Health & Research Journal

Vol 10, No 2 (2024)

Volume 10 Issue 2 April - June 2024

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doi: 10.12681/healthresj.36980

HEALTH AND RESEARCH JOURNAL
E-ISSN:2459-3192

(2024), Volume 10, Issue 2

ORIGINAL ARTICLE

THROMBOSIS IN SEVERELY ILL PATIENTS ADMITTED IN ICU DUE TO COVID-19 PNEUMONIA. DATA FROM A GREEK HOSPITAL

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Abstract

Background: SARS-CoV-2 can lead to a prothrombotic state and the activation of the body's coagulation mechanism, resulting in thrombotic episodes, especially in critically ill patients. The rates of thromboembolic disease in patients with COVID-19 vary and range from 10-40%, while in Greece the existing epidemiological data on the incidence of thromboembolic disease in the ICU are limited.

Aim This study aimed to determine the proportion of hospitalized COVID-19 patients who developed thromboembolic disease (pulmonary embolism, deep vein thrombosis, or arterial embolism). It was also crucial to investigate at the relationship between the incidence of VTE (venothrombosis-VTE) and Covid infection in ICU patients. After 28 days from ICU admission, the survival rate of patients with Covid infection admitted to ICUs within the specified time frame was also noted.

Method and Material: The study included 85 patients with Covid-19 infection who were hospitalized in two ICU departments in a large adult hospital in Athens between June and September 2021. The occurrence of VTE was diagnosed by computed tomography angiography, regarding the pulmonary embolism and with triplex veins of the lower extremities. Various epidemiological factors, laboratory findings and characteristics of the patients' hospitalization in the Intensive Care Unit were recorded.

Results: The incidence of VTE in patients with Covid-19 infection admitted to the Intensive Care Unit was 14% (12/85 patients). Patients who experienced VTE during their hospitalization in the Intensive Care Unit had more days on mechanical ventilation support, more days on vasoconstrictor drugs, and had been transfused more times with blood plasma. In the multivariate analysis that followed, it was found that total days of mechanical ventilation ($p=0.02$), total days of vasoconstrictor administration ($p=0.03$) and plasma transfusion ($p=0.03$) were still statistically significant.

Conclusion: In patients with Covid-19 infection and hospitalization in the Intensive Care Unit, longer stay on mechanical respiratory support, more days of vasoconstrictor drug administration and plasma administration are independent predisposing factors for the occurrence of VTE.

Keywords: Thrombosis, critically ill patients, ICU, VTE.

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Cite as: Pouriki, S., Agapitou, T., Liolιousis, G., Tsikrikas, S., Manthou, P. (2024). Thrombosis in severely ill patients admitted in ICU due to COVID-19 pneumonia. Data from a Greek Hospital. Health and Research Journal,10(2),105-115. https://ejournals.epublishing.ekt.gr/index.php/HealthResJ

INTRODUCTION

Coagulation disorders and blood clots are a significant cause of morbidity and mortality from the SARS-CoV-2 coronavirus. The American Society of Hematology reported that blood clots were first observed in COVID-19 patients with severe pneumonia who had increased δ-dimers, indicating thrombosis. The coagulation system disorder in COVID-19 patients has unique features, such as elevated fibrinogen levels compared to those with disseminated intravascular coagulation (DEC). These disorders and thrombosis significantly increase the mortality rate in those infected with the coronavirus and hospitalized in the Intensive Care Unit.[1]

AIM

This study aimed to determine the proportion of hospitalized COVID-19 patients in two ICU departments in a large adult hospital in Athens who developed thromboembolic disease (pulmonary embolism, deep vein thrombosis, or arterial embolism) as well as the survival rate ,after 28 days from ICU admission. It was also crucial to investigate at the relationship between the incidence of VTE (venothrombosis-VTE) and Covid infection in ICU patients.

METHOLOGY

Retrospective observational study conducted in the ICU/PP and ICU/CAA in a large adult hospital in Athens. Patient anonymity was maintained. After approval from the scientific committee (17696/07-07-22) and after written informed consent, data from patients were registered between June 2021 and September 2021 were collected.

