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The Potential Survival Advantages of Rivaroxaban in Patients with COVID-19 and its Relationship with D-Dimer Levels at the Time of Early Onset of Anticoagulation

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Abstract: ***The current work aimed to assess the rate of death, hospitalization, and oxygen supplementation, in addition to assessing major or clinically relevant non-major bleeding. Methods: In a prospective cohort study involving 392 outpatients diagnosed with COVID-19, all patients were followed up for one month, and the patients received Rivaroxaban 20 mg once daily. The investigators took out patients' information regarding their sociodemographic data, past medical history, laboratory investigation (complete blood picture, D-Dimer, renal and liver functions tests), side effects of drugs, and clinical outcomes. Results: Most of the cases had moderate COVID-19, and the rest had severe COVID-19; regarding death, only 2% died, 3.6% were hospitalized during the follow-up period, and 2.3% received oxygen supplementation. Total bleeding as a complication accounted for 17.3%, 0.5% had major bleeding, and 16.8% had clinically irrelevant bleeding. There was no association between COVID severity, D-dimer levels, death and hospitalization, and total bleeding. Conclusion: Rivaroxaban 20 mg once daily as a prophylactic option for COVID-19 with moderate to severe appears to be safe and effective.***

Keywords: COVID-19, Rivaroxaban, bleeding, anticoagulation, death

1. Introduction

The global pandemic of COVID-19, which was brought about by the SARS-CoV-2 virus, has resulted in an unparalleled level of illness and death. The global count of recorded cases exceeds 200 million, with a mortality rate of over 4 million individuals [1]. Early observations in hospitalized COVID-19 patients revealed disturbances in laboratory indicators of coagulation, specifically highlighting a correlation between raised levels of D-dimer and a heightened likelihood of fatality [2, 3]. Various pathological processes have been proposed to explain the laboratory abnormalities and clinical thrombotic correlations, commonly called "COVID-19-associated coagulopathy." [4].

COVID-19 is distinguished by mononuclear cell reactivity and pan-endothelialitis, which collectively contribute to a notable occurrence of in situ thrombosis in various blood vessels, encompassing both arterial and venous pathways. This phenomenon is observed in larger and smaller vessels, including the capillary-alveolar interface. Such thrombotic events may play a significant role in the elevated frequency of respiratory failure associated with this disease [5-8].

SARS-CoV-2 enters host cells by interacting with the transmembrane angiotensin-converting enzyme two receptor (ACE2R). The expression of this receptor is observed in various organs, including the endothelium, all of which exhibit susceptibility to viral infection [9].

The process of viral penetration into the endothelium has the potential to induce inflammation, known as endothelialitis, and result in vascular damage. Additionally, the activation of mononuclear cells can independently initiate cytokine release and promote increased blood clotting [10, 11]. The activation of mononuclear cells is an additional independent factor contributing to the development of endothelialitis [11]. These processes are characterized by an excessive release of cytokines, specifically tumor necrosis factor-alpha and interleukins-1 and -6 [12]. The excessive release of cytokines can potentially induce the upregulation of tissue factor on mononuclear cells, hence initiating the activation of the coagulation cascade and prominently leading to the generation of thrombin [13]. The processes potentially implicated in the diffuse in situ pulmonary micro-thrombosis observed in advanced cases of COVID-19, along with conventional venous and arterial thrombotic events, are worth considering [14].

Multiple studies indicate that anticoagulation enhances outcomes for critically ill COVID-19 patients [15-18]. Nevertheless, two reports originating from France documented instances of unforeseen pulmonary embolism (PE) occurring despite the administration of therapeutic anticoagulation [19, 20]. This occurrence is believed to be attributed to the heightened severity of the hypercoagulable state. However, a trial that included noncritically sick patients found no observed advantage in administering higher dosages of anticoagulation [21]. The results above were reiterated in a study conducted by five research facilities in New York City. The study revealed that prophylactic and therapeutic anticoagulation positively correlated with enhanced mortality rates. However, it is

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important to note that the observed difference between these two groups was not statistically significant [22]. Notwithstanding these encouraging indications, a substantial randomized trial examining the effectiveness of therapeutic anticoagulation (NIH ACTIV-4) has recently halted the recruitment of participants due to insufficient efficacy observed in critically ill individuals [23]. The current work aims to assess the rate of death, hospitalization, oxygen supplementation, and major or clinically relevant non-major bleeding.

