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A NOVEL DESCRIPTION OF AT DEFICIENCY IN HOSPITALIZED COVID-19 PATIENTS

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ABSTRACT – *Objective:* Antithrombin (AT) has anti-inflammatory and anti-coagulant properties, but its role in COVID-19 and the rate of deficiency is unknown. We hypothesize that AT3 deficiency is common in COVID-19, and supplementing AT3 will impact COVID-19 coagulopathy.

Patients and Methods: This is a prospective randomized control trial. Patients with plasma AT3<100% were randomized to either standard of care (SOC) or SOC+AT3 q48hr weight-based for a goal of 120% for up to 5 doses. An additional reference group with AT3>100% received SOC.

Results: 531 subjects were assessed for eligibility; 324 did not meet inclusion criteria, 151 did not consent, 6 withdrew consent, and 50 subjects completed the study. Enrollment AT3 (M±SD) was 91±13%. AT3 levels were <100% in 38 (76%) and <80% in 11 (22%) patients. SOC+AT3, SOC only, and AT3>100% had a disseminated intravascular coagulation (DIC) score change (M±SD) of 0.4±1.5, -0.13±1.85 and 0±1.54, respectively, (p=0.63). Hospital length of stay was 11.7 [6-14], 6 [4.5-10], 8.5 [6-21] respectively, (p=0.176). Mortality occurred in 2 (11%), 3 (15%), and 3 (25%) patients, respectively (p=0.56). There was one bleeding event in a subject with AT3>100%, and no bleeding events were observed with exogenous AT3. There were no observed drug-related adverse events. Subjects received a median dose of 1,825.5 IU (IQR 794).

Conclusions: COVID-19 is associated with relative AT3 deficiency (22% of this cohort). No bleeding complications or drug-related adverse events with exogenous AT3 were observed. There were no significant differences in length of stay or mortality. Further studies should evaluate higher doses of exogenous AT3 and focus on higher-risk groups.

ClinicalTrials.gov: NCT04899232.

KEYWORDS: COVID-19, Antithrombin, Coagulopathy, Critical care, Physiopathology.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The pathogenic mechanism involves a dysregulated inflammatory state superimposed on potential disseminated intravascular coagulation (DIC) with consumptive coagulopathy and a potential phenomenon of antithrombosis[1-4]. The coagulation derangements contribute to both macro- and microvascular disease sequelae, such as venous thromboembolism (VTE) and respiratory failure[2,5]. These patients are at high risk for both thrombosis and bleeding[6-8], as well as an overwhelming cytokine storm[9,10]. DIC, a known marker of severe sepsis, has been seen[11] in over 70% of non-survivors *vs.* <1% in survivors with COVID-19.

In the early stages of the pandemic, VTE prophylaxis was recommended for all COVID-19 inpatients and increased doses for critically ill patients[12]. Despite adequate chemoprophylaxis, VTE complications continued to occur[11,13]. Bocci et al[14] showed that thromboelastogram derangements persisted despite full-dose anticoagulation[14]. Another approach[15] demonstrated that increased doses of chemical VTE prophylaxis were associated with increased bleeding risks without decreasing VTE events. More recent studies have shown the benefit of early and broad initiation of prophylactic anticoagulation[16], particularly with heparin, which may confer anticoagulant and anti-inflammatory properties[17].

Antithrombin (AT) has both anti-inflammatory and anti-coagulant properties that may be beneficial for COVID-19 patients. However, at least one prior study[3] has reported a relative deficiency in AT activity among patients with COVID-19. AT deficiency is associated with heparin resistance and an increased rate of venous thromboembolism[18-20]. The exact rate of acquired AT deficiency in hospitalized patients is not well defined, but the predicted incidence of genetic deficiency in the general population is estimated to be 0.2 to 0.02%[21,22] and acquired as high as 20% in injured hospitalized patients[23]. We hypothesize that AT deficiency is common in COVID-19 patients and that exogenous AT supplementation will impact coagulopathy.

PATIENTS AND METHODS

Trial design and oversight

This multicenter, randomized clinical trial was approved by the University of Miami and Jackson Memorial Hospital Ethics Committees (IRB #20201048) in December 2020. All patients provided written informed consent, and procedures were followed in accordance with the ethical standards of the responsible committee on human experimentation. The University and Hospital provided ongoing oversight of data collection and safety monitoring. The trial was registered on ClinicalTrials.gov (NCT04899232 "Antithrombin III in Infectious Disease Caused by COVID-19"; Investigational New Drug #26893).

From July 2021 to March 2022, patients with COVID-19 were enrolled at two university-affiliated county hospitals. Groups were defined by serum AT activity levels drawn at enrollment. Those with normal activity levels (AT≥100) served as a reference group. Patients with AT activity levels <100 were randomized to receive treatment with exogenous AT supplementation (www.thrombate.com, 50 U/ml x q48 h, dosed according to the algorithm below) or standard of care. Antithrombin activity levels of 100 were chosen because we were unsure of the rate of true deficiency (defined as <80%) in this population at the time of trial design. The goal AT level was set to 120% activity. The dose was calculated according to the following formula, where the dose calculation is based on an expected incremental *in vivo* recovery of 1.4% per unit per kilogram above serum levels:

$$\text{Dose} = \frac{(120\% - \text{serum AT\%}) \times \text{body weight (kg)}}{1.4\%}$$

AT was then drawn every other day for dose calculation and monitoring. Repeat dosing was performed if levels were <100 on subsequent testing. The dosing schedule occurred on hospital days 1, 3, 5, 7, and 9. After the last blood draw, only routine clinical data were used to monitor for outcomes.

