



Observational study on safety and efficacy of rivaroxaban in covid-19 and post covid-19 patients

Abstract

Background: Rivaroxaban used to treat the coagulation is prescribed for covid 19 and post covid 19 (viral pneumonia and LRTI). To study the role of rivaroxaban in subjects with covid 19 and post covid 19 and assess the role of Rivaroxaban in covid 19 and post covid 19 subjects (LRTI or Viral pneumonia). To check the D DIMER value pre and post-giving Rivaroxaban.

Methodology: A total of hundred subjects were taken between the age of eighteen to eighty years having increased d dimer in covid-19 and post covid-19 subjects. The subjects were prescribed rivaroxaban with the dose of 10 mg orally administered once a day. The d-dimer is checked prior to the drug administration and after taking rivaroxaban.

Results: A rapid reduction in d-dimer values occurred from the administering the drug. It is observed statistically that the rivaroxaban prescribed is safe and effective in managing coagulation of covid19 and post covid-19 subjects.

Conclusion: This study confirms that the Rivaroxaban is desirable for subjects having coagulation during covid19 or post covid-19.

Keywords: case report • sneddon syndrome • cerebral venous sinus thrombosis • livedo reticularis rash

Introduction

Coronavirus Disease 2019 (COVID-19), caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), has developed into a pandemic disease and affected nearly every country in the world. There is no comprehensive and strong clinical evidence to support the efficacy of any drugs that specifically target the SARS-CoV-2 [1].

Previous research has found that coagulopathy is very common in COVID-19 patients, and includes thrombosis and coagulation abnormalities and dysfunction such as an elevated D-dimer level and prolonged Prothrombin Time (PT), respectively [2].

Autopsy histopathologic analysis has identified widespread thrombosis and microangiopathy in small vessels and capillaries of the lung, which are different from the pathologies observed in respiratory failure caused by other diseases [3-8]. Some scholars have therefore proposed Anticoagulation (AC) treatment as an integral part of systemic therapy in the early stage of COVID-19 [9].

Generally, retrospective studies have suggested that AC may decrease mortality in COVID-19 patients. However; these conclusions are not completely reliable nor applicable to all COVID-19 patients due to limitations in methodology such as no prospective control or matching cohort, large heterogeneity in anticoagulant therapy, and a lack of subgroup analysis [9-13].

Methodology

This study is an observational study and is proposed to be conducted for a duration of 6 months. Subjects includes who are visiting RVM Hospital, diagnosed with Covid 19, and are on treatment with rivaroxaban. The study will be conducted at RVM hospital. A total of 100 samples will be taken for the study from the various departments of the hospital and inclusion criteria for the sample was subjects with covid symptoms are considered and subjects with D-Dimer more than 500 will be considered. Exclusion criteria for the study includes children under the age of fifteen years are not considered, pregnant and lactating women are not considered. Data was collected through the

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patient profile forms from MDR and Wards. The Institutional Human Ethical Committee of GCPK approved the study.

■ Statistical analysis

Descriptive statistics presentation of data in Bar chart, Pie chart values are expressed as Frequency, percentage, mean, SD, and SE. Comparison of mean D DIMER values Pre and post- study groups by using paired Student t-test. In all analysis, $P < 0.05$ was considered to be significant. All statistical analyses were performed using SPSS statistical software, version 22.

Results

■ Statistical analysis

Descriptive statistics presentation of data in Bar chart, Pie chart values are expressed as Frequency, percentage, mean, SD, and SE. Comparison of mean D DIMER values Pre and post-study

groups by using the paired Student t-test (Figure 1-7). In all analysis, $P < 0.05$ was considered to be significant. All statistical analyses were performed using SPSS statistical software, version 22 (TABLE 1-14).

Discussion

A recently completed Randomized Controlled Trial (RCT) found that, compared with usual-care thromboprophylaxis, an initial strategy of therapeutic-dose anticoagulation did not result in a higher probability of survival in critically ill COVID-19 patients [14].

