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ORIGINAL ARTICLE

Therapeutic versus Prophylactic Anticoagulation with Low Molecular Weight Heparin for Moderate COVID-19 Patients

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ABSTRACT

Background: COVID-١٩ is linked to an increased susceptibility to thrombotic problems, but the effectiveness of therapeutic-dose anticoagulation is uncertain. The research aim was to detect whether the therapeutic-dose anticoagulation improves clinical status of moderate Covid 19 patients in comparison to prophylactic dose anticoagulation.

Methods: The protocol for this trial was approved by the institutional review board of Menoufia university (trial registration No.:12/2021 ANET 23). This study is a prospective randomized comparative trial included 70 patients with moderate COVID-19 assigned into group A (receiving therapeutic anticoagulation with subcutaneous low-molecular-weight heparin (LMWH) at a dose of 1 mg/kg twice daily) and group B (receiving thromboprophylaxis with subcutaneous LMWH at a dose of 40 mg once daily). The primary aim was to assess the clinical status on an ordinal scale of 8 points from world health organization.

Results: Patients on group A were well matched with the patients on group B regarding the efficacy outcome (clinical status assessed by World Health Organization (WHO), laboratory data , 28-day mortality and the length of hospital stay) except the D-dimer level at week 2 that was elevated in group B than in the group A (2200 vs 1100 ng/mL, $P<0.05$), as well as the result of PaO_2/FiO_2 which were higher on week 2 in the group A (190 vs 145 respectively, $P<0.05$).

Conclusions: The prophylactic anticoagulation had priority over the therapeutic one in the treatment of moderate COVID-19 individuals as the therapeutic dose had no impact on either the clinical status assessed by WHO scale or overall mortality rate.

Key words: Anticoagulation; Coagulopathy; Heparin; Mortality; Thrombosis.

INTRODUCTION

Individuals diagnosed with COVID-19 have an increased susceptibility to thromboembolism. Venous thromboembolism (VTE) and arterial thrombotic events (ATE) are commonly seen in COVID-19 patients who are hospitalized, and both complications contribute to the elevated mortality rate in these individuals. [1].The total incidence of VTE in patients with COVID-19 is 21 percent, with a greater prevalence observed in those referred to the Intensive Care Unit (ICU). Moreover, the combined death rate is 23 percent for individuals with VTE & 13 percent for those without VTE. [2]

The circulatory condition, characterized by impaired function of the endothelium, increased blood clotting, and activation of the clotting factors, results in a higher likelihood of both small and large blood vessel blockages. The blockage of small blood vessels may potentially contribute to the widespread lung damage observed in COVID-19 patients. Systemic inflammatory and coagulation activation indicators, such as d-dimer and C-reactive protein, are directly associated with an increased risk of respiratory failure, thrombosis, and mortality in individuals diagnosed with COVID-19.[3, 4]

Some COVID-19 advice statements have included therapeutic dosage anticoagulation regimens for critically sick patients, based on data indicating an elevated risk of thrombosis. Nevertheless, the efficacy and safety of using therapeutic-dose anticoagulation to enhance results in COVID-19 remain questionable.[5]

The aim of this study was to detect whether an initial strategy of therapeutic-dose anticoagulation improves clinical results of moderate COVID-19 patients in comparison to prophylactic dose anticoagulation.

METHODS

This prospective comparative single blinded randomized trial by envelope technique was conducted from December 2021 to April 2022 on 70 adult patients with COVID-19 through their admission to Chest and ICU department at Menoufia University hospitals after a written informed consent from patient's legal surrogates and the approval of the institutional review board (IRB) of Menoufia university (trial registration No.: 12/2021 ANET 23).