Inclusion criteria-Exclusion criteria

Inclusion criteria were patients, over 18 years of age, admitted to the ICU/CAA and ICU/PP needed to stay in for more than 48 hours regardless of gender, race and socio-economic status. Exclusion criteria were. Preexisting thromboembolic disease, active cancer under treatment, active bleeding on admission to the ICU and length of ICU stay <48 hours.

Collection of epidemiological, clinical and laboratory data

Following the completion of the clinical examination and obtaining the history of each participant, the following information was recorded: vaccination status, total hospital days, APACHE II and SOFA severity ratings, and the day on which the participants' symptoms first appeared. Other conditions include cancer, heart failure, kidney illness, atrial fibrillation, diabetes mellitus, and H.A.P.N. In addition, the number of days the patient was on mechanical ventilation, the number of days vasoconstrictor drugs were administered, and the patient's survival on day 28 following hospital admission were considered inclusion criteria. Additionally, the quantity of fresh frozen plasma (FFP), platelet bags, and blood transfusions was noted. Both patients with suspected pulmonary embolism throughout their ICU stay and the majority of patients upon hospital admission got chest CT with a pulmonary embolism procedure. Additionally, research participants who had a clinical suspicion of deep vein thrombosis (DVT) underwent a triplex of lower extremity veins.

The clinical suspicion of DVT was indicated by the presence of thermal, edematous, and red tip symptoms, while the suspicion of a pulmonary embolism during a patient's stay in the intensive care unit was indicated by a sudden worsening of the patient's airometric and objective clinical picture without radiological deterioration. An ultrasound machine with Doppler technology was used by a qualified physician at the patient's bedside to perform imaging examinations. The CT scanner was part of the radiology laboratory infrastructure, and it was used in accordance with the protocol of pulmonary embolism and the use of iodinated contrast material regarding the CT scan of the chest's pulmonary vessels.

Statistical analysis

After conducting a descriptive statistical analysis of the data, all continuous variables' means, variances, and standard deviations were reported, along with percentages for categorical variables like patient demographics and clinical and laboratory parameters that were divided into two groups based on the presence or absence of VTE. The t-test was used to compare continuous variables with a normal distribution, while the Mann-Whitney test was used to compare variables with a non-normal distribution. The results are displayed as the mean, standard deviation, and range of values. Qualitative factors were subjected to the Chi squared test. We performed multivariate logistic regression analysis (stepwise logistic regression) on variables that showed significant differences between the two groups. Results of logistic regression are displayed as 95% confidence intervals and odds ratios. In addition, biologically significant factors, including age, gender, and APACHE score, were taken into account in the logistic regression models. The STATA v.17 statistical tool (StataCorp LLC, College Station, Texas 77845 USA) was used to conduct the statistical analysis. $P < 0.05$ was used to indicate statistically significant differences.

RESULTS

With a mean age of 64.2 years (range 26–93 years and standard deviation (SD) 15.26 years), 85 patients—31 women and 54 men—completed the trial. With a mean age of 63.4 years, the presence of VTE was found in 14.1% of cases. Table 1 displays patient features. In Table 2, comorbidities are displayed.

Eight patients (66.7%) were male and four patients (33.3%) were female in the VTE patient population, with a mean age of 63.4 years. Of the patients who did not have VTE, 27 were female (37%), and 46 were male (63%) ($p > 0.05$). The mean APACHE score for patients with VTE was (14±7), and the mean SOFA score was (5.9±3). The SOFA score was 5.7±4 (4–24) and the average APACHE score was 14±7 ($p = 0.44$ and $p = 0.67$, respectively) in the patients without VTE. The two groups did not differ statistically significantly in terms of blood transfusion ($p = 0.14$), mechanical or non-support breathing ($p = 0.45$), the administration or non-administration of vasoconstrictor drugs ($p = 0.89$), the submission or non-submission of CRRT ($p = 0.45$), or patient survival at 28 days of hospitalization. There were statistically significant differences in the total number of days that patients with VTE were supported with mechanical ventilation [39±18.4(0-165)] compared to patients without VTE [16.5± 18.4 (0-69)], (p=0.05); in the total number of days that patients with VTE were supported with vasoconstrictor days [28±35(0-80)] compared to patients without VTE 13.4±16(80-100), (p=0.02); and in the total number of days that patients with VTE received plasma transfusion—patients with VTE received less transfusions (p=0.004) or not at all (p=0.002) compared to patients without VTE (Table 3). There was no statistically significant difference in comorbidities among patients with and without VTE (Table 4).