The conclusion of this RCT may be inconsistent with that of previous retrospective studies. At present, the recommendations for empiric systemic AC treatment currently differ between COVID-19 management guidelines, with some recommending using anticoagulant drugs preventively for patients who have no contraindications to AC and a significantly

FIGURE 1. Pie diagram representing.

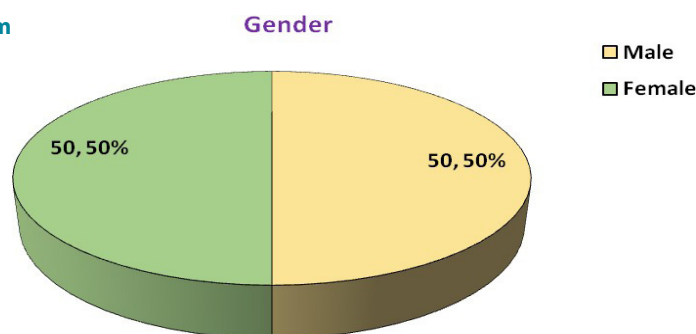


TABLE 1. Gender distribution.

GENDER	Frequency	Percent
Male	50	50
Female	50	50
Total	100	100

TABLE 2. Distribution by disease.

DISEASE STATE	GENDER	Frequency	Percent
COVID19	Male	48	96
	Female	2	4
	Total	50	100
POST COVID19	Male	48	96
	Female	2	4
	Total	50	100

TABLE 3. Distribution by age.

Age (Years)	Frequency	Percent
20 to 30	23	23
31 to 40	21	21
41 to 50	19	19
51 to 60	16	16
More than 60	21	21
Total	100	100

FIGURE 2. Graph representing Table 3.

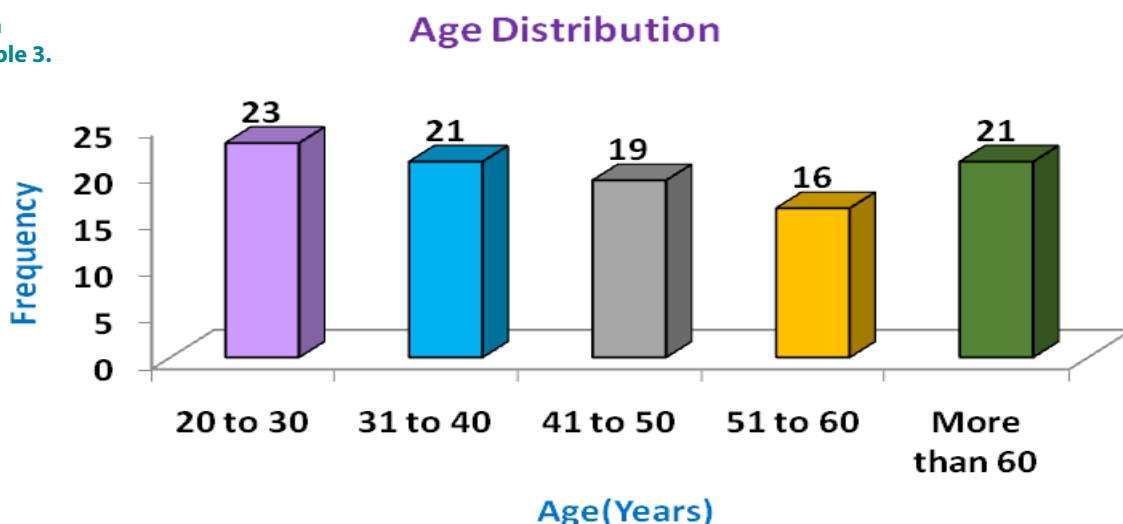


TABLE 4. Disease State Based on Age.