Sample size was calculated to achieve an estimated power of 80%, and confidence level of 95% and an effect size based on review of the past literature (Elmelhat et al, 2020) that found that 38.5% of the patients on therapeutic group anticoagulation needed mechanical ventilation in comparison to only 10 percent of prophylactic group patients which was statistically significant. A total sample size of 70 was calculated and divided into two equal groups.[6]

Inclusion criteria included patients with moderate SARS-CoV-2 on the ordinal scale of WHO diagnosed clinically by signs and symptoms (fever and lower respiratory symptoms) or laboratory and radiologically (imaging finding of pneumonia) and age ≥18 years. The points of the ordinal scale of WHO are mentioned in **(Table 1).**[7]

Exclusion criteria include patients with indication for therapeutic anticoagulation during randomization, active bleeding, factors associated with increased bleeding tendency (Platelet count less than 50 $x10^9$/L, INR greater than 2.0, or aPTT greater than 50), hemoglobin less than 7 gm/dL in the past 72 hours, previous occurrence of heparin induced thrombocytopenia (HIT) or other allergic reactions to heparin, ongoing use of dual antiplatelet medications, & pregnancy.

All cases received ICU protocol according to the patient's condition. All patients were monitored (non-invasive blood pressure, respiratory rate, heart rate & oxygen saturation).

Thorough Clinical examination was done and routine investigations (CBC, Full electrolyte, kidney, and liver function tests, ABGs and INR) were done.

Cases were separated into 2 equal groups: **Group A:** 35 cases received therapeutic-dose anticoagulation using low-molecular-weight heparin (specifically subcutaneous enoxaparin at a dosage of 1 mg/kg twice daily). This treatment was given for a maximum of fourteen days, or until the individuals showed signs of recovery, which was defined as either being discharged from the hospital or no longer requiring supplementary oxygen for a minimum of twenty-four hours **Group B:** 35 cases received usual-care thromboprophylaxis with low-molecular-weight heparin (subcutaneous enoxaparin at a dose of 40 mg once daily).

Patients were observed for significant bleeding, which was assessed based on the International Society of Thrombosis and Haemostasis (ISTH) criteria. This included lethal hemorrhage, bleeding in critical areas or organs, and a decrease in hemoglobin level of 2gm/dL or higher.[8] Anticoagulation was stopped, and the bleeding was treated as indicated when any major bleeding occurred.

All patients were monitored for major thrombotic events including Deep Venous Thrombosis (DVT) (clinical, colour Doppler if symptomatic), pulmonary embolism (clinical, CT Pulmonary angiography, ECHO), Stroke (clinical, brain imaging), Myocardial Infarction (MI) (clinical, Lab, ECHO). Patients in prophylactic anticoagulation group who developed major thrombotic events were shifted to therapeutic anticoagulation or fibrinolysis as indicated.

Demographic data (Age, sex, and BMI) and comorbidities if present at baseline, laboratory investigation (CBC, Full electrolyte, kidney function tests, liver function tests, INR, D-dimmer, serum ferritin, procalcitonin and CRP), Clinical status assessed by ordinal scale of 8 points from world health organization at day 0, 7, 14., major thrombotic events (DVT, PE, Stroke and MI) and major bleeding according to ISTH. Need for renal replacement therapy, need for mechanical ventilation, length of hospital stays, need for vasopressors and 28-day mortality were monitored and recorded.

STATISTICAL ANALYSIS

The statistical analysis was conducted using SPSS version 28 (IBM Co., Armonk, NY, USA). The study presented quantitative parametric data as mean and standard deviation (SD), which were analyzed using an unpaired Student t-test. The quantitative non-parametric data were presented as

median and interquartile range (IQR) and analyzed using the Mann Whitney-test. The categorical data were presented as frequency and percentage and analyzed using either the Chi-square test or Fisher's exact test. The overall survival analysis was calculated using the Kaplan-Meier curve with Log-rank test. Spearman's rank correlation coefficient was calculated to estimate the degree of correlation between two quantitative variables. A linear regression analysis was conducted to evaluate different factors related to the WHO scale for clinical status. A logistic regression analysis was conducted to evaluate different factors related to thromboembolic events. A two-tailed P value less than 0.05 was deemed to be statistically significant.