The enrollment goal was to obtain three groups of 25 COVID-19 (+) patients: 25 patients with endogenous AT >100% who receive standard of care only (reference group), 25 patients with endogenous AT<100% who receive standard of care only (control), and 25 patients with endogenous AT<100% who receive standard of care plus supplemental AT (treatment group). Insufficient information at the time of study design was present for power analysis, so this pilot study was performed without power analysis. Enrollment was concluded early due to reduced COVID-19 admissions. This decision was made to maintain a more uniform study population and minimize variability in COVID-19 severity over time.

Patients

This multicenter study enrolled adult patients hospitalized with COVID-19 who had the ability to consent for themselves. Due to variations in hospital practice with changes in the availability of COVID-19 testing, we allowed for COVID-19 infection to be defined as positive PCR, antigen, or outside facility testing validated by the clinical team.

Patients were excluded if they were found to have multisystem organ failure (MSOF), defined as two or more organ systems requiring support. Patients were also excluded if expected to die within 24 hours or with a "do not resuscitate order" or had an incurable or terminal condition for which they were receiving palliative care. We excluded patients with ongoing massive surgical or unexplained bleeding, a history of bleeding or clotting disorder, severe traumatic brain injury, or spinal trauma. Patients enrolled in another

concurrent clinical interventional study were also excluded, as well as the special population of pregnant women or prisoners.

Randomization

Randomization occurred after the first AT level was obtained. If AT was found to be <100, then an opaque envelope was used to ensure blinded randomization, and once opened, subjects were assigned to either standard of care (control) or exogenous AT supplementation (treatment). Team members uninvolved in enrollment handled the creation and randomization of opaque envelopes. The study was non-blinded and the study group was known once randomization was complete.

Outcome measures

The primary outcomes were the International Society on Thrombosis and Hemostasis (ISTH) Disseminated Intravascular Coagulation (DIC) score change. The ISTH scoring system correlates with illness severity in diseases associated with DIC, including COVID-19[24,25]. Sequential Organ Failure Assessment (SOFA) score was also calculated and monitored for daily changes in patient status. At enrollment and each 24-hour period thereafter, blood samples were collected and assayed for routine clinical coagulation and inflammation markers, including AT activity, D-dimer, anti-Xa activity, fibrinogen, and prothrombin time until hospital day 9. Laboratory investigations were conducted only when patients were already having blood drawn for clinical purposes. If the treating team determined that blood testing was not necessary, no labs were collected on those days. ISTH DIC score and SOFA score were calculated on admission and at 2-day intervals subsequently, until hospital day 11. Delta DIC score and delta SOFA score were calculated by taking the difference between the index and maximum scores. Patients were followed for major adverse events and disposition until hospital discharge.

Statistical analysis

Statistical analysis was performed using SAS® Studio Release 3.8, Enterprise Edition (SAS Institute Inc., Cary, NC, USA). Demographic characteristics were analyzed. Patient outcomes, including mortality, hospital length of stay (LOS), and VTE rates, were compared. Quantitative variables were analyzed using ANOVA and are reported as mean ± standard deviation for normally distributed variables or median [interquartile range (IQR)] for non-parametric variables. Categorical variables were compared using Fischer's exact test. Statistical significance was defined as $p<0.05$ unless otherwise specified.

RESULTS

Patient characteristics

Of 531 subjects assessed for eligibility, 324 did not meet inclusion criteria, 151 did not consent, and 6 withdrew consent, leaving a total of 50 subjects who completed the study, as shown in the Consort Diagram below (Figure 1). There were 18 patients who received AT treatment (36%), 20 controls (40%), and 12 in the reference group (24%). The cohort included 33 (66%) males. The median age was 56 years (IQR 44-65), ranging from 27 to 84. Sixty-four percent of the cohort was White (n=32), and sixty percent of the cohort was Hispanic (n=30). Baseline demographics and characteristics were similar between groups, as shown in Table I. For the entire cohort, the mean serum AT was 91±13 at the time of enrollment. Index AT levels were found to be less than 100 in 38 patients (76%) and less than 80 in 11 (22%).

Primary outcome

There were no significant differences in AT levels throughout the study period (Figure 2). The primary outcome, change in ISTH DIC score, was not significantly different between the reference, control, and treatment groups (Table II). Likewise, there was no difference in the delta SOFA scores between groups.

