors and all-cause death were quantified by the adjusted hazard ratio with a 95% confidence interval. Two more models were created for sensitivity analysis: (i) propensity score (PS) adjusted multivariable Cox proportional hazard and (ii) mixed Cox proportional hazard model after PS matching. To obtain the PS, we fit the multivariable logistic regression analysis with the previous OAC as the outcome conditional on the following covariates: age, gender, HT, DM, HF, CAD, pulmonary thromboembolism eGFR, albumin, CRP, D-dimer, hemoglobin, platelet count, LDH, oxygen saturation, troponin, procalcitonin, ferritin, and white blood cell. The nearestneighbor 2:1 matching algorithm was used with calipers of 0.2 SDs of the logit of the PS. When creating both the primary analysis and the PS score, numerical variables were included in the models with a restricted cubic spline (4 knots) transformation. Due to the non-collapsibility of the hazard ratio, to obtain a more precise hazard ratio, the PS-adjusted multivariable Cox proportional hazard model included age, gender, and PS with previous OAC use, while the mixed Cox proportional hazard model after PS matching model included age and gender with previous OAC use.

Results

A total of 5575 patients were enrolled in the study. The median age was 64 (IQR 51–74), and 2801 patients were male (50.2%). Among the patients, 451 (8.1%) were using previous OAC. The baseline characteristics of the patients using and not using OAC are shown in Table 1. Among the 451 patients using OAC, 383 were using DOAC, and 68 were using warfarin. Among the 383 patients using DOAC, 178 were using rivaroxaban, 164 were using apixaban, 29 were using edoxaban, and 12 were using dabigatran. Previous OAC patients had significantly more comorbidity, were older, and had higher levels of inflammatory biomarkers than those who did not use OAC. After PS matching, a good balance was observed between the groups that used the previous AC and those that did not (Table 2). The median follow-up time was 4 days (8–12) in previous OAC patients and 7 days (4–11) in patients who did not receive previous OAC (overall median follow-up 7 days, IQR 4–11). A total of 4961 (88.9%) patients were discharged alive, and 616 (10.1%) died at follow-up. Among the 616 patients who died, 62 had received OAC, and 554 had not received OAC (previous OAC patients were 62/451 = 14%, previous OAC was 554/5124 = 11%, unadjusted hazard ratio = 1.08, 95% CI 0.83–1.40, p = 0.575). Table 2 shows the clinical characteristics of the patients who died and survived during follow-up.

In the adjusted multivariable Cox proportional hazard model, previous OAC use was found to be associated with a significantly lower mortality risk (adjusted hazard ratio 0.62, 95% CI 0.42–0.92, p = 0.030) (Fig. 1). In the PS-based secondary analyses of both the PS-adjusted multivariable Cox proportional hazard model (adjusted hazard ratio 0.72, 95% CI 0.54–0.95, p = 0.018) and the multivariable mixed Cox proportional hazard model made in the propensity matched population (adjusted hazard ratio 0.65, 95% CI 0.47–0.88, p = 0.030), previous OAC use was associated with a significantly lower mortality risk.

In the subgroup analyses, a significant interaction was found between previous OAC use and sex, CAD, HF, and eGFR (interaction p < 0.05). The lower risk of mortality with the previous use of AC was more apparent in males than in females.
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The lower risk of mortality with previous OAC use was more evident in those with HF than in those without, while the lower risk of mortality with previous use of OAC was more evident in those without CAD than in those with CAD. The risk of mortality with previous OAC use was similar when the eGFR was < 100 compared with previous OAC use, whereas the use of previous OAC was associated with higher mortality when it was > 100 (Fig. 2).

Table 1 The baseline characteristics of the patients using and not using OAC according to before-after propensity score matching analysis