RESULTS

The trial profile describing subjects flow was shown in the study's flowchart **(Figure 1).** One hundred and five patients were assessed for their eligibility, and 35 patients have been excluded. Seventy patients were eligible and were randomly allocated into 2 equal groups. No dropouts were reported in our study.

The baseline data was statistically insignificant between both treatment arms regarding baseline demographics (age, sex distribution, BMI, comorbidities, time from symptoms onset) and baseline laboratory data (Hb, PLT, creatinine, BUN, ALT, INR, D-dimer, ferritin, procalcitonin, CRP and PaO_2/FiO_2) ($P>0.05$). The mean time from symptoms onset to hospital admission was 8.4 ± 1.14 days in group A and 8.2 ± 1.11 days in group B. **(Table 2).**

Regarding the efficacy outcome assessed by the ordinal scale of WHO, laboratory data, 28- day mortality, and the length of stay, all the studied patients (35 or 100% of both groups) had WHO clinical status score of 3 indicating moderate clinical status at baseline. After one week of treatment, 20 patients (57.2%) of the therapeutic group (group A) became critical compared to 24 patients (68.6%) of prophylactic group (group B), as well as 15 patients (42.9%) of group A became severe compared to 11 patients (31.4%) of group B. After two weeks, 7 patients (20%) of group A improved from critical and severe degree and returned to moderate status which is less observed in group B and occurred only in 3 patients (8.6%). Inspite of showing an improvement of the clinical status on group A rather than the group B after 2 weeks but with no statistically significant difference observed ($P>0.05$)**. (Table 3a).** Regarding the lab data, CBC, kidney function test, liver function test, INR, procalcitonin and ferritin evidenced no statistically significant difference among both groups at any timepoint ($P>0.05$). **(Table 3b).**

As for D-dimer, it was insignificantly different at baseline (1850 ng/mL in group A vs 1500 ng/mL in group B) and after one week (1500 vs 2400 ng/mL respectively), meanwhile, we observed a significant difference after 2 weeks as it was lower in group A in comparison to group B (1100 vs 2200 ng/mL, $P<0.05$). **(Table 3b).** PaO_2/FiO_2 level was insignificantly different between both groups at baseline (385 in group A vs 386 in group B) and after one week (173 vs 170, respectively), but after 2 weeks, patients on group A elicited significantly increased PaO_2/FiO_2 ratio than those on group B (with a median of 190 vs 145 respectively, $P<0.05$). **(Table 3b).**

Regarding 28-day mortality as an efficacy outcome, we didn't observe any statistically significant difference between both groups regarding 28-day mortality (10 pt (28.6%) of group A vs 15 pt (42.9%) of group B) ($P>0.05$). Also, no statistically significant difference was detected among groups A & B regarding length of hospital stay. (**Table 3c).**

Regarding safety outcome assessed by respiratory, hemodynamic, renal, and hematological parameters, the occurrence of thromboembolic events was insignificantly different among groups A and B (1 patient (2.9%) vs 5 patients (14.3%), ($P>0.05$). No statistically significant difference was noted among groups A & B regarding vasopressors need, need for MV, and renal replacement therapy. Also, only 3 patients (8.6%) of group A experienced major bleeding, with no statistically significant difference among the 2 groups. Noteworthy, no cases in either group had Heparin Induced Thrombocytopenia (HIT) ($P>0.05$). **(Table 4).**

Table (1): WHO ordinal scale for clinical Improvement.

Patient state	Descriptor	Score
Uninfected	No clinical evidence of infection	0
Mild	No limitation of activities	1
	Limitation of activities	2
Moderate	Hospitalized, no oxygen therapy	3
Severe	Oxygen by mask or nasal prongs	4
Critical	Non-invasive ventilation or high-flow oxygen	5
	Intubation and mechanical ventilation	6
	Ventilation + additional organ support-vasopressors, Renal Replacement Therapy, Extracorporeal membrane oxygenation	7
Dead	Death	8

Table (2): Baseline data of the studied groups.

