ORIGINAL RESEARCH

DOI: 10.4274/globecc.galenos.2023.86580
Glob Emerg Crit Care 2024;3(2):69-74

Comparison of Oral Anticoagulant Users with Non-users Admission Laboratory Parameters, Length of Hospital Stay and Outcomes in COVID-19 Infection

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Abstract

Objective: We aimed to investigate the effect of oral anticoagulant (OA) use during coronavirus disease-2019 (COVID-19) on early admission laboratory parameters and/or length of hospital stay in patients receiving chronic OA medication.

Materials and Methods: This retrospective study included two groups; group 1 (n=62) consisted of OA users, and group 2 (n=75) of age and sex-matched OA non-users at the time of COVID-19 diagnosis. Early admission laboratory measures, numbers of comorbidities, length of hospital stay, and outcomes of patients were recorded and analyzed.

Results: Despite higher comorbidities in group 1, serum C-reactive protein (CRP) and D-dimer levels were significantly lower than group 2 ($p<0.05$, all). The mortality rate was higher in group 2 but did not reach statistical significance ($p>0.05$). Regression analysis showed that OA users (compared to OA non-users) had 0.980 and 0.520 times lower serum CRP and D-dimer levels, respectively.

Conclusion: This study showed a beneficial effect of OA use on early admission serum CRP, and D-dimer levels, which are important prognostic predictors of COVID-19. Additionally, OA use is associated with fewer hospital stays for COVID-19 patients. These beneficial effects of OA use might help improve the management of this infection after further studies in this field.

Keywords: Anticoagulant, COVID-19, C-reactive protein, D-dimer, length of hospital stay, outcome

Introduction

Coronavirus disease-2019 (COVID-19) has a high morbidity and/or mortality rate. Coagulopathy is one of the main determinants of outcomes. In general, these patients have an increased risk of both venous and arterial thrombotic events [1]. These may be presented as micro or macro thrombotic events [2,3]. The presence of cardiac valvular diseases and/or atrial fibrillation (AF) increases the risk of thromboembolism in COVID-19-infected patients [4-6]. Therefore, elevated serum D-dimer level is regarded as a bad prognostic marker [3,6-8]. Therefore, most local and international guidelines recommend anticoagulation treatment with heparins among hospitalized patients with COVID-19 [9]. Despite this, thromboembolic complications are still not preventable even with high doses of heparin therapy protocols [2,10,11]. As active managing physicians in pandemic clinics at our hospitals, we encounter thromboembolic complications in patients with COVID-19 who are managed with optimal doses of low-molecular-weight (LMWH) or unfractionated heparins (UH) [9]. In light of the high burden of microvascular thrombosis and immunothrombosis in this disease, some researchers recommend the use of

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Received: 06.10.2023 **Accepted:** 15.11.2023

antiplatelet therapies (as aspirin) in hospitalized patients with COVID-19 [12]. As known, oral anticoagulants (OAs) are used in the treatment or prevention of thrombotic events in high-risk individuals. These drugs are vitamin K antagonists (warfarin or acenocoumarol) or direct OAs (dabigatran, apixaban, rivaroxaban, and edoxaban). To our knowledge, these drugs are not indicated for preventing or treating COVID-19-related thromboembolic events. Additionally, at the time of the development of COVID-19 in anticoagulated patients, researchers advise switching to heparin treatment. The rationale for this is the difficulty in monitoring the effects and/or side effects of OAs [13-15]. The most notable outcome is the controversial results of their impact on the outcomes of COVID-19 infection [13,14,16-20]. Our national guidelines recommend switching to LMWH or standard UH at the time of COVID-19 diagnosis in patients already on OA treatment [9]. During our daily practice, we manage such patients in our COVID-19 inpatient clinics. Due to their special clinical status, we were obligated to continue treatment in some patients with OA successfully. These positive observations encouraged us to collect retrospective data on OA users newly diagnosed with COVID-19 and compare it with those of their peers who are OA non-users. Therefore, in this study, we aimed to compare early admission laboratory parameters, hospital stay length, and outcomes of OA users newly diagnosed with COVID-19 who were already on OA use with those who were not.