2. Methods

A. Study design

In a prospective cohort study that involved 392 outpatients diagnosed with COVID-19, all patients were followed up for one month. The patients received the following treatment (levofloxacin 500 mg, omeprazole 20 mg, third-generation cephalosporin, remdesivir 200 mg as a single dose on day 1, followed by 100 mg once daily for a duration generally 5 - 10 days, and Rivaroxaban 20 mg once daily based on ACTION trial.[24]

The investigators took out patients' information regarding their sociodemographic data, past medical history, laboratory investigation (complete blood picture, D-Dimer, renal and liver functions tests), side effects of drugs, and clinical outcomes.

A reverse transcriptase polymerase chain reaction confirmed the COVID-19 infection in all subjects (RT-PCR). According to the most recent Iraqi guidelines approved by the Iraqi Ministry of Health in 2021, the severity of COVID-19 infections ranges from (mild, moderate, severe, and critically ill patients) [25].

B. Study setting

The study was conducted in the first author's outpatient private clinic in Basarah, starting in May 2021 and ending in May 2022.

C. Inclusion criteria

1) Patients with a confirmed diagnosis of COVID-19
2) Both gender
3) Age above 18 years
4) Body mass index <30 kg/m^2
5) Agreement to participate by providing the informed consent form (ICF).

D. Exclusion criteria

1) Patients with indication for full anticoagulation during inclusion (for example, diagnosis of venous thromboembolism, atrial fibrillation, mechanical valve prosthesis).
2) Platelets < 50,000 /mm3
3) Need for ASA therapy > 100 mg.
4) Need for P2Y12 inhibitor therapy (clopidogrel, ticagrelor or prasugrel).
5) Chronic use of non-hormonal anti-inflammatory drugs.
6) Uncontrolled systolic blood pressure (BP) of ≥180 mmHg or diastolic BP of ≥100 mmHg.
7) INR > 1,5.
8) Patients contraindicated to full anticoagulation (active bleeding, liver failure, blood dyscrasia, or prohibitive hemorrhage risk as evaluated by the investigator).
9) Criteria for disseminated intravascular coagulation (DIC).
10) A history of hemorrhagic stroke or any intracranial bleeding at any time in the past or current intracranial neoplasm (benign or malignant), cerebral metastases, arteriovenous (AV) malformation, or aneurysm.
11) Active cancer (excluding non-melanoma skin cancer) is defined as cancer not in remission or requiring active chemotherapy or adjunctive therapies such as immunotherapy or radiotherapy.
12) Hypersensitivity to Rivaroxaban.
13) Use of strong inhibitors of cytochrome P450 (CYP) 3A4 and/or P-glycoprotein (P-gp) (e.g., protease inhibitors, ketoconazole, Itraconazole) and/or use of P-gp and strong CYP3A4 inducers (such as but not limited to rifampin/rifampicin, rifabutin, rifapentine, phenytoin, phenobarbital, carbamazepine, or St. John's Wort);
14) HIV infection.
15) Creatinine clearance < 30 ml/min according to the Cockcroft-Gault Formula.
16) Pregnancy or breastfeeding.

E. The outcome of the study

The primary efficacy outcome was death, hospitalization, and oxygen supplementation. The primary safety outcome was major or clinically relevant non-major bleeding defined according to the International Society on Thrombosis and Hemostasis (ISTH) criteria [26].

F. Assessment of D-Dimer level

The serum samples were used to determine the level of D-Dimer, ng/mL ("Human D-Dimer, D2D ELISA Ki", product ID SL0598Hu, Sunlong biotech®, China) by ELISA technique by manufacturer's procedure. In Brief, 50 µl of serum samples were put in wells of ELISA plates for twohr. at room temperature. Then, 50 µl of detection antibody was added for 90 minutes [27]. It's followed by washing three times using a prepared washing buffer. The spectrophotometer was used to measure the optical density of samples, and a standard curve was used to assess the concentration of samples (ELISA reader, Diagnostic Automation / Cortez Diagnostics®, California, USA).