			Group A (n=35)	Group B (n=35)	P value
Age (years)		**Mean ± SD**	57.49 ± 13.25	56.74 ± 15.49	0.83
		Range	25 - 83	24 - 90	
Sex	**Male**		17 (48.6%)	21 (60%)	0.337
	Female		18 (51.4%)	14 (40%)	
BMI (kg/m2)		**Mean ± SD**	31.57 ± 4.2	32.34 ± 4.51	0.462
		Range	25 - 43	24 - 43	
Comorbidities	**DM**		12 (34.3%)	14 (40%)	0.621
	HTN		18 (51.4%)	16 (45.7%)	0.632
	Liver disease		1 (2.9%)	3 (8.6%)	0.614
	Malignancy		2 (5.7%)	2 (5.7%)	>0.99
	Chest disease		7 (20%)	4 (11.4%)	0.324
	Cardiac disease		5 (14.3%)	2 (5.7%)	0.428
Time from symptoms onset to hospital admission (days)		**Mean ± SD**	8.4 ± 1.14	8.2 ± 1.11	0.459
		Range	7 - 10	7 - 10	
Laboratory data at baseline (day 0)					
Hb (g/dL)		**Mean ± SD**	11 ± 1.52	10.7 ± 1.58	0.43
PLT (x103cells/µl)		**Mean ± SD**	254.97 ± 69.06	234.91 ± 61.17	0.203
Creatinine (mg/dL)		**Median**	0.9 (0.5 - 1.1)	0.8 (0.6 - 1.1)	0.863
BUN (mg/dL)		**Median**	20 (16 - 22)	20 (18 - 26)	0.633
ALT (U/L)		**Median**	19 (17 - 23)	21 (18 - 25)	0.07
INR		**Median**	1.2 (1 - 1.3)	1.2 (1 - 1.3)	0.86
D-dimer (ng/mL)		**Median**	1850 (900 - 3100)	1500 (750 - 2900)	0.747
Ferritin (ng/mL)		**Median**	800 (600 - 1000)	700 (500 - 930)	0.304
Procalcitonin (ng/mL)		**Median**	0.01 (0.01 - 0.01)	0.01 (0.01 - 0.5)	0.174
CRP (mg/L)		**Median**	48 (12 - 96)	24 (12 - 48)	0.415
PaO2/FiO2		**Mean (Range)**	385 (365 - 400)	386 (370 - 400)	0.521

Group A: patients who received therapeutic anticoagulation, **Group B:** patients who received prophylactic anticoagulation, data are presented as frequency (%), mean ± SD or median (IQR) as appropriate**, BMI:** Body mass index, **DM:** Diabetes Mellitus, **HTN:** Hypertension, **Hb:** Hemoglobin, **PLT**: Platelets, **BUN**: blood urea nitrogen, **ALT:** Alanine transaminase**, INR**: International Normalized ratio.

Table (3a): Efficacy outcome of the studied groups by Clinical status assessment (by ordinal scale of WHO).

		Group A (n=35)		**Group B (n=35)**		**P value**
Day 0						
Moderate (3)		35 (100%)		35 (100%)		---
Scale		3 (3 – 3)		3 (3 – 3)		>0.999
Day 7						
Severe (4)		15 (42.9%)		11 (31.4%)		
Critical	Critical (5) Critical (6) Critical (7)	17 (48.6%) 1 (2.9%) 2 (5.7%)	20(57.2%)	21 (60%) 3 (8.6%) 0 (0%)	24(68.6%)	0.182
Scale		5 (4 – 5)		5 (4 – 5)		0.42
Day 14						
Moderate (3)		7 (20%)		3 (8.6%)		
Severe (4)		10 (28.6%)		10 (28.6%)		
critical	Critical (5) Critical (6) Critical (7)	8 (22.9%) 2 (5.7%) 7 (20%)	17 (48.6%)	7 (20%) 4 (11.4%) 11(31.4%)	22(62.8%)	0.457
Death (8)		1 (2.9%)		0 (0%)		
Scale		5 (4 – 6)		5 (4 – 7)		0.207

Group A: patients who received therapeutic anticoagulation, **Group B**: patients who received prophylactic anticoagulation, data are presented as frequency (%) or median (IQR) as appropriate.