Pre- and post-intubation blood gas measurements and the pO_2/FiO_2 ratio did not show a statistically significant difference between individuals with VTE and those without. Additionally, no statistically significant variations were seen in the following variables: age, sex, hematocrit, hemoglobin, white blood cells, platelets, fibrinogen, urea, creatinine, creatine phosphokinase, triglycerides, ferritin, and C-reactive protein.

According to the multivariate analysis, blood plasma transfusions (odds ratio: 4.71, 95% confidence limits (CI): 1.13-19.7; P=0.03), total days of vasoconstrictor administration (odds ratio: 1.03, 95% confidence limits (CI): 1-1.05; P=0.04), and total days of mechanical ventilation (odds ratio: 1.02, 95% confidence limits (CI): 1-1.05; P=0.02) were found to be independent predisposing factors for the occurrence of VTE. During their ICU stay, patients who received plasma had an approximately five-fold increased risk of developing VTE (Table 5).

The association of plasma transfusion with VTE did not change substantially after adjustment for age and sex or APACHE score, but decreased after controlling for duration of CRRT (Table 6). Similarly, the association of duration of vasopressor use or mechanical ventilation was independent of age and sex or APACHE score but was marginal after adjustment for duration of CRRT (Tables 7).

DISCUSSION

According to the international literature, the risk of VTE in hospitalized patients with COVID-19 infection in the Intensive Care Unit ranges between 10% and 40% .[1-4] The current study had similar results as the incidence rate of VTE among patients with the COVID-19 infection was around 14%, confirming that VTE is a common consequence of the COVID-19 infection. Statistical analysis indicates that there is no statistically significant difference between patients with and without VTE in terms of sex, age, the severity of the disease as measured by the APACHE II and SOFA scores, whether or not the patient is intubated, whether or not vasoconstrictors are administered, whether or not the patient is submitted to extranephrology dialysis, whether or not blood is transfused, and whether or not there are two comorbidities such as diabetes mellitus, chronic kidney failure, coronary disease, atrial fibrillation, and cancer.

From other studies, it is known that obesity is a significant risk factor for SARS-COV-2 replication, with adipose tissue acting as a potent inflammatory reservoir. In critically ill patients, inflammatory mediators and hormone administration can increase blood coagulation and thromboembolic disease. In ICU admission, mechanical ventilation, and surgery can cause vascular endothelial injury, increasing the risk of VTE. ARDS patients secondary to COVID-19 have more thrombosis complications.[9-10]

In addition, there was no statistically significant difference in survival at day 28 of hospitalization between the two groups of patients, indicating that the presence of VTE is a poor predictive indicator for patient survival. On the other hand, during their stay in the Intensive Care Unit, patients with VTE were observed to have more mechanical days of ventilation, more days of vasoconstrictor therapy overall, and more FFP overall than the unaffected patients with VTE. This can be explained by the fact that the majority of mechanical ventilation days correspond to longer periods of immobility and repressive treatment.[5-8] Longer periods of vasoconstrictor administration increase the formation of blood clots, vasoconstriction generated by vasoconstrictors, especially in subcutaneous capillaries, prevents complete absorption of administered subcutaneous anticoagulant injections.[11,12]

Moreover, it should be noted that administering plasma only includes one extra clotting factor. [13,14] According to a comparison of the two groups' laboratory results, the VTE patients had a higher bilateral value; this finding can be explained by the patients' thrombotic conditions as well as their elevated aspartate aminotransferase (AST), a fact that has been explored in other studies.[6,14] The total number of days of mechanical ventilation and administration of vasoconstrictor medications, as well as plasma-independent predictors of VTE occurrence, were discovered to be among the basic characteristics and conditions of the included patients in the study.With the exception of CRRT, which caused a slight alteration, the correlation did not change significantly after accounting for a number of co-factors, including age, gender, submission to CRRT, and the severity of the condition as determined by the APACHE score.