|                          | Before matching |                  | After matching |                  |
|--------------------------|-----------------|------------------|----------------|------------------|
|                          | No previous OAC | Previous OAC (n=451) | SMD            | No previous OAC | Previous OAC (n=446) | SMD            |
| Age (median [IQR])       | 64.00 [51.00, 73.00] | 69.00 [59.00, 77.00] | 0.385 | 67.00 [57.00, 76.00] | 69.00 [59.00, 77.00] | 0.091 |
| Sex, male (%)            | 2582 (50.4)     | 219 (48.6)       | 0.037 | 429 (49.8)       | 216 (48.4)       | 0.028 |
| DM, (%)                  | 1379 (26.9)     | 120 (26.6)       | 0.007 | 229 (26.6)       | 119 (26.7)       | 0.002 |
| HT, (%)                  | 2440 (47.6)     | 320 (71.0)       | 0.489 | 589 (68.4)       | 315 (70.6)       | 0.048 |
| CAD, (%)                 | 963 (18.8)      | 199 (44.1)       | 0.567 | 353 (41.0)       | 194 (43.5)       | 0.051 |
| HF, (%)                  | 183 (3.6)       | 111 (24.6)       | 0.634 | 172 (20.0)       | 106 (23.8)       | 0.092 |
| COPD, (%)                | 661 (12.9)      | 113 (25.1)       | 0.314 | 141 (16.4)       | 111 (24.9)       | 0.212 |
| AF, (%)                  | 17 (0.3)        | 275 (61.0)       | 1.746 | 2 (0.2)          | 273 (61.2)       | 1.761 |
| CKD, (%)                 | 131 (2.6)       | 17 (3.8)         | 0.069 | 35 (4.1)         | 17 (3.8)         | 0.013 |
| PTE, (%)                 | 107 (2.1)       | 26 (5.8)         | 0.190 | 47 (5.5)         | 25 (5.6)         | 0.006 |
| LDH, U/L (median [IQR])  | 295.00 [235.19, 379.73] | 312.00 [238.79, 397.93] | 0.109 | 297.20 [244.00, 395.17] | 312.00 [238.39, 397.46] | 0.039 |
| TG, mg/dL (median [IQR]) | 128.00 [94.00, 179.00] | 121.00 [90.11, 167.79] | 0.098 | 123.50 [95.00, 180.20] | 121.03 [90.06, 167.86] | 0.079 |
| LDL, mg/dL (median [IQR])| 86.90 [67.79, 110.00] | 81.00 [64.33, 104.55] | 0.160 | 84.80 [66.00, 110.50] | 81.00 [64.33, 104.76] | 0.128 |
| HDL, mg/dL (median [IQR])| 33.67 [27.44, 41.70] | 32.59 [26.46, 38.94] | 0.146 | 33.41 [27.55, 42.06] | 32.53 [26.42, 38.90] | 0.156 |
| Albumin, g/dL (median [IQR]) | 3.80 [3.41, 4.10] | 3.70 [3.33, 4.03] | 0.160 | 3.70 [3.33, 4.03] | 3.70 [3.33, 4.03] | 0.004 |
| eGFR, ml/min (median [IQR]) | 83.03 [61.49, 98.39] | 74.11 [53.83, 93.80] | 0.313 | 75.70 [53.83, 93.80] | 74.31 [53.83, 93.80] | 0.077 |
| CRP, mg/L (median [IQR])  | 35.57 [12.01, 73.52] | 41.95 [15.85, 81.12] | 0.111 | 40.71 [14.71, 84.61] | 41.48 [15.84, 80.89] | 0.009 |
| D-Dimer, ng/ml (median [IQR]) | 5.28 [1.06, 436.67] | 72.19 [1.54, 715.79] | 0.110 | 54.81 [1.33, 697.00] | 63.39 [1.54, 703.87] | 0.012 |
| Ferritin, ng/ml (median [IQR]) | 249.75 [106.46, 528.92] | 254.95 [110.86, 599.27] | 0.029 | 255.58 [109.33, 554.04] | 255.32 [111.24, 600.51] | 0.001 |
| Procalcitonin, ng/ml (median [IQR]) | 0.10 [0.02, 0.51] | 0.16 [0.04, 0.68] | 0.140 | 0.16 [0.04, 0.67] | 0.16 [0.04, 0.69] | 0.077 |
| Troponin, ng/ml (median [IQR]) | 8.14 [2.93, 17.74] | 7.50 [2.50, 18.44] | 0.029 | 7.53 [2.50, 15.00] | 7.50 [2.50, 18.59] | 0.010 |
| SO2, % (median [IQR])     | 61.60 [46.89, 74.53] | 62.55 [48.77, 76.65] | 0.073 | 62.20 [48.70, 75.13] | 62.55 [48.76, 76.68] | 0.043 |
| Hemoglobin, g/dL (median [IQR]) | 13.34 [12.15, 14.47] | 13.03 [11.77, 14.27] | 0.146 | 13.10 [11.78, 14.30] | 13.04 [11.80, 14.29] | 0.002 |
| WBC, 10^3 mm^2 (median [IQR]) | 7.15 [5.51, 9.44] | 7.66 [5.81, 10.42] | 0.122 | 7.61 [5.94, 9.98] | 7.64 [5.79, 10.28] | 0.028 |
| Platelet, 10^3 mm^2 (median [IQR]) | 232.57 [185.15, 289.70] | 218.50 [173.25, 281.44] | 0.097 | 228.67 [177.29, 286.00] | 217.92 [172.75, 281.52] | 0.041 |