Secondary outcomes

Median hospital length of stay was 8.5 [6-21], 6 [4-5-10.0], and 11.7 [6-14 days for reference, control, and treatment groups, respectively (p=0.176)]. There was no difference in mortality rate (Table II). There were 2 VTE events in the reference group and none in the treatment or control group (p=0.037). There were two bleeding events in the reference group, one in the control group and none in the treatment group (p=0.165). There were no observed drug-related adverse events. A median of 2 infusions (IQR 2) of AT per subject was given. There were a total of 38 infusions of AT with a median dose of 1,825.5 IU (IQR 794). The subsequent AT levels did not show a statistically significant difference in serum levels between groups (Figure 2). Chemical deep vein thrombosis (DVT) prophylaxis and antiplatelet use were not significantly different between groups (Table I).

DISCUSSION

In these hospitalized COVID-19 patients, AT deficiency was relatively common (22%), which suggests that routine coagulation tests do not adequately describe the complex coagulopathy of

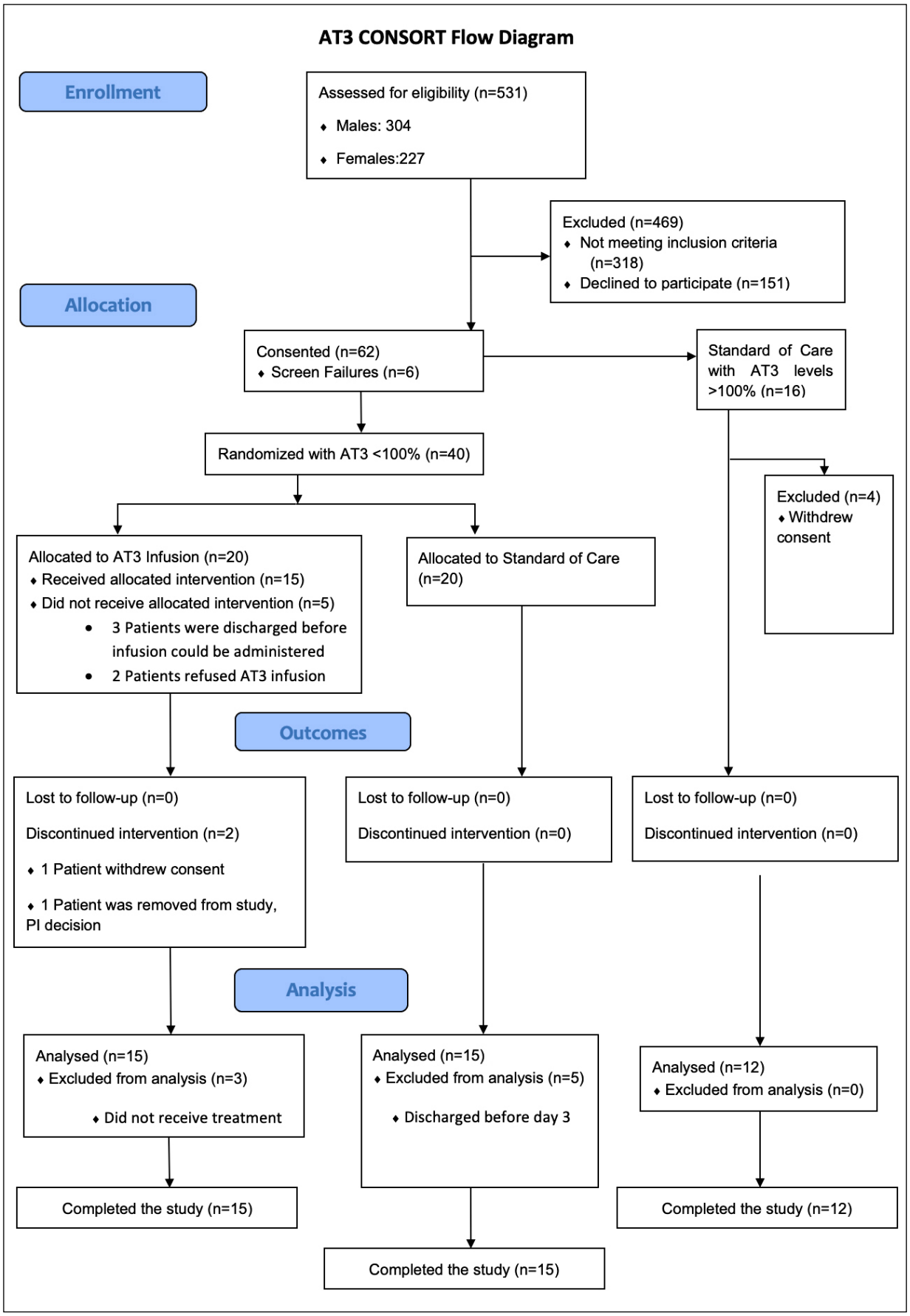

Figure 1. Consort flow diagram.

Table I. Demographics and disease characteristics by treatment group at enrollment.