Table (3b): Efficacy outcome of the studied groups by laboratory data.

	Group A (n=35)	**Group B (n=35)**	**P value**
CBC			
Hb (g/dL)	10.7 ± 1.57	10.4 ± 1.63	0.441
PLT (x10^3cells/µl)	250.54 ± 72.4	233.64 ± 57.15	0.282
Kidney function			
Creatinine (mg/dL)	0.83 (0.65 - 1.09)	0.88 (0.64 - 1.19)	0.335
BUN (mg/dL)	19.88 (16.63 - 24.88)	22.38 (18.56 - 26.5)	0.272
Liver function			
ALT (U/L)	22.25 (17.63 - 29.63)	26 (19.75 - 30.63)	0.304
Coagulation profile			
INR			
Day 0	1.2 (1 - 1.3)	1.2 (1 - 1.3)	0.86
Day 7	1.1 (1 - 1.2)	1.2 (1 - 1.3)	0.117
Day 14	1.1 (1 - 1.2)	1.2 (1 - 1.3)	0.162
D-dimer (ng/mL)			
Day 0	1850 (900 - 3100)	1500 (750 - 2900)	0.747
Day 7	1500 (700 - 3000)	2400 (1100 - 3200)	0.107
Day 14	1100 (650 - 2000)	2200 (950 - 3500)	**0.008***
Inflammatory markers			
Ferritin (ng/mL)			
Day 0	800 (600 - 1000)	700 (500 - 930)	0.304
Day 7	900 (540 - 1250)	920 (620 - 1100)	0.805
Day 14	730 (300 - 1200)	1100 (530 - 1500)	0.169
Procalcitonin (ng/mL)			
Day 0	0.01 (0.01 - 0.01)	0.01 (0.01 - 0.5)	0.174
Day 7	0.01 (0.01 - 2.5)	0.4 (0.01 - 1)	0.902

	Group A (n=35)	Group B (n=35)	P value
Day 14	0.04 (0.01 - 0.9)	0.4 (0.01 - 1.5)	0.302
CRP (mg/L)			
Day 0	48 (12 - 96)	24 (12 - 48)	0.415
Day 7	96 (24 - 120)	96 (12 - 120)	0.406
Day 14	96 (12 - 120)	96 (12 - 160)	0.809
PaO_2/FiO_2			
Day 0	385 (365 - 400)	386 (370 - 400)	0.521
Day 7	173 (140 - 199)	170 (133 - 192)	0.321
Day 14	190 (100 - 250)	145 (70 - 230)	**0.024***

Group A: patients who received therapeutic anticoagulation, **Group B:** patients who received prophylactic anticoagulation, data are presented as mean ± SD or median (IQR) as appropriate, Hb: Hemoglobin, **PLT**: Platelets, BUN: blood urea nitrogen, ALT: Alanine transaminase, **INR:** International Normalized Ratio, **CRP**: C-reactive protein, *: Statistically significant as P value<0.05.

Table (3c): Efficacy outcome of the studied groups by hospital mortality and length of stay.

	Group A (n=35)	Group B (n=35)	P value
28-day mortality	10 (28.6%)	15 (42.9%)	0.212
Hospital stay (days)	21 (17 – 25)	20 (15 – 21)	0.153

Group A: patients who received therapeutic anticoagulation, **Group B:** patients who received prophylactic anticoagulation, data are presented as frequency (%) or median (IQR) as appropriate.

Table (4): Safety outcome of the studied groups regarding respiratory, hemodynamic, renal, and hematological parameters.