OAC ORAL anticoagulant, DOAC direct oral anticoagulant, DM diabetes mellitus, HT hypertension, CAD Coronary artery disease, HF heart failure, CPD chronic obstructive pulmonary disease, AF atrial fibrillation, CKD chronic kidney disease, PTE pulmonary thromboembolism, LDH lactate dehydrogenase, TG triglyceride, LDL low density lipoprotein, HDL high density lipoprotein, eGFR estimated glomerular filtration rate, CRP C reactive protein, SO2 oxygen saturation, WBC white blood cell.
Discussion

This study found that previous use of OAC associated with lower mortality in patients hospitalized due to COVID-19. COVID-19 is a viral infection that causes a sepsis-like clinical presentation in severe cases, causing systemic inflammation and hypercoagulopathy. Although the main mechanism of hypercoagulopathy in COVID-19 is not clearly understood, micro- and macro-embolisms have been detected in some postmortem studies [15–17]. Inflammation causes vascular damage as a result of endothelial dysfunction and hypercoagulopathy. Occasionally, disseminated intravascular coagulation and venoarterial TE develop secondary to an excessive inflammatory response. Pulmonary and extrapulmonary microvascular thrombosis can cause acute lung injury, progression of the disease, and subsequent

| Table 2 The baseline characteristics of the alive and death patients |
|----------------|----------------|---------------|
|               | Alive (n = 4959) | Death (n = 616) | p    |
| OAC (%)       |                |               | 0.205|
| Apixaban      | 138 (2.8)      | 26 (4.2)      |      |
| Dabigatran    | 12 (0.2)       | 0 (0.0)       |      |
| Edoxaban      | 26 (0.5)       | 3 (0.5)       |      |
| Rivaroxaban   | 155 (3.1)      | 23 (3.7)      |      |
| Warfarin      | 58 (1.2)       | 10 (1.6)      |      |
| No            | 4570 (92.2)    | 554 (89.9)    |      |
| OAC (%)       | 0.157          |               |      |
| No            | 4570 (92.2)    | 554 (89.9)    |      |
| DOAC          | 331 (6.7)      | 52 (8.4)      |      |
| Warfarin      | 58 (1.2)       | 10 (1.6)      |      |
| Warfarin + DOAC, (%) | 389 (7.8) | 62 (10.1) | 0.068|
| Age (median [IQR]) | 62.00 [49.00, 72.00] | 75.00 [68.00, 82.00] | < 0.001|
| Sex, male (%) | 2566 (51.7)    | 235 (38.1)    | < 0.001|
| DM, (%)       | 1312 (26.5)    | 187 (30.4)    | 0.044|
| HT, (%)       | 2391 (48.2)    | 369 (59.9)    | < 0.001|
| CAD, (%)      | 978 (19.7)     | 184 (29.9)    | < 0.001|
| HF, (%)       | 243 (4.9)      | 51 (8.3)      | 0.001|
| COPD, (%)     | 653 (13.2)     | 121 (19.6)    | < 0.001|
| AF, (%)       | 252 (5.1)      | 40 (6.5)      | 0.165|
| CKD, (%)      | 116 (2.3)      | 32 (5.2)      | < 0.001|
| PTE, (%)      | 116 (2.3)      | 17 (2.8)      | 0.613|
| LDH, U/L (median [IQR]) | 284.00 [230.21, 356.58] | 508.57 [386.10, 647.48] | < 0.001|
| TG, mg/dl (median [IQR]) | 126.00 [93.00, 176.50] | 141.38 [104.88, 194.59] | < 0.001|
| LDL, mg/dl (median [IQR]) | 88.00 [69.00, 110.89] | 72.00 [53.32, 95.47] | < 0.001|
| HDL, mg/dl (median [IQR]) | 34.13 [28.04, 41.93] | 28.02 [22.17, 34.87] | < 0.001|
| Albumin, g/dl (median [IQR]) | 3.85 [3.50, 4.15] | 3.12 [2.85, 3.48] | < 0.001|
| eGFR, ml/min (median [IQR]) | 84.93 [65.91, 99.65] | 51.77 [31.25, 72.10] | < 0.001|
| CRP, mg/L (median [IQR]) | 31.05 [10.27, 63.17] | 102.32 [61.03, 151.56] | < 0.001|
| D-Dimer, ng/ml (median [IQR]) | 4.24 [1.01, 419.00] | 28.30 [3.88, 1190.94] | < 0.001|
| Ferritin, ng/ml (median [IQR]) | 224.00 [96.55, 459.82] | 646.95 [314.80, 1176.45] | < 0.001|
| Procalcitonin, ng/ml (median [IQR]) | 0.08 [0.02, 0.36] | 1.08 [0.37, 3.21] | < 0.001|
| Troponin, ng/ml (median [IQR]) | 7.50 [2.65, 15.02] | 15.00 [5.39, 80.06] | < 0.001|
| SO2, % (median [IQR]) | 60.70 [46.05, 73.45] | 71.63 [58.21, 83.01] | < 0.001|
| Hemoglobin, g/dl (median [IQR]) | 13.38 [12.27, 14.47] | 12.40 [10.45, 14.30] | < 0.001|
| WBC, 10³ mm³ (median [IQR]) | 6.96 [5.39, 8.99] | 10.75 [7.78, 14.15] | < 0.001|
| Platelet, 10³ mm³ (median [IQR]) | 237.00 [189.25, 294.07] | 189.39 [142.21, 243.54] | < 0.001|