		AT3 deficient		Normal AT3	*p*-value*
		Treatment n=18 (36%)	Control n=20 (40%)	Reference n=12 (24%)	
Demographic information					
Age, years^		56.3 (14.0)	55.5 (14.6)	50.7 (14.6)	0.5414
Ethnicity	Hispanic	9 (50%)	14 (70%)	7 (58%)	0.4552
	Nonhispanic	9 (50%)	6 (30%)	5 (42%)	
Sex	Male	12 (70%)	13 (65%)	8 (67%)	1.000
	Female	6 (30%)	7 (35%)	4 (33%)	
Comorbidities					
Hypertension		9 (50%)	8 (40%)	5 (42%)	0.811
Diabetes mellitus		3 (17%)	6 (30%)	3(25%)	0.620
Obesity		5 (28%)	5 (25%)	2 (17%)	0.777
Baseline laboratory values					
AT3 (% activity)		87±13	85±11	106±5	**<0.001**
Fibrinogen (mg/dL)		530±138	569±217	621±185	0.420
Platelet count (10^3/mcL)		285±115	237±118	255±108	0.440
Prothrombin time (seconds)		14.3±1.1	13.9±1.0	13.5±0.7	0.089
D-Dimer (μ/mL)		3.2±5.3	1.2±1.2	1.6±1.5	0.181
P/F Ratio		243±185	266±108	249±117	0.884
Creatinine (mg/dL)		0.9±0.6	0.8±0.4	0.8±0.3	0.738
Chemical prophylaxis used					
Enoxaparin (LMWH)		9 (50%)	11 (55%)	9 (75%)	0.228
Subcutaneous heparin (UFH)		7 (40%)	7 (35%)	1 (8%)	
LMWH switched to UFH		1 (5%)	2 (10%)	1 (8%)	
Antiplatelet alone		1 (5%)	0 (0%)	0 (0%)	
None		0 (0%)	0 (0%)	1 (8%)	

*Fisher's exact test (categorical) and ANOVA (continuous). ^Reported as Mean (SD).

COVID-19. We did not observe a statistically significant change in ISTH DIC score with our level of AT supplementation. It was demonstrated that AT deficiency is prevalent in this cohort and that supplementing to a level of 120% was not linked to bleeding events or adverse drug reactions. VTE events were significantly more common in the reference group with AT levels over 100. We have shown that although AT deficiency is a rare genetic condition in the general population and not well recognized among hospitalized patients, it is relatively common in the COVID-19 population.

This complements previous studies[3], indicating that AT activity was notably lower than in controls, with no differences across COVID-19 subtypes severity. Previous studies have suggested routine evaluation of D-dimer[1,26] and AT[3] in COVID-19. Acquired AT deficiency remains a complex condition with varying presentation in some cohorts of severe sepsis and major trauma[18,20]. However, the widespread use of AT in septic patients is not standard practice and is only approved for sepsis in Japan[27,28]. AT deficiency is more common in non-survivors of COVID-19 and may even occur without classical markers of DIC[2,29]. The AT deficiency may manifest differently in varied cohorts, with COVID-19 being a potentially unique variation of coagulopathy[28-30].

In this prospective, randomized controlled trial, exogenous AT supplementation was not associated with bleeding complications or drug-related adverse events. There was no significant change in DIC-score or mortality, potentially due to under-dosing and small sample size. Although previous studies have shown safety up to levels at 200%[23], a conservative goal of 120% was set since this was the first evaluation in this pop-