DISEASE STATE	Age(Years)	Frequency	Percent
COVID19	20 to 30	13	26
	31 to 40	12	24
	41 to 50	12	24
	51 to 60	7	14
	More than 60	6	12
	Total	50	100
POST COVID19	20 to 30	10	20
	31 to 40	9	18
	41 to 50	7	14
	51 to 60	9	18
	More than 60	15	30
	Total	50	100

FIGURE 3. Graph representing Table 4

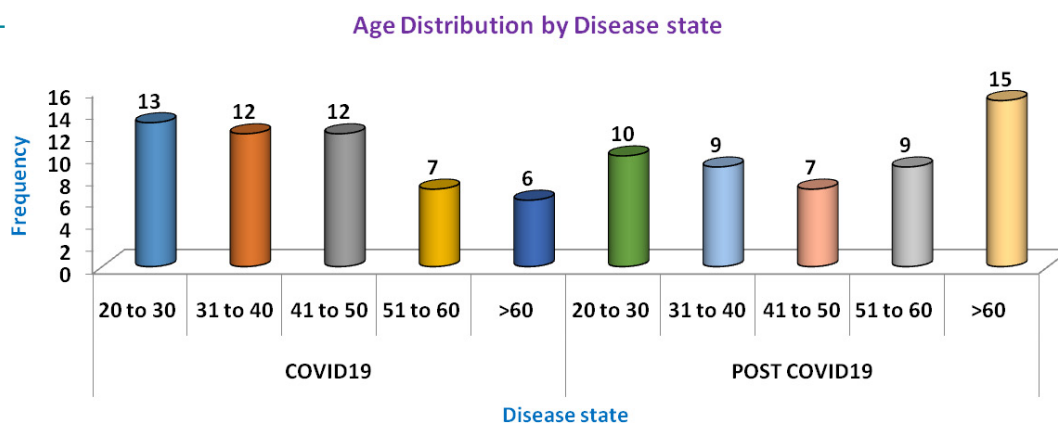


TABLE 5. Age SD

Parameter	N	Minimum	Maximum	Mean	SD
AGE(years)	100	20	80	45.86	16.05

TABLE 6. D-dimer value based of severity of disease state

D DIMER Prior drug	Frequency	Percent
Normal	0	0
Mild	1	1
Moderate	62	62
Severe	37	37
Total	100	100

FIGURE 4. graph representing Table 6.

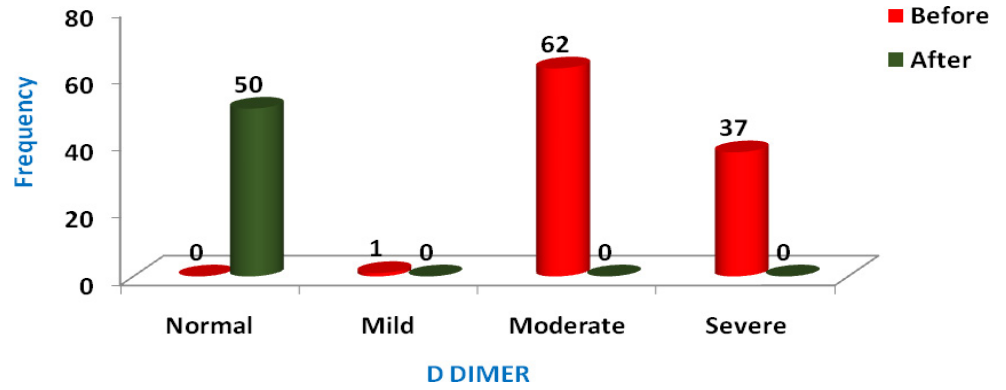


TABLE 7. SD of D-Dimer

D DIMER	Mean	N	SD	Std. Error Mean
Pre	5228.58	100	2516.56	251.66
Post	292.03	100	108.4	10.84

TABLE 8. Disease state vs D-dimer

DISEASE STATE	D DIMER	Frequency	Percent
COVID19	Normal	0	0
	Mild	1	2
	Moderate	27	54
	Severe	22	44
	Total	50	100
POST COVID19	Normal	0	0
	Moderate	35	70
	Severe	15	30
	Total	50	100