Materials and Methods

This retrospective study was approved by University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee (decision number: 2020-24-12, date: 07.12.2020). Informed consent form was obtained from all patients. Data of COVID-19 patients admitted to the pandemic medical departments of University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital and University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital from November 1, 2020, to January 1, 2021. The 1st group consisted of patients using OA at the time of diagnosis of COVID-19 (n=62). The second group consisted of age- and sex-matched COVID-19 patients who did not use any OA at the time of COVID-19 diagnosis (n=75). For admission criteria, and management of these patients, the Turkish Ministry of Health's guidelines were followed. According to Turkish guidelines, all COVID-19-diagnosed outpatients and inpatients are given antiviral treatment favipiravir as soon as possible [9]. The main symptoms of these patients were shortness of breath, fever, myalgia, and cough. These patients were selected according to the following inclusion and exclusion criteria;

Inclusion criteria: (1) confirmed COVID-19 diagnosis (by real-time reverse transcription-polymerase chain reaction test) (both groups), (2) age ≥60 years old (both groups), 3) using of OA on the day of diagnosis of COVID-19 (at least >1 month) (group 1 only).

Exclusion criteria: (1) using any OA at the time of diagnosis of COVID-19 (group 2 only), (2) incomplete hospital laboratory and/or follow-up records (both groups).

Complete hospital admission clinical and laboratory data were recorded. The number of comorbidities, length of hospital stay, and outcomes were also recorded. A total of 155 patient records were screened, and 18 were excluded (3 of them from group 1, and 15 from group 2). The exclusion criteria were incomplete hospital records for group 1 patients. For group 2; age (<60 years old), suspicious diagnosis of COVID-19, and incomplete hospital records were the causes of patient exclusion. Thus, the final analysis was performed with a total of 137 patients [group 1 (n=62), and group 2 (n=75)]. Seventeen of the group 1 patients used warfarin, and the remainder 45 patients were using new OAs; apixaban (n=17), rivaroxaban (n=15), edoxaban (n=9), and dabigatran (n=3) (see Figure 1).

Data Availability

All necessary data are presented in the manuscript. Nevertheless, for reasonable requests, the corresponding author can be reached by e-mail.

Statistical Analysis

Statistical analyses were performed using the SPSS 22.0 statistical package for Windows. The distribution of variables was evaluated using the Kolmogorov-Smirnov test. The data were not distributed normally. Therefore, the description of the data was expressed as median (minimum-maximum). The Mann-Whitney U test was used to compare variables. The effect size was estimated using the rank-biserial correlation coefficient [$r^{r\text{-}b}$]. Chi-square analysis was used to compare categorical variables between groups. The Spearman test was used to evaluate the correlation between quantitative variables. Logistic regression (model: forward logistic regression) [adjusting od ratio at 95% confidence interval (CI)] analysis was applied to find the simplest model that could predict the outcome. A p-value <0.05 was accepted as significant [21].

Results

A total of 137 patients were included in this study. The comparison of the study parameters of group 1 with group 2 is shown in Table 1. The ratio of female (F)/male (M), and mean ± standard deviation [median (minimum-maximum)] age of group 1 (n=62) and group 2 (n=75) was 25 F/37 M, and 71.30±8.89 [69.00 (60.00-94.00)] years versus 37 F/38 M, and 70.30±6.48 [70 (60.00-88.00)] years, respectively (p>0.05, both). The timing of hospital admission (i.e., duration of disease's symptom(s) at the time of admission) did not differ between the

2 study groups (p>0.05). The median number of comorbidities was significantly higher in group 1 patients, but the median serum CRP and D-dimer levels were significantly lower in the same group (in comparison to group 2 patients) (p<0.05, all). The median mortality rate was higher in group 2 patients but did not reach statistical significance (p>0.05) (see Table 1).

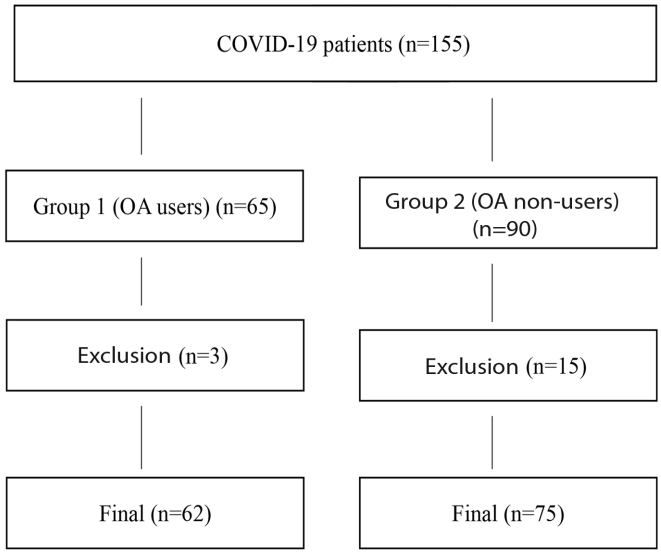

Figure 1. The study groups and study flow diagram

OA: Oral anticoagulant, COVID-19: Coronavirus disease-2019

A comparison of patients who survived with those who died is presented in Table 2. The median serum CRP level was higher, but the median lymphocyte and platelet counts were significantly lower in patients who died (see Table 2 for medians, p-values, and effect sizes).