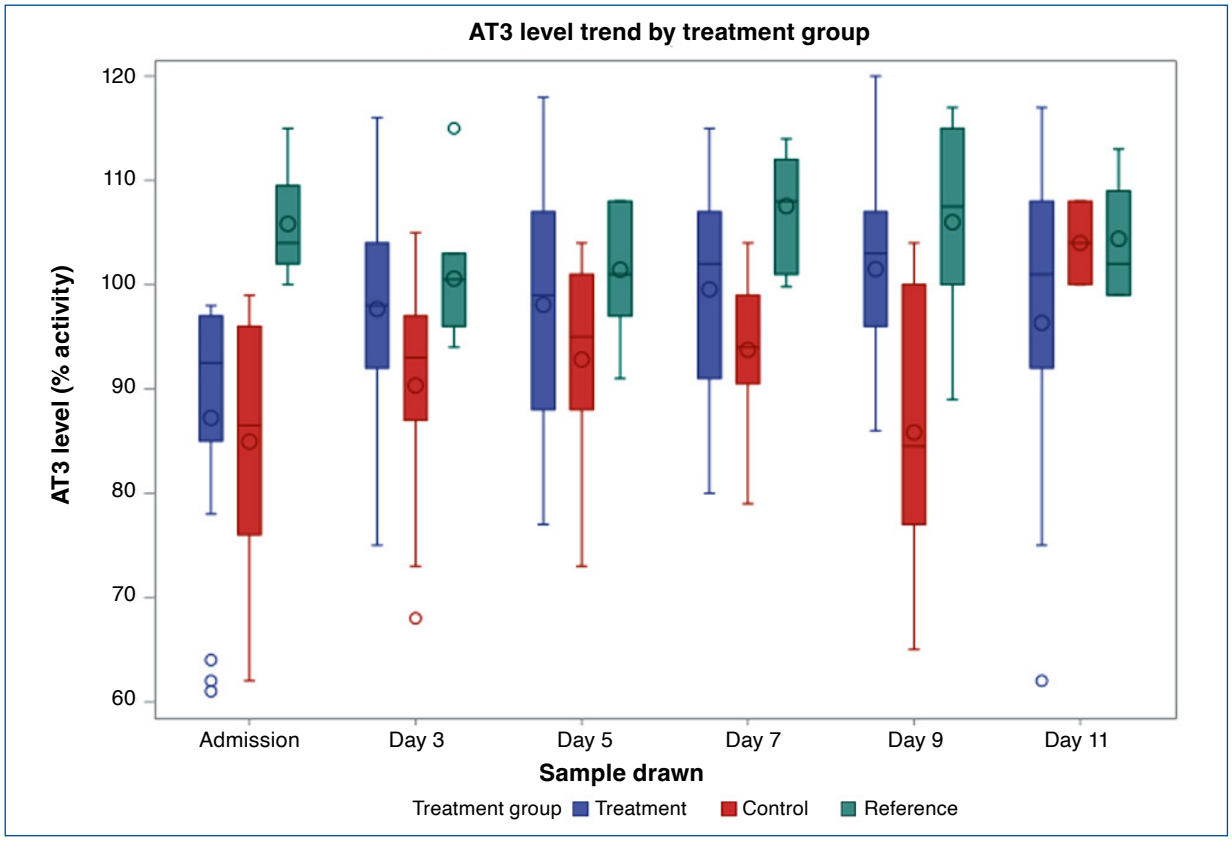

Figure 2. Distribution of AT3 levels by treatment group and day.

ulation. We also chose to investigate a cohort without critical illness (not intubated on admission and excluded MSOF) due to many unknowns at the onset of the pandemic. Previous studies[31] on patients with non-COVID-19 severe sepsis showed potential improved 90-day mortality with high-dose AT (30,000 IU over 4 days) with a potential increased benefit when heparin was used.

Limitations

This study does have limitations. The study chose to use a lower goal of 120% AT activity instead of a higher goal in the absence of known safety data and this contributes to one of the limitations of the data. The exogenous AT supplementation did not elevate the AT level to a statistically significant level when comparing the treatment and control groups, thereby limiting

Table II. Outcomes across groups.

	AT3 deficient		Normal AT3	
	Treatment n=18 (36 %)	Control n=20 (40%)	Reference n=12 (24%)	*p*-value*
Outcomes				
Hospital length of stay median [IQR]	11.7 [6-14]	6 [4.5-10]	8.5 [6-21]	0.176
Mortality	2 (11%)	3 (15%)	3 (25%)	0.589
Venous thromboembolism	-	-	2 (17%)	**0.037**
Bleeding event	-	1 (5%)	2 (17%)	0.165
SOFA score change Mean (SD)	-0.07±1.94	-0.33±2.16	0.08±1.98	0.863
DIC score change Mean (SD)	0.4±1.5	-0.13±1.85	0±1.54	0.630

Disseminated intravascular coagulation (DIC); Sequential Organ Failure Assessment (SOFA). *Fisher's exact test (categorical) and ANOVA (continuous).

the evaluation of this group. It is possible the exogenous AT could confer a clinical effect on inflammation or coagulation without a change in serum levels, but this was not seen in our data. The cohort was also limited in size and severity of illness. We did not collect data on vaccination status; however, due to the low number in the cohort, a comparison of vaccinated *vs.* unvaccinated individuals would not be possible. The statistically significant finding of more VTEs in the reference group was unexpected, considering our hypothesis regarding the impact of AT levels on COVID-19 clinical presentation. However, this finding is highly tenuous due to the occurrence of only two events. The study ended early with a smaller cohort size than planned, as enrollment was restricted by the criteria of including only patients who were not intubated upon admission and who did not have MSOF. These patients fall within a specific category; they are ill enough to require admission but not so critically ill as to necessitate a previously unused therapy. The study also ended early due to a decrease in hospital admissions in the later stages of the pandemic. The statistical analysis is not adequate to draw definitive conclusions given these limitations and the nature of the pilot study.

CONCLUSIONS

In patients admitted with COVID-19 who are not intubated and do not have MSOF, AT deficiency is common, and intervening with exogenous AT to a goal level of 120% was not shown to have a clinical impact when compared to patients not receiving exogenous AT or presenting with AT levels over 100%. With acquired AT deficiency now known to be common in the COVID-19 population, we believe that further studies should evaluate higher doses of exogenous AT and focus on higher-risk groups.

Conflict of Interest

B.M. Parker and E. Ginzburg received a monetary grant from Grifols Biologicals. All other authors have no conflict of interest to disclose.

Informed Consent

All patients provided written informed consent, and procedures were followed in accordance with the ethical standards of the responsible committee on human experimentation as outlined in the Helsinki Declaration.

Ethics Approval

The study was approved by the University of Miami (IRB# 20201048) in December 2020. The University and Hospital provided ongoing oversight of data collection and safety monitoring. The trial was registered on ClinicalTrials.gov (NCT04899232 "Antithrombin III in Infectious Disease Caused by COVID-19"; Investigational New Drug #26893).

Data Availability

Data is available upon request to the corresponding author.

AI Disclosure

AI was not used in the production of this manuscript or interpretation of the data.