		Group A (n=35)	Group B (n=35)		P value
Thromboembolic manifestation	**Pulmonary embolism**	1 (2.9%)	2(5.7%)	5 (14.3%)	0.198
	DVT		2(5.7%)		
	Stroke		1(2.8%)		
Need for MV		24 (68.6%)	28(80%)		0.274
Need for vasopressors		9 (25.7%)	11 (31.4%)		0.597
Renal replacement therapy		2 (5.7%)	2 (5.7%)		>0.999
Major bleeding		3 (8.6%)	0 (0%)		0.239
HIT		0 (0%)	0 (0%)		---

Group A: patients who received therapeutic anticoagulation, **Group B**: patients who received prophylactic anticoagulation, data are presented as frequency (%), **MV**: Mechanical ventilation, **DVT**: Deep venous thrombosis, **HIT**: Heparin induced thrombocytopenia.

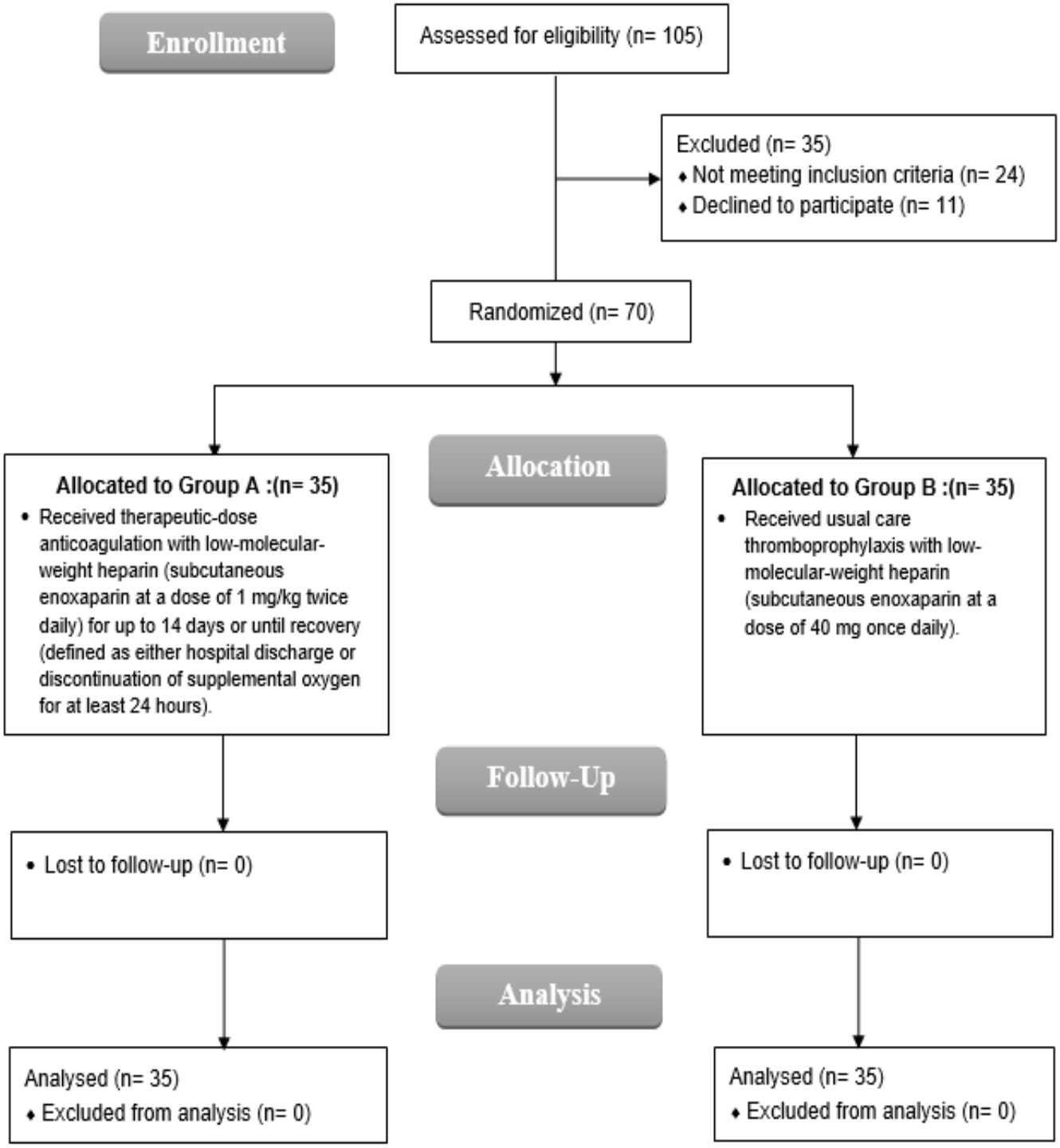

Figure (1): CONSORT flowchart showing patient progress through the study phases

DISCUSSION

The likelihood of thrombotic problems related to COVID-19 is significantly higher when compared to other respiratory infections, and the severity of these events is also significantly increased. Anticoagulation is a crucial aspect of treating COVID-19 patients. Our goal was to assess whether therapeutic anticoagulation could improve the clinical condition of patients and affect the mortality rate compared to using prophylactic anticoagulants in moderate COVID-19 cases.

In this study there was no statistically significant difference seen between the two groups in terms of age, sex distribution, BMI, time from symptoms onset, comorbidities, and baseline laboratory data**.**

The current study reported an improvement of

clinical status assessed by WHO scale in therapeutic group in comparison to prophylactic group as after one week of treatment, 20 cases of group A became critical in comparison to 24 patients of group B, but 15 cases of group A became severe in comparison to 11 patients of group B and after two weeks, 7 patients of group A improved and returned to moderate status which is less observed in group B & occurred only in 3 cases, and the critical patients were 17 cases in group A & 22 in group B. This improvement of clinical status may be correlated with the increased PaO2/FiO2 ratio in group B after 2 weeks. But this improvement was statistically insignificant for both groups. **Rauch-Kröhner et al.**[9] in an open-label, multicenter, randomized, clinical trial comparing prophylactic (n = 56) versus therapeutic anticoagulation (n = 55) also found that therapy with therapeutic dose in comparison to prophylactic dose was not linked to a significant improvement on the WHO ordinal scale at a week.