FIGURE 5. Graph representing Table 8

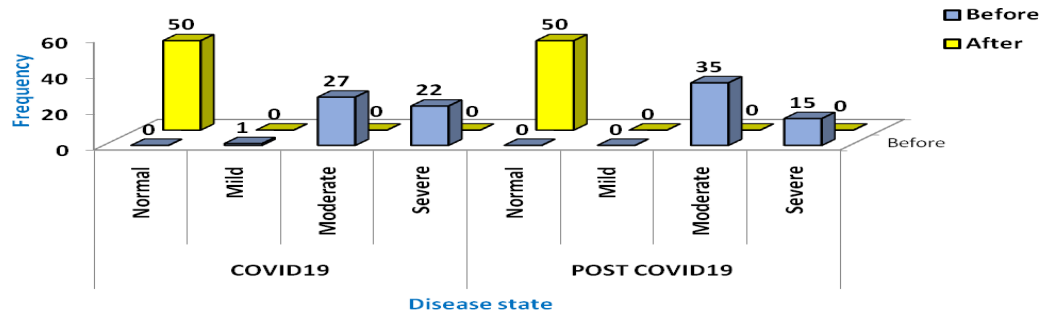


TABLE 9. SD, Std error, mean of d-dimer

D DIMER	Mean	N	SD	Std. Error Mean
Pre	5228.58	100	2516.56	251.66
Post	292.03	100	108.4	10.84

TABLE 10. Mean difference and t-value of d-dimer.

D DIMER	Mean	Mean difference	t-value	Significance
Pre	5228.58±2516.56	4936.55	19.81	0.0001*
Post	292.03±108.40			

*- P<0.05; mean D DIMER values are statistically significant between Pre and Post by using paired Student t-test.

FIGURE 5. Bar diagram representing Table 10



TABLE 11. SD, Std error, Mean difference of D-Dimer pre and post administration of the drug

DISEASE STATE	D DIMER	Mean	N	SD	Std. Error Mean
COVID19	Pre	5304.68	50	2373.4	335.65
	Post	258.88	50	104.12	14.73
POST COVID19	Pre	5152.48	50	2674.05	378.17
	Post	325.18	50	103.23	14.6

TABLE 12. T-Value and D-Dimer significance pre and post administration of Rivaroxaban

DISEASE STATE	D DIMER	Mean	Mean difference	t-value	Significance
COVID19	Pre	5304.68±2373.40	5045.8	15.34	0.0001*
	Post	258.88±104.12			
POST COVID19	Pre	5152.48±2674.05	4827.3	12.8	0.0001*
	Post	325.18±103.23			

*- P<0.05; In both Covid19 and Post covid19 the mean D DIMER values are statistically significant between pre and post-drug by using paired Student t-test.