Spearman's rank correlation analysis identified a negative correlation between the use of OA and serum CRP, D-dimer, and length of hospital stay (correlation coefficient r were -0.377, -0.260, and -0.207, and p-values were <0.001, 0.002, and 0.015, respectively).

Regression analysis showed that OA users (in comparison to OA non-users) had 0.980 and 0.520 times lower serum CRP and D-dimer levels, respectively (95% CI) were 0.982-0.995, and 0.280-0.991, respectively).

Discussion

The median number of comorbidities was significantly higher in group 1 than in group 2 patients ($r^{r\text{-}b}$=0.423, and p<0.001). It is well known that comorbidities are among the important determinants of mortality in COVID-19 infection.

Table 1. Comparison of oral anticoagulant users (group 1) with non-users (group 2) COVID-19 patients' data

Order	Parameter	Group 1 (n=62)	Group 2 (n=75)	p	Effect size*
1	**Age (years)** Median (min-max)	69.00 (60.00-94.00)*+	70.00 (60.00-88.00)	NS	-
2	**Gender** Female/male	25/37	37/38	NS	-
3	**Duration of symptom(s) at hospital admission (days)**	5 (1-10)*+	3 (1-12)	NS	-
4	**Hospital's stay days** Median (min-max)	10.00 (2.00-42.00)*+	12.00 (3.00-31.00)	0.016	0.239
5	**Number of comorbidities** Median (min-max)	3.00 (1.00-7.00)*+	2.00 (0.00-7.00)	<0.001	0.429
6	**Leucocyte count (x10^3/uL)** Median (min-max)	7.30 (1.87-25.10)*+	7.18 (0.82-21.67)	NS	-
7	**Lymphocyte (x10^3/uL)** Median (min-max)	1.02 (0.30-3.24)*+	1.07 (0.20-3.32)	NS	-
8	**Platelet (x10^3/uL)** Median (min-max)	199.50 (52.00-495.00)*+	205.00 (77.00-822.00)	NS	-
9	**CRP (mg/L)** Median (min-max)	41.65 (1.30-248.00)	118.00 (1.60-418.00)	<0.001	0.437
10	**D-dimer (µg FEU/mL)** Median (min-max)	0.25 (0.02-1.96)*+	0.45 (0.07-3.90)	0.002	0.301
11	**Mortality rate** n (%)	9 (14.75)	12 (16.00)	NS	-

NS: Not significant

*Rank-biserial correlation

*+Non-normal distribution

COVID-19: Coronavirus disease-2019, min: Minimum, max: Maximum, CRP: C-reactive protein

Table 2. Comparison of COVID-19 patients that survived with those that not survived

Order	Parameter	Survivors (n=115)	Non-survivors (n=21)	p	Effect size*
1	**Age (years)** Median (min-max)	70.00 (60.00-90.00)*+	68.00 (61.00-89.00)*+	NS	-
2	**Gender** Female/male	54/64	7/14	NS	-
3	**Hospital's stay days** Median (min-max)	10.00 (2.00-42.00)*+	12.00 (3.00-31.00)*+	NS	-
4	**Number of comorbidities** Median (min-max)	2.00 (0.00-7.00)*+	2.00 (0.00-5.00)*+	NS	-
5	**Leucocyte count (x10^3/uL)** Median (min-max)	7.42 (0.82-25.10)*+	7.13 (2.74-12.76)*+	NS	-
6	**Lymphocyte (x10^3/uL)** Median (min-max)	1.10 (0.20-3.20)*+	0.73 (0.37-2.77)*+	0.019	0.323
7	**Platelet (x10^3/uL)** Median (min-max)	211.00 (52.00-822.00)*+	158.00 (71.00-272.00)*+	0.002	0.427
8	**CRP (mg/L)** Median (min-max)	79.80 (1.30-340.00)*+	128.00 (25.00-418.00)*+	0.007	0.371
9	**D-dimer (µg FEU/mL)** Median (min-max)	0.37 (0.02-3.90)*+	0.26 (0.02-3.90)*+	NS	-

NS: Not significant

*Rank-biserialcorrelation

*+Non- normal distribution

COVID-19: Coronavirus disease-2019, min: Minimum, max: Maximum, CRP: C-reactive protein