OAC oral anticoagulant, DOAC direct oral anticoagulant, DM diabetes mellitus, HT hypertension, CAD coronary artery disease, HF heart failure, COPD chronic obstructive pulmonary disease, AF atrial fibrillation, CKD chronic kidney disease, PTE pulmonary thromboembolism, LDH lactate dehydrogenase, TG triglyceride, LDL low density lipoprotein, HDL high density lipoprotein, eGFR estimated glomerular filtration rate, CRP C reactive protein, SO2 oxygen saturation, WBC white blood cell

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multiorgan dysfunction [18]. This situation causes serious morbidity and even mortality. Therefore, parenteral or oral anticoagulant therapy is recommended to prevent TE events.

Parenteral anticoagulants are used for TE prophylaxis in COVID-19 both during treatment and after discharge. In addition to the anticoagulant effects of these agents, antiviral, anti-inflammatory, and cytoprotective effects have also been observed [19]. DOAC (e.g., dabigatran, rivaroxaban, apixaban, edoxaban), especially factor Xa inhibitors, may be considered as another option in the treatment of these patients due to their similar effects [20–22]. In our study, some patients used warfarin and DOAC. We consider our findings on mortality to be due to the effects of DOAC.

In the review written by Harenber et al., the clinical course of patients with severe COVID-19 and a history of non-valvular AF or deep vein thrombosis and using OAC was milder
other drugs used by patients with anticoagulant drugs was also be considered limitations. Moreover, the interaction of single center andthe relatively low number of patients can confounding. The fact that the patients were taken from a caution because of unmeasured confounding and residual propensity matching, the results should be interpreted withewed confounding wasreduced by regression analysis and measured confounding wasreduced by regression analysis and propensity matching, the results should be interpreted with caution because of unmeasured confounding and residual confounding. The fact that the patients were taken from a single center and the relatively low number of patients can also be considered limitations. Moreover, the interaction of other drugs used by patients with anticoagulant drugs was not detected.

Conclusion

In hospitalized COVID-19 patients, in patients who previously used anticoagulants was associated with lower risk of in-hospital death than in those who did not. However, these findings should be interpreted carefully because of unmeasured confounding and supported by further research.

Limitations

Our study has some limitations. Primarily due to the nature of retrospective studies, the results may be biased because of measured and unmeasured confounding. Although measured confounding was reduced by regression analysis and propensity matching, the results should be interpreted with caution because of unmeasured confounding and residual confounding. The fact that the patients were taken from a single center and the relatively low number of patients can also be considered limitations. Moreover, the interaction of other drugs used by patients with anticoagulant drugs was not detected.

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