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Authors' Contributions

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REFERENCES

1. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020; 395: 497-506.
2. Arachchillage DRJ, Laffan M. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost 2020; 18: 1233-1234.
3. Han H, Yang L, Liu R, Liu F, Wu KL, Li J, Liu XH, Zhu CL. Prominent changes in blood coagulation of patients with SARS-CoV-2 infection. Clin Chem Lab Med 2020; 58: 1116-1120.
4. Helms J, Iba T, Connors JM, Gando S, Levi M, Meziani F, Levy JH. How to manage coagulopathies in critically ill patients. Intensive Care Med 2023; 49: 273-290.
5. Ranucci M, Ballotta A, Di Dedda U, Baryshnikova E, Dei Poli M, Resta M, Falco M, Albano G, Menicanti L. The procoagulant pattern of patients with COVID-19 acute respiratory distress syndrome. J Thromb Haemost 2020; 18: 1747-1751.
6. Al Raizah A, Al Askar A, Shaheen N, Aldosari K, Alnahdi M, Luhanga M, Alshuaibi T, Bajhmoum W, Alharbi K, Alsahari G, Algahtani H, Alrayes E, Basendwah A, Abotaleb A, Almegren M. High rate of bleeding and arterial thrombosis in COVID-19: Saudi multicenter study. Thromb J 2021; 19: 13.
7. Al-Samkari H, Karp Leaf RS, Dzik WH, Carlson JCT, Fogerty AE, Waheed A, Goodarzi K, Bendapudi PK, Bornikova L, Gupta S, Leaf DE, Kuter DJ, Rosovsky RP. COVID-19 and coagulation: bleeding and thrombotic manifestations of SARS-CoV-2 infection. Blood 2020; 136: 489-500.
8. Parvu S, Muller K, Dahdal D, Cosmin I, Christodorescu R, Duda-Seiman D, Man D, Sharma A, Dragoi R, Baneu P, Dragan S. COVID-19 and cardiovascular manifestations. Eur Rev Med Pharmacol Sci 2022; 26: 4509-4519.
9. Hu B, Huang S, Yin L. The cytokine storm and COVID-19. J Med Virol 2021; 93: 250-256.
10. Yang CL, Qiu X, Zeng YK, Jiang M, Fan HR, Zhang ZM. Coronavirus disease 2019: a clinical review. Eur Rev Med Pharmacol Sci 2020; 24: 4585-4596.
11. Gacche RN, Gacche RA, Chen J, Li H, Li G. Predictors of morbidity and mortality in COVID-19. Eur Rev Med Pharmacol Sci 2021; 25: 1684-1707.
12. Barnes GD, Burnett A, Allen A, Blumenstein M, Clark NP, Cuker A, Dager WE, Deitelzweig SB, Ellsworth S, Garcia D, Kaatz S, Minichiello T. Thromboembolism and anticoagulant therapy during the COVID-19 pandemic: interim clinical guidance from the anticoagulation forum. J Thromb Thrombolysis 2020; 50: 72-81.
13. Klok FA, Kruip M, van der Meer NJM, Arbous MS, Gommers D, Kant KM, Kaptein FHJ, van Paassen J, Stals MAM, Huisman MV, Endeman H. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res 2020; 191: 145-147.
14. Bocci MG, Maviglia R, Consalvo LM, Grieco DL, Montini L, Mercurio G, Nardi G, Pisapia L, Cutuli SL, Biasucci DG, Gori C, Rosenkranz R, De Candia E, Carelli S, Natalini D, Antonelli M, Franceschi F. Thromboelastography clot strength profiles and effect of systemic anticoagulation in COVID-19 acute respiratory distress syndrome: a prospective, observational study. Eur Rev Med Pharmacol Sci 2020; 24: 12466-12479.