Cardiovascular disease and AF are the leading determinants of mortality in these patients [22,23]. As expected, our group 1 of OA users with COVID-19 had significantly higher rates of these comorbidities. Although not statistically significant, the mortality rate of group 1 COVID-19 patients was lower than that of group 2 COVID-19 patients (see Table 1 for the rates). One of the important prognostic factors of COVID-19 is serum CRP levels [23]. Our study results showed significantly higher early admission median (minimum-maximum) serum CRP levels in patients who died (n=21) than in those who survived (n=115) [128.00 (25.00-41800) versus 79.80 (1.30-340.00) mg/dL, r=0.371, p=0.007] (Table 2). Our study group 1 (OA users) had lower serum CRP levels than the 2 (OA non-users) patients (r^{r-b}=0.437, p<0.001) (see Table 1). As is well known, longer hospital stay increases mortality, healthcare-associated infection, and economic burden as well [24]. The median length of hospital stay days was significantly lower for OA users than for OA non-users (10 versus 12 days, r^{r-b}=0.240, and p=0.016). In other words, there was a significant negative correlation between OA use and length of hospital stay (correlation coefficient r=-0.207, p<0.05). Age, presence of comorbidities, serum CRP, and D-dimer levels are some of the predictors of length of hospital stay in COVID-19 infection [25]. The number of comorbidities was significantly higher in OA users (in comparison to OA non-users) (p<0.05). Serum CRP and D-dime levels were significantly lower in COVID-19 patients with OA. They showed a significant negative correlation with OA use (correlation coefficient r were -0.377, and -0.260, respectively, p<0.05, both). Therefore, it seems that lower serum CRP and D-dimer levels in OA users are good prognostic factors [7,8]. OA treatment has a lowering effect on serum CRP and D-dimer levels [26]. Additionally, in patients that OA has been discontinued, the elevation of serum CRP and D-dimer levels may predict venous thromboembolism recurrence [27]. Heparin has no effect on serum CRP levels but a lowering effect on D-dimer levels in COVID-19 [28]. OA therapy is not routinely used in the management of COVID-19. Some guidelines recommend the D-dimer levels-based approach (the international medical prevention registry on venous thromboembolism-D-dimer score), whereas others do not [13,14]. Also, some studies showed that OA positively affects the outcome of COVID-19, whereas other studies showed no benefit. Can these different results be population-related? However, the most important point is that none of the studies showed harmful effects of OA use in COVID-19 [16-19]. The main characteristic of our study is the inclusion of a different population (i.e., Turkish population). We should mention that the aforementioned studies evaluated the effect of OA use on the mortality and outcomes of COVID-19. As far as we know, our study is the 1st that studies the effect of chronic OA use on

the CRP and D-dimers levels in early COVID-19 infection, and most importantly, its relationship with hospital stay length. Herd immunity is one of the main goals of decision-makers and researchers worldwide [29-31]. Reaching herd immunity with available vaccination and prevention strategies in the near future appears difficult (if not impossible) [31]. Complete and/or great shutdowns have major economic sequences that make most countries' decision-makers escape from them and prefer less strict policies in this issue [32,33]. Whether using the beneficial early effects of OA use with vaccination and maximum-tolerated shutdown policies could help reach herd immunity easier and as early as possible needs to be considered. At least, as shown in previous studies and in our COVID-19 patients, there were no major adverse outcomes. One may find this nonsense. However, as Jean Piaget (9th August 1896-16th September 1980) stated: "intelligence is what you use when you don't know what to do: when neither innateness nor learning has prepared you for the particular situation." [34].

Study Limitations

The main limitation of this study is that it did not include young patients with COVID-19. If included, the results would be expected to be more useful. We could continue the OA use in only one of our COVID-19 patients. If we were able to continue OA use after diagnosing COVID-19 infection in more patients, the results might be more comprehensive. Nevertheless, its early use effect on the progress and outcome of COVID-19 infection is promising.

Conclusion

Our pilot study results showed that OA use at the early stage of COVID-19 infection was beneficial. It was associated with lower serum CRP and D-dimer levels at early admission. In addition, these patients had a shorter hospital stay length (in comparison to age and sex-matched OA non-user COVID-19 patients). The beneficial effects of OA use in patients with COVID-19 might help decision makers in the challenging war with this pandemic. However, further dedicated studies are required in this field.

Acknowledgement

We would like to confirm that all authors fulfilled the authorship criteria.

Ethics

Ethics Committee Approval: This retrospective study was approved by University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee (decision number: 2020-24-12, date: 07.12.2020).

Informed Consent: Informed consent form was obtained from all patients.

Authorship Contributions

Surgical and Medical Practices: F.K., E.E., E.B., B.E., H.K., R.K., Concept: F.K., M.H., Z.K., K.K.Y., Design: F.K., M.H., Z.K., Data Collection or Processing: F.K., M.H., E.E., E.B., Z.K., B.E., H.K., R.K., Analysis or Interpretation: M.H., H.İ., K.K.Y., Literature Search: F.K., M.H., Writing: F.K., M.H.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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