Regarding D-dimmer it was decreased after 2 weeks on both groups but with a significant decrease in therapeutic AC group (group A) compared to the prophylactic AC one (group B) (1100 vs 2200 ng/mL, $P<0.05$). This could be explained by decreased coagulation leading to decreased fibrin production and decreased D-dimer levels and this explanation was documented by **van der Wal et al.**[10] who studied the influence of heparin on D-dimer on COVID-19 patients. The findings are consistent with the research conducted by **Lemos et al.**[11] who conducted a randomized study involving 20 COVID-19 patients. The patients were divided into two groups: one receiving therapeutic enoxaparin and the other receiving thromboprophylaxis. The study found that the levels of D-dimer significantly decreased over a 14-day period in the therapeutic enoxaparin group (from 4176 µg/L to 1469 µg/L, p = 0.009). In contrast, the prophylactic anticoagulation group showed a statistically significant increase in D-dimer levels (from 3408 µg/L to 4878 µg/L, p = 0.004). Concluding that therapeutic anticoagulation (AC) can enhance the condition of patients who are at a high risk of thrombosis and have increased levels of D-dimer.

Patients on therapeutic dose anticoagulation (group A) elicited a significantly increased PaO_2/FiO_2 ratio than those on prophylactic dose anticoagulation (group B) after 2 weeks of treatment (with a median of 190 vs 145 respectively, $P<0.05$). This improvement in gas exchange can be attributed to the occurrence of microvascular thrombosis in the pulmonary circulation, which hampers gas exchange leading to hypoxemia ameliorated by the administration of therapeutic anticoagulation, which dissolved these microthrombi, this corresponds to the results of **Ackermann et al.**[4]

Lemos et al. [11] also evaluated the gas exchange through PaO_2/FiO_2 in 10 patients in therapeutic versus 10 patients in prophylactic groups found that there was a statistically significant rise in the PaO2/FiO2 ratio over 14 days in the therapeutic group. On the other hand, there was no improvement in the prophylactic group ratio. Concluding that therapeutic AC improved gas exchange in these patients.