15. Pesavento R, Ceccato D, Pasquetto G, Monticelli J, Leone L, Frigo A, Gorgi D, Postal A, Marchese GM, Cipriani A, Saller A, Sarais C, Criveller P, Gemelli M, Capone F, Fioretto P, Pagano C, Rossato M, Avogaro A, Simioni P, Prandoni P, Vettor R. The hazard of (sub) therapeutic doses of anticoagulants in non-critically ill patients with Covid-19: The Padua province experience. J Thromb Haemost 2020; 18: 2629-2635.
16. Rentsch CT, Beckman JA, Tomlinson L, Gellad WF, Alcorn C, Kidwai-Khan F, Skanderson M, Brittain E, King JT, Jr., Ho YL, Eden S, Kundu S, Lann MF, Greevy RA, Jr., Ho PM, Heidenreich PA, Jacobson DA, Douglas IJ, Tate JP, Evans SJW, Atkins D, Justice AC, Freiberg MS. Early initiation of prophylactic anticoagulation for prevention of coronavirus disease 2019 mortality in patients admitted to hospital in the United States: cohort study. BMJ 2021; 372: n311.
17. ATTACC Investigators; ACTIV-4a Investigators; REMAP-CAP Investigators; Lawler PR, Goligher EC, Berger JS, Neal MD, McVerry BJ, Nicolau JC, Gong MN, Carrier M, Rosenson RS, Reynolds HR, Turgeon AF, Escobedo J, Huang DT, Bradbury CA, Houston BL, Kornblith LZ, Kumar A, Kahn SR, Cushman M, McQuilten Z, Slutsky AS, Kim KS, Gordon AC, Kirwan BA, Brooks MM, Higgins AM, Lewis RJ, Lorenzi E, Berry SM, Berry LR, Aday AW, Al-Beidh F, Annane D, Arabi YM, Aryal D, Baumann Kreuziger L, Beane A, Bhimani Z, Bihari S, Billett HH, Bond L, Bonten M, Brunkhorst F, Buxton M, Buzgau A, Castellucci LA, Chekuri S, Chen JT, Cheng AC, Chkhikvadze T, Coiffard B, Costantini TW, de Brouwer S, Derde LPG, Detry MA, Duggal A, Dzavik V, Effron MB, Estcourt LJ, Everett BM, Fergusson DA, Fitzgerald M, Fowler RA, Galanaud JP, Galen BT, Gandotra S, Garcia-Madrona S, Girard TD, Godoy LC, Goodman AL, Goossens H, Green C, Greenstein YY, Gross PL, Hamburg NM, Haniffa R, Hanna G, Hanna N, Hegde SM, Hendrickson CM, Hite RD, Hindenburg AA, Hope AA, Horowitz JM, Horvat CM, Hudock K, Hunt BJ, Husain M, Hyzy RC, Iyer VN, Jacobson JR, Jayakumar D, Keller NM, Khan A, Kim Y, Kindzelski AL, King AJ, Knudson MM, Kornblith AE, Krishnan V, Kutcher ME, Laffan MA, Lamontagne F, Le Gal G, Leeper CM, Leifer ES, Lim G, Lima FG, Linstrum K, Litton E, Lopez-Sendon J, Lopez-Sendon Moreno JL, Lother SA, Malhotra S, Marcos M, Saud Marinez A, Marshall JC, Marten N, Matthay MA, McAuley DF, McDonald EG, McGlothlin A, McGuinness SP, Middeldorp S, Montgomery SK, Moore SC, Morillo Guerrero R, Mouncey PR, Murthy S, Nair GB, Nair R, Nichol AD, Nunez-Garcia B, Pandey A, Park PK, Parke RL, Parker JC, Parnia S, Paul JD, Perez Gonzalez YS, Pompilio M, Prekker ME, Quigley JG, Rost NS, Rowan K, Santos FO, Santos M, Olombrada Santos M, Satterwhite L, Saunders CT, Schutgens REG, Seymour CW, Siegal DM, Silva DG, Jr., Shankar-Hari M, Sheehan JP, Singhal AB, Solvason D, Stanworth SJ, Tritschler T, Turner AM, van Bentum-Puijk W, van de Veerdonk FL, van Diepen S, Vazquez-Grande G, Wahid L, Wareham V, Wells BJ, Widmer RJ, Wilson JG, Yuriditsky E, Zampieri FG, Angus DC, McArthur CJ, Webb SA, Farkouh ME, Hochman JS, Zarychanski R. Therapeutic Anticoagulation with Heparin in Noncritically Ill Patients with Covid-19. N Engl J Med 2021; 385: 790-802.