FIGURE 6. Bar diagram representing Table 12

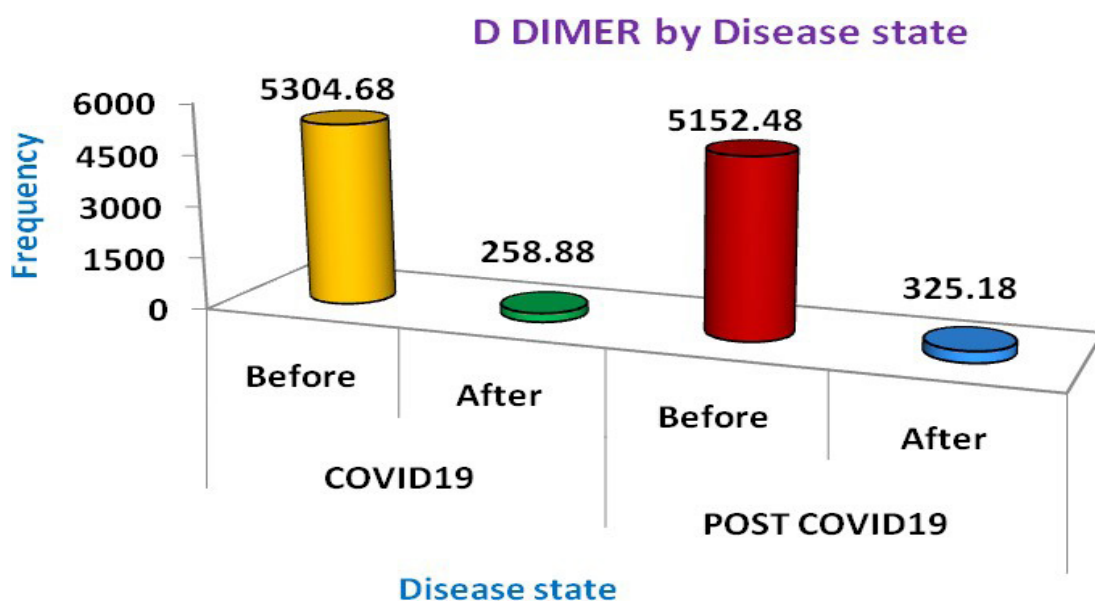


TABLE 13. Mean duration and SD of treatment.

Parameter	N	Minimum	Maximum	Mean	Std. Deviation
DURATION OF TREATMENT	100	5	11	5.92	1.41

TABLE 14. Mean duration and SD for Covid 19 and post Covid 19

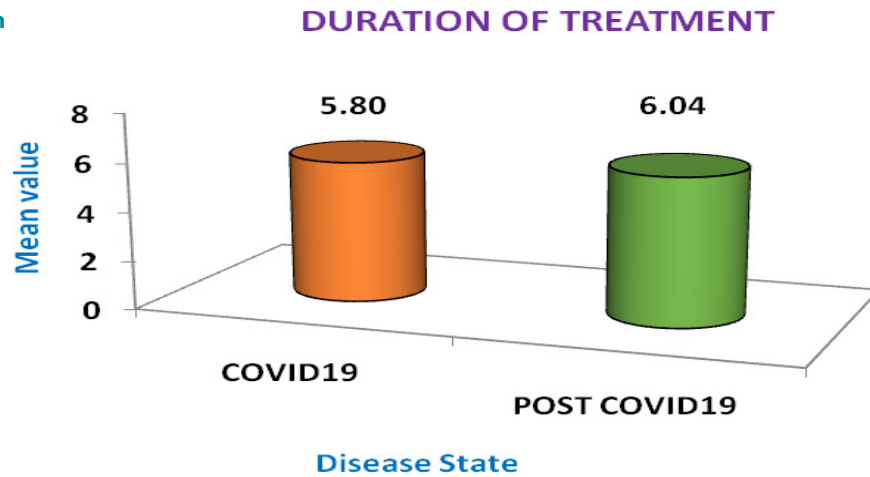
DISEASE STATE	Parameter	N	Minimum	Maximum	Mean	SD
COVID19	DURATION OF TREATMENT	50	5	9	5.8	1.25
POST COVID19	DURATION OF TREATMENT	50	5	11	6.04	1.56

increased D-dimer level, while others recommend that all hospitalized adults with COVID-19 should receive pharmacologic thromboprophylaxis with Low Molecular Weight Heparin (LMWH) rather than Unfractionated Heparin (UFH) [15-17].

We conducted a retrospective cohort study using a comprehensive database of COVID-19 patients to investigate whether AC treatment was protective and safe for COVID-19 patients. Innovative analyses using Propensity Score

Matching (PSM) and Inverse Probability Of Treatment Weighting (IPTW) were performed to balance baseline covariates, variates related to AC treatment assignment and variates related to the outcome between patients with or without AC treatment. Further sensitivity analyses were carried out to explore the association between outcome and duration, dosage and type of AC treatment. The second aim of the study was to identify the patients who benefited most from AC treatment using subgroup analysis that involved

FIGURE 7. Bar diagram representing Table 14



stratifying the data according to the severity of the Acute Respiratory Distress Syndrome (ARDS), COVID-19 clinical classification, and D-dimer levels. Taking into account the heterogeneity of the patients, clinically relevant patient subpopulations were identified by unsupervised machine learning algorithms. The effectiveness of AC treatment was verified further in identified clusters [17, 18].