G. Sample size calculation

It was determined using G*Power version (3.1.9.7)[28, 29], the effect size was 0.10, α-level 0.05, power (1-β error prob) was 0.99 [the program was run under "Proportion: Sign test (binomial test)"], the total sample size calculated to be 392 with actual power = 0.99.

H. Statistical analysis

All analyses were carried out using SPSS version 24.0, independent t-test, and chi-square for assessing the differences according to total bleeding; the p-value was considered significant if ≤0.05.

3. Results

Three hundred ninety-two patients infected with COVID-19 were included in the study, with a mean age of 38.8 years;

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the majority were females, 68.1%, and a minority were smokers, 8.2%. Hypertension was the most common comorbid disease, followed by DM, IHD, and previous lung disease (COPD, asthma, and bronchitis). Most of the cases had moderate COVID-19, and the rest had severe COVID-19; regarding death, only 2% died, and 3.6% were hospitalized during the follow-up period, 2.3% received oxygen supplementation. Total bleeding as a complication accounted for 17.3%, 0.5% had major bleeding, and 16.8% had clinically irrelevant bleeding, as illustrated by Table 1.

Table 1: Assessment of patient's characteristics

Parameters	Value
Number	392
Age (years)	38.8 ± 12.2
BMI (kg/m^2)	24.9 ± 2.3
Sex	
Female	267 (68.1%)
Male	125 (31.9%)
Smoking	32 (8.2%)
Comorbid diseases	
DM	68 (17.3%)
Hypertension	76 (19.4%)
IHD	31 (7.9%)
Previous lung disease	30 (7.7%)
COVID severity	
Moderate	314 (80.1%)
Severe	78 (19.9%)
Death	8 (2%)
Hospitalization	14 (3.6%)
Oxygen supplementation	9 (2.3%)
D-dimer (ng/mL), mean ± SD	1062.4 ± 516.8
(Elevated) >500 ng/mL	320 (81.6%)
Adverse effects	
Total bleeding	68 (17.3%)
Major blessing	2 (0.5%)
Clinically relevant non-major bleeding	66 (16.8%)

There was no association between COVID severity, D-dimer levels, death and hospitalization, and total bleeding, as illustrated by Table 2.

Table 2: Association between patient's characteristics and total bleeding

Parameters	No bleeding	Bleeding	p-value
Number			
COVID severity			0.623
Moderate	261(80.6%)	53(77.9%)	
Severe	63(19.4%)	15(22.1%)	
D-Dimer, mean ± SD	1082.7 ± 514.6	965.5 ± 519.9	0.089
Normal (0 – 500) ng/mL	54(16.7%)	18(26.5%)	0.058
(Elevated) >500 ng/mL	270(83.3%)	50(73.5%)	
Death	7(2.2%)	1(1.5%)	0.715
Hospitalization	12(3.7%)	2(2.9%)	0.758

4. Discussion

The current study showed a low mortality rate of 2%, which was not associated with bleeding tendency during COVID-19 infection. All patients received Rivaroxaban 20 mg once daily; in addition, most of the cases had moderate COVID, and the rest had severe COVID-19 death; only 2% died, and 3.6% were hospitalized during the follow-up period, 2.3% received oxygen supplementation. Total bleeding as a complication accounted for 17.3%, 0.5% had major bleeding, and 16.8% had clinically irrelevant bleeding. And parameters associated with total bleeding.

Seven significant randomized controlled trials have investigated the impact of therapeutic-dose anticoagulation in individuals diagnosed with COVID-19. The study encompassed individuals with a minimum of mild COVID-19 infection, elevated levels of D-dimer, and a low propensity for bleeding. The trials discussed in this context had notable shortcomings, including the absence of a universally accepted criterion for illness severity and inconsistent use of anticoagulation treatments such as DOACs and heparin. Additionally, there were variations in the duration of anticoagulation, the timing of randomization, and the length of the follow-up period, all of which differed significantly among the trials. Moreover, it is important to note that all studies included in the analysis employed an open-label approach, which introduces the potential for bias. There were variations in the thromboprophylaxis practices among the control patients, with certain individuals receiving intermediate-dose thromboprophylaxis. Notwithstanding the inherent constraints, these trials were executed under the challenging circumstances of a persistent pandemic. They yielded vital knowledge regarding the efficacy of therapeutic-dose anticoagulation, particularly heparin, in the context of hospitalized individuals afflicted with COVID-19[30-35].