Regarding 28-day mortality this study showed no statistically significant difference among therapeutic (group A) in comparison to prophylactic (group B) (10 pt of group A vs 15 pt of group B, $P>0.05$). These findings align with the research conducted by **Duo et al.**[12], which involved a comprehensive analysis of randomized clinical trials and observational studies conducted between January 8, 2019, and January 8, 2022, assessing the effectiveness of prophylactic and therapeutic anticoagulant treatments in patients with COVID-19. Upon analysis, it was determined that there was no statistically significant disparity in the relative risk of death between COVID-19 patients receiving therapeutic treatment and those receiving prophylactic treatment. However, it is important to note that these findings were based on an average observation period of 33 days.

Regarding the need for MV in this study, it was lower in therapeutic group (group A) in comparison to prophylactic group (group B) (24 patients vs 28 patients with $P=0.274$) but with no statistically significant difference between the 2 groups. There was also no significant difference among both groups regarding the need for vasopressors, renal replacement therapy, and hospital stay duration. These results were supported by **Sholzberg et al.** [13] in randomized controlled, adaptive, open label clinical trial involving 465 moderately ill COVID-19 cases that found no significant difference in time to the primary composite result, ICU admission, or mechanical ventilation among the groups. The incidence of thromboembolic events at 2 weeks was lower in therapeutic AC (group A) group compared to prophylactic group (group B) but was statistically insignificant (1 patient (2.9%) vs 5 patients (14.3%), ($P>0.05$). Similarly, **Lopes et al.**[14] also found that at the end of 30-days, there was no significant difference in the occurrence of thromboembolic events between the groups.

However, **Ena et al.** [15] demonstrated that therapeutic-dose anticoagulation significantly

decreased the occurrence of venous thromboembolism in comparison to thromboprophylaxis. This discrepancy between both studies can be explained by the different levels of clinical severity as they included sever COVID-19 patients on oxygen support and we included moderate patients.

Regarding major bleeding, this current study showed no statistically significant difference among 2 groups as only 3 patients (8.6%) of the therapeutic anticoagulation group (group A) experienced major bleeding and no major bleeding occurred in the prophylactic group (group B). **Lemos et al.**[11] also discovered that the occurrence of clinically apparent bleeding was minimal in both groups, including the group receiving therapeutic anticoagulation. However, different results were observed in the study of, **Duo et al**.[12] that found that COVID-19 patients who were treated with therapeutic anticoagulation had a significant greater relative risk of major bleeding events than those who received prophylactic anticoagulant.

Despite that the study yielding significant results, there were several limitations that need to be addressed. Firstly, the research was performed at a single center, which may limit the generalizability of the results, thus, further multi-center research is warranted to validate the results. Secondly, there might be potential confounders that were not accounted for, which could have influenced the outcomes. For instance, variations in medical management, steroid use, or other interventions might have contributed to the observed differences between the two groups. Finally, the study's follow-up period was limited to 28 days, which may not fully capture long-term results such as long-term mortality, thromboembolic events, major bleeding, etc.

CONCLUSIONS

In conclusion, the prophylactic dose anticoagulation had priority over the therapeutic one in the treatment of moderate COVID-19 patients as the therapeutic dose had no impact on either the clinical status assessed by WHO scale or overall mortality rate.

CONFLICT OF INTEREST: None
FINANCIAL DISCLOSURES: None .

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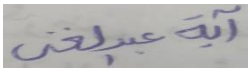
Corresponding author: Aya Abdelghany Mohamed  _26/3/2024

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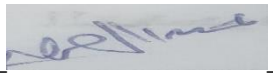
Authors Abdel Rahman Ahmed Ahmed __  _____ 26/3/2024
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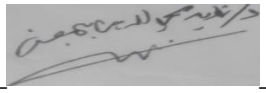
Nadia Mohee ELdin Bahgat _____  _____26/3/2024
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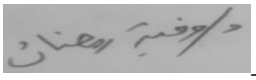
Wafiya Ramadan Mahdy  _____26/3/2024
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