COVID-19 infections have affected patients globally. The ISTH pointed out that COVID-19 patients develop a clinically significant coagulopathy, characterized by thrombocytopenia, mildly prolonged prothrombin time, and elevated serum D-dimer levels [27]. Recent research indicates that coagulopathy is not only common in COVID-19 patients but is also associated with increased mortality. The potential mechanism for the development of coagulopathy in COVID-19 patients may be related to endothelial cell dysfunction and hypoxia-induced thrombosis following a SARS-CoV-2 infection. Because the endothelium plays an important role in regulating hemostasis, fibrinolysis, and vessel wall permeability, endothelial dysfunction in pulmonary microvessels may act as a trigger for immunothrombosis, resulting in coagulopathy. Histological analysis of pulmonary vessels in COVID-19 patients shows more widespread thrombosis with microangiopathy compared to that observed in patients with influenza. Based on this preliminary evidence, AC treatment may be beneficial for COVID-19 patients by inhibiting thrombin generation and thereby reducing mortality. The ISTH suggests that a prophylactic dose of LMWH should be considered in all patients without contraindications. Moreover, the Chinese Diagnosis and Treatment Protocol for COVID-19 Patients (Version 8.0), also suggested using AC treatment in selected patients. However, these recommendations

require additional clinical evidence to determine the association between AC treatment and the outcome of COVID-19 patients, and also to clarify the indications, contradictions and optimal duration, dose, and time to use AC. We conducted this matched cohort study using a comprehensive source of COVID-19 patients. In general, results showed that receiving AC treatment was associated with a decreased in-hospital mortality in these patients. Although patients who received AC treatment exhibited a significant increase in CRNMB and microscopic hematuria, they had no increase in the incidence of major bleeding. A clinical subgroup analysis was also carried out to identify patient subgroups who receive greater benefit from AC treatment. At hospital admission, patients of severe COVID-19 clinical cases, patients with mild ARDS or patients who had a D-dimer level $\geq 0.5 \mu\text{g/mL}$ were more likely to benefit from AC therapy. During hospitalization, patients who developed severe ARDS or critical COVID-19 cases were more likely to benefit from AC therapy. Results of clusters identified by unsupervised machine learning revealed similar results as of clinical subgroups. Critical patients of cluster 3 could benefit from AC treatment whereas non-critical patients in clusters 1 and 2 did not. Nevertheless, a sub-phenotype (cluster 4) exhibited even severe multiple organ dysfunction and excessive inflammation might not benefit from AC therapy [9, 19-37].

To date, several research works have investigated systemic AC therapy in COVID-19 patients. Although the results generally suggested that AC treatment was associated with lower mortality of COVID-19 patients, a constant instruction for clinic application was not easy to conclude. Several possible reasons are worth to be noted. As a retrospective cohort study, imbalance of baseline covariates, covariates related to outcome and covariates related to exposure assignment might

lead to biased results [9, 10]. Among the existing studies, some studies used propensity score methods for reducing the effects of confounding, some did not. In our study, we applied PSM which yield a relatively balanced cohort. We also did IPTW analysis, another propensity score method, to detect the selective bias potentially caused by PSM in the full cohort. The results from PS matched cohort and IPTW analysis in the full cohort both revealed that AC treatment was associated with lower death risk. We also noted that, without the PS method, either the crude results or baseline-adjusted results will lead to an adverse conclusion. Immortal time is a gap period between exposure (usually the span after cohort follow-up) and initiation of follow-up [12, 13]. This might cause potential immortal time bias and exaggerate the association between the exposure and outcome. As a result, we carried out a Cox proportional hazards model with a time-dependent manner for the drug exposure in this study [20, 38, 39].