The initial randomized controlled data was obtained from an open-label trial conducted in Brazil. This trial investigated the use of therapeutic-dose Rivaroxaban or enoxaparin as anticoagulant therapy in patients admitted with COVID-19. The study encompassed a cohort of hospitalized individuals exhibiting elevated levels of D-dimers, with a minimum of one-third of participants in each group presenting with severe illness. The trial findings did not demonstrate a statistically significant difference in the key composite outcome, encompassing death, hospitalization duration, and the length of time oxygen was required up to day 30. However, concerning safety outcomes, it was shown that the therapeutic anticoagulation group had a greater occurrence of bleeding episodes [32].

The New England Journal of Medicine (NEJM) published a comprehensive multinational randomized controlled trial in August 2021, which examined the effects of therapeutic-dose anticoagulation in patients with COVID-19. The researchers classified the patients into two groups, namely moderate and severe disease, based on their need for intensive care unit (ICU) treatment. The findings were subsequently reported and analyzed independently for each group. In the subgroup of patients with moderate illness, the researchers observed that therapeutic anticoagulation, as opposed to preventative anticoagulation, resulted in more days free from the need for organ support. This finding was statistically significant and independent of the patient's initial D-dimer level. No statistically significant disparity was observed in the incidence of serious bleeding [33], which agrees with the current study. The study above presented distinct findings for the severe subgroup, indicating that therapeutic anticoagulation did not yield a statistically significant disparity in the number of days free from organ support required for life [36].

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The RAPID experiment was a multicenter, open-label, randomized controlled trial that involved 465 individuals with COVID-19 and increased D-dimer levels. These patients were admitted to a non-ICU level of care setting. While there were no significant differences in the key composite outcomes of death, invasive or noninvasive mechanical ventilation, or ICU hospitalization, the therapeutic anticoagulation group exhibited a considerably lower all-cause mortality rate (1.8% vs. 7.6%, odds ratio 0.22, 95% confidence interval 0.07 to 0.65; p = 0.006). There was no observed elevation in significant hemorrhaging among the therapeutic anticoagulation cohort [34].

The investigation of anticoagulation's involvement in outpatients has also encompassed examining thrombosis concerns within this subset of patients. The ACTIV 4B trial conducted a comparative analysis of antithrombotic and anticoagulant treatments in symptomatic individuals diagnosed with COVID-19, specifically focusing on patients receiving care outside of a hospital or clinical setting. The trial had four cohorts: the low-dose aspirin group, the 2.5 mg apixaban group, the 5 mg apixaban group, and the placebo group. All cohorts had comparable primary outcomes, which encompassed a combination of all-cause mortality, symptomatic venous or arterial thromboembolism, and hospitalization due to pulmonary and cardiovascular events, such as myocardial infarction and stroke. There were no instances of significant hemorrhaging [35].

In a separate multicenter trial conducted in Brazil, the administration of Rivaroxaban upon discharge in patients with a high susceptibility to venous thromboembolism resulted in a decrease in the likelihood of experiencing venous or arterial thromboembolic events, as well as cardiovascular mortality within 35 days[37].

5. Conclusions

Rivaroxaban 20 mg once daily as a prophylactic option for COVID-19 with moderate to severe appears to be safe and effective.

Author contribution

Conceived and designed the analysis (Dhiaa Al-Saadde, Oday Alsawad); Collected the data (Dhiaa Al-Saadde, Oday Alsawad); Contributed data or analysis tools (Dhiaa Al-Saadde, Oday Alsawad); Performed the analysis (Dhiaa Al-Saadde, Oday Alsawad); Wrote the paper (Dhiaa Al-Saadde, Oday Alsawad).

Conflict of interests

None

Funding

None

Ethical consideration

All procedures performed in the study were per the ethical standards of the institutional research committee of the Department of Internal Medicine, Basra Educational Hospital (code number: IB-2021-032), and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed written consent was obtained from all participants in this study.

Informed consent

Written informed consent was acquired from all individual subjects included in the study.

Data and materials availability

The datasets obtained during this work can be obtained by making a reasonable request to the corresponding author.

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