18. Rahbar E, Cotton BA, Wade CE, Cardenas JC. Acquired antithrombin deficiency is a risk factor for venous thromboembolism after major trauma. Thromb Res 2021; 204: 9-12.
19. Murakami N, Hayden R, Hills T, Al-Samkari H, Casey J, Del Sorbo L, Lawler PR, Sise ME, Leaf DE. Therapeutic advances in COVID-19. Nat Rev Nephrol 2023; 19: 38-52.
20. White B, Perry D. Acquired antithrombin deficiency in sepsis. Br J Haematol 2001; 112: 26-31.
21. Patnaik MM, Moll S. Inherited antithrombin deficiency: a review. Haemophilia 2008; 14: 1229-1239.
22. Tait RC, Walker ID, Perry DJ, Islam SI, Daly ME, McCall F, Conkie JA, Carrell RW. Prevalence of antithrombin deficiency in the healthy population. Br J Haematol 1994; 87: 106-112.
23. Cardenas JC, Wang YW, Karri JV, Vincent S, Cap AP, Cotton BA, Wade CE. Supplementation with antithrombin III ex vivo optimizes enoxaparin responses in critically injured patients. Thromb Res 2020; 187: 131-138.
24. Taylor FB, Jr., Toh CH, Hoots WK, Wada H, Levi M, Scientific Subcommittee on Disseminated Intravascular Coagulation of the International Society on T, Haemostasis. Towards definition, clinical and laboratory criteria, and a scoring system for disseminated intravascular coagulation. Thromb Haemost 2001; 86: 1327-1330.
25. Hosseini SF, Behnam-Roudsari S, Alavinia G, Emami A, Toghyani A, Moradi S, Zadeh MM, Mohseni S, Shafiee MA. Diagnostic and prognostic value of Sepsis-Induced coagulopathy and International Society on Thrombosis and Hemostasis scoring systems in COVID-19-associated disseminated intravascular coagulopathy. J Res Med Sci 2021; 26: 102.
26. Zhang L, Yan X, Fan Q, Liu H, Liu X, Liu Z, Zhang Z. D-dimer levels on admission to predict in-hospital mortality in patients with Covid-19. J Thromb Haemost 2020; 18: 1324-1329.
27. Egi M, Ogura H, Yatabe T, Atagi K, Inoue S, Iba T, Kakihana Y, Kawasaki T, Kushimoto S, Kuroda Y, Kotani J, Shime N, Taniguchi T, Tsuruta R, Doi K, Doi M, Nakada TA, Nakane M, Fujishima S, Hosokawa N, Masuda Y, Matsushima A, Matsuda N, Yamakawa K, Hara Y, Sakuraya M, Ohshimo S, Aoki Y, Inada M, Umemura Y, Kawai Y, Kondo Y, Saito H, Taito S, Takeda C, Terayama T, Tohira H, Hashimoto H, Hayashida K, Hifumi T, Hirose T, Fukuda T, Fujii T, Miura S, Yasuda H, Abe T, Andoh K, Iida Y, Ishihara T, Ide K, Ito K, Ito Y, Inata Y, Utsunomiya A, Unoki T, Endo K, Ouchi A, Ozaki M, Ono S, Katsura M, Kawaguchi A, Kawamura Y, Kudo D, Kubo K, Kurahashi K, Sakuramoto H, Shimoyama A, Suzuki T, Sekine S, Sekino M, Takahashi N, Takahashi S, Takahashi H, Tagami T, Tajima G, Tatsumi H, Tani M, Tsuchiya A, Tsutsumi Y, Naito T, Nagae M, Nagasawa I, Nakamura K, Nishimura T, Nunomiya S, Norisue Y, Hashimoto S, Hasegawa D, Hatakeyama J, Hara N, Higashibeppu N, Furushima N, Furusono H, Matsuishi Y, Matsuyama T, Minematsu Y, Miyashita R, Miyatake Y, Moriyasu M, Yamada T, Yamada H, Yamamoto R, Yoshida T, Yoshida Y, Yoshimura J, Yotsumoto R, Yonekura H, Wada T, Watanabe E, Aoki M, Asai H, Abe T, Igarashi Y, Iguchi N, Ishikawa M, Ishimaru G, Isokawa S, Itakura R, Imahase H, Imura H, Irinoda T, Uehara K, Ushio N, Umegaki T, Egawa Y, Enomoto Y, Ota K, Ohchi Y, Ohno T, Ohbe H, Oka K, Okada N, Okada Y, Okano H, Okamoto J, Okuda H, Ogura T, Onodera Y, Oyama Y, Kainuma M, Kako E, Kashiura M, Kato H, Kanaya A, Kaneko T, Kanehata K, Kano KI, Kawano H, Kikutani K, Kikuchi H, Kido T, Kimura S, Koami H, Kobashi D, Saiki I, Sakai M, Sakamoto A, Sato T, Shiga Y, Shimoto M, Shimoyama S, Shoko T, Sugawara Y, Sugita A, Suzuki S, Suzuki Y, Suhara T, Sonota K, Takauji S, Takashima K, Takahashi S, Takahashi Y, Takeshita J, Tanaka Y, Tampo A, Tsunoyama T, Tetsuhara K, Tokunaga K, Tomioka Y, Tomita K, Tominaga N, Toyosaki M, Toyoda Y, Naito H, Nagata I, Nagato T, Nakamura Y, Nakamori Y, Nahara I, Naraba H, Narita C, Nishioka N, Nishimura T, Nishiyama K, Nomura T, Haga T, Hagiwara Y, Hashimoto K, Hatachi T, Hamasaki T, Hayashi T, Hayashi M, Hayamizu A, Haraguchi G, Hirano Y, Fujii R, Fujita M, Fujimura N, Funakoshi H, Horiguchi M, Maki J, Masunaga N, Matsumura Y, Mayumi T, Minami K, Miyazaki Y, Miyamoto K, Murata T, Yanai M, Yano T, Yamada K, Yamada N, Yamamoto T, Yoshihiro S, Tanaka H, Nishida O. The Japanese Clinical Practice Guidelines for Management of Sepsis and Septic Shock 2020 (J-SSCG 2020). J Intensive Care 2021; 9: 53.
28. Wiedermann CJ. Antithrombin as Therapeutic Intervention against Sepsis-Induced Coagulopathy and Disseminated Intravascular Coagulation: Lessons Learned from COVID-19-Associated Coagulopathy. Int J Mol Sci 2022; 23: 12474.
29. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost 2020; 18: 844-847.
30. Godoy LC, Goligher EC, Lawler PR, Slutsky AS, Zarychanski R. Anticipating and managing coagulopathy and thrombotic manifestations of severe COVID-19. CMAJ 2020; 192: E1156-E1161.
31. Wiedermann CJ, Hoffmann JN, Juers M, Ostermann H, Kienast J, Briegel J, Strauss R, Keinecke HO, Warren BL, Opal SM, KyberSept I. High-dose antithrombin III in the treatment of severe sepsis in patients with a high risk of death: efficacy and safety. Crit Care Med 2006; 34: 285-292.