Another key question concerns the confounders involving various durations, dosages and types of AC treatment. In a retrospective cohort study from the Mount Sinai Health System, the duration of hospitalization (median 5 days, IQR 3-8 days) and the course of AC treatment (median 3 days, IQR 2 days-7 days) were relatively short. Within the current consensus on anticoagulant therapy for venous thromboembolism, it is generally considered that patients with confirmed deep vein thrombosis or pulmonary embolism need LMWH treatment for at least 5 days followed by Dabigatran or Edoxaban. As a new disease without comprehensive study until now, to determine the optimal duration, type and dosage of AC treatment need more evidence. In our study, we conducted a series of sensitivity analyses to investigate the relationship between outcome and AC treatment duration, dosage and type. We found that AC treatment for 7 days or longer was associated with a lower death risk while AC treatment for <7 days was not. Low dose thromboprophylaxis, intermediate dose thromboprophylaxis and therapeutic dose anticoagulation were all associated with lower death risk. Although we recorded detailed AC treatment type, the majority was LMWH, we only investigated LMWH and non-LMWH for sensitivity analyses here. It is revealed that both LMWH and non-LMWH treatment were associated with a lower death rate [11, 40].

The heterogeneity of the research population is another vital confounder that influences the results. In our study, we analyzed a full cohort of unselected patients from two designated hospitals

including mild to critical cases. In general, we found that AC treatment was associated with low mortality, which had a constant result with the previous studies. Furtherly, we investigated who might benefit from AC treatment in subgroup analyses. The stratification criteria used in our study included the most frequently used classification of clinical severity of the COVID-19 patients. It is well-known that hypoxia is a core clinical manifestation and major pathophysiology change that contributes to the death of COVID-19 patients. The classification of both ARDS and COVID-19 clinical severity classification indicates the severity of hypoxia and accordingly, they are used frequently by clinicians to evaluate and triage patients and to decide major treatments (e.g., levels of oxygen therapy). As a result, we stratified patients according to ARDS classification, COVID-19 clinical classification, and D-dimer levels at both hospital admission and during hospitalization [9, 12]. By this strategy, we found that, at admission, severe cases of COVID-19 clinical classification, mild ARDS cases and patients with a D-dimer level $\geq 0.5 \mu\text{g/mL}$ may benefit from AC [17, 18, 29]. While during the hospital stay, critical cases and severe ARDS cases may benefit from AC. These results were in constant with Sun et al.' study with severe cases and subgroup analysis from Shen et al. and CORIST Studies [39, 41-45].

Clustering the study population may help minimize the influence of heterogeneity on the results. The traditional way to categorize patients is based on pre-defined standards. The standards are usually defined by a group of experienced experts with a strong background and prior knowledge in the medical area. Therefore, the procedure for generating the standards alone takes considerable effort and time. In addition, these standards cannot easily be quickly established or updated for a new situation in a short period, which was apparent when we faced this new pandemic, COVID-19. Unsupervised clustering algorithms in machine learning offer another perspective to perform the identification of data subclasses. Unsupervised clustering approaches can achieve more stable and robust clustering results without any prior knowledge of the meaning of each variable in the data. In addition, it may also identify some intrinsic correlations between the variables which sometimes cannot be easily noticed by human experts. Considering the heterogeneity of COVID-19 patients, an innovative strategy was carried out to identify subphenotype of patients who exhibited distinct clinical characteristics and respond to certain treatment using unsupervised learning approach.

To this end, a four-class PAM-based clustering model was established, representing four distinct COVID-19 patient subphenotypes with different clinical characteristics. In particular, clusters 1 and 2 were non-critical cases with significantly lower mortality. Patients in these two clusters did not benefit from AC treatment. Clusters 3 and 4 were critical cases both exhibited significant abnormal laboratory testing results at admission and unstable vital sign. Cluster 3 had mild to moderate ARDS at admission and progressed to severe ARDS during the hospital stay. Patients in cluster 3 can benefit from AC treatment and had no significant increase in bleeding events. Compared to cluster 3, cluster 4 was the most critical cases and has the highest mortality. A novel result by the clustering approach was that, among these most critical patients (clusters 4), who had moderate or severe ARDS at admission and developed severe ARDS during the hospital stay, AC treatment was not associated with a lower death risk. Further characteristic analysis of these clusters revealed cluster 4 was characterized by multiple organ dysfunction and excessive inflammation. This led us to conclude that critical COVID-19 patients with these features cannot benefit from AC treatment. Recently, an open-label, adaptive, multiplatform, randomized control trial was published, with the researchers noting that the initial strategy of therapeutic-dose anticoagulation did not result in a greater probability of survival in critically ill COVID-19 patients (defined as COVID-19 that led to the receipt of ICU-level respiratory or cardiovascular organ support in an ICU) compared to usual-care thromboprophylaxis. This result was different from our clinical subgroup analysis but similar to the phenotypes of clusters 4 in our unsupervised clustering analysis [14, 46].

Analysis of safety endpoints showed that although the risk of bleeding events, including CRNMB and microscopic hematuria, were higher in the AC group compared to the non-AC group, there was no significant difference in the risk of major bleeding events or thrombocytopenia between the two groups. In brief, the above findings suggested that the use of AC treatment for 7 days or longer in hospitalized COVID-19 patients was associated with increased CRNMB and microscopic hematuria but not with other bleeding events, especially major bleeding. These key observations are consistent with those reported in recent studies. Although the competing risk model analysis in this study revealed that there was no significant difference in bleeding risk between the AC and non-AC groups when considering death as a competitive

event, the increase of CRNMB still reminds clinicians should be more cautious when using anticoagulation treatment [11, 39].

This study had several limitations. Firstly, as a retrospective cohort study, imbalanced confounders and selective bias may exist. Large-scale, multicenter, randomized, controlled trials are urgently needed to fully assess the efficacy of AC in patients with COVID-19. Besides, our unsupervised clustering model did not take the importance of each variable into consideration, as it treated all the variables equally as numerical values and measured the similarity between patients based on geometric distance. However, the variables could have completely different semantic meanings. Therefore, it is still necessary for human experts to inspect the clustering results to make sure that the results are explainable. Future work could be to intrinsically integrate the importance of clinic variables into the similarity measurements of unsupervised cluster models.

■ Strengths

As the study was conducted in 2021-2022, covid 19 cases are high in this period, that helped to know the efficacy and safety of rivaroxaban more in the ground levels. Rivaroxaban is an anticoagulant used widely in recent days when compared to warfarin as it has lesser side effects which became helpful for our study.

■ Limitations

There are certain limitations to our study which include:

- The small size of the subjects consisting 100 subjects.
- This study was primarily limited to the covid department as we know covid 19 is infectious it restricts us from patient counseling or patient education and ward visits.
- As only the D-dimer parameter for coagulation is considered in covid 19 and post covid 19 subjects, the subjects are limited to a small group of individuals.
- As our study is based on the safety and efficacy of rivaroxaban particularly, the subjects who are receiving other anticoagulants are not taken and are restricted to the small group.
- As our study is on anticoagulant (RIVAROXABAN), the post covid 19 subjects with symptoms other than symptoms of thrombotic events are not considered.

Conclusion

The subject's D-dimer levels are marked pre and post the drug use. The D-dimer levels which indicate coagulation are decreased drastically post administration of rivaroxaban-10 mg/OD. Out of 100 subjects, 50 subjects were covid 19 subjects and 50 subjects were post covid 19(LRTI or viral pneumonia) with higher D-dimer values which indicate coagulation. Post administration of RIVAROXABAN-10 mg/OD, there is a rapid decrease in the D-dimer values.

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None

Conflict of interest

The authors declare that there is no conflict of interest.

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