The University of Michigan experienced a surge in nephrology consultations for acute kidney injury (AKI) due to the COVID-19 pandemic, leading to a significant increase in CRRT utilization.[15] KDIGO guidelines recommend RCA for CRRT, but centers with limited experience may require training to establish and implement protocols, potentially unavailable during stress periods like the COVID-19 pandemic.[16] Ultrafiltration's impact on respiratory status in ARDS may not be immediately noticeable and may require longer observation. The modest fluid removal observed from other studies may not have led to clinical improvements. The positive fluid balance may be inaccurate, especially in COVID-19 patients with gastrointestinal symptoms and volume-depleted states.[17,18] The management of COVID-19 patients requires careful assessment and an individualized approach to determine the optimal strategy.

CONCLUSION

In conclusion, it was discovered that the incidence of VTE in COVID-19 patients admitted to the ICU, along with thrombotic cases, correlates with parameters indicating the length of the patient's stay in the ICU. These processes are initiated by the COVID-19 virus itself. The longer the patient is intubated and takes vasoconstrictor medication, the higher the patient's risk of getting VTE.

VTE treatment should follow accepted principles, as COVID-19 severity increases the risk of multiorgan failure. Parenteral anticoagulation is preferred for VTE patients. A multidisciplinary PE response team can assist with difficult treatment decisions during the pandemic.

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ANNEX

TABLE 1. Baseline characteristics*

Characteristics	Patients(%)
Sex	
• **Male**	54/85 (63,5%)
• **Female**	31/85 (36,5%)
Age (Years)	64,2 ± 15,3 (26-93)
Days of Mechanical Ventilation	19,7 ± 26,5 (0-165)
Days of vasoconstrictor **drugs**	15,4± 20,2 (0-100)
Length of Icu stay (days)	23,5 ± 29,7 (2-191)
APACHE II score (Acute Physiology and Chronic Health Evaluation II)	16,9 ± 7,3 (6-38)
SOFA score (Sequential organ Failure Assessment)	5,78± 3,6
Days before the hospital entry	6,98± 3,2 (1-16)
Length of Hospital stay (days)	32,86± 29,34 (3-193)

* Quantitative characteristics are reported as mean ± standard deviation (limits of variation).
Qualitative characteristics are reported as number N and percentage (%).

TABLE 2. Patients' co morbidities.

Co morbidities	**Percentage %**
Diabetes Mellitus	24/85 (28%)
Chronic Kidney Disease	3/85 (3,5%)
Heart Failure	8/85 (9,4%)
Coronary artery disease	14/85 (16,5%)
Atrial fibrillation	11/85(12,9%)
Chronic Obstructive Pulmonary Disease	12/85 (14,11%)
Cancer	9/85(10,6%)
Patient survival at 28 days	53/85(62%)

TABLE 3. Comparison of epidemiological and clinical characteristics according to the presence or absence of VTE *

Characteristics	Patients with VTE	Patients without VTE	p value
Sex			
Male	8/12 (66,7%)	46/73 (63%)	0,80
Female	4/12 (33,3%)	27/73 (37%)	
Age (Years)	63,4 ±13,8	64,3 ± 15,6	0,85
Days of Mechanical Ventilation	39±18,4(0-165)	16,5± 18,4(0-69)	0,05
Days of vasopresor drugs	28±35(0-80)	13,4±16(0-100)	0,02
APACHE II score (Acute Physiology and Chronic Health Evalution II)	14±7(8-21)	16±7(5-36)	0,4
SOFA score (Sequental organ Failure Assesement)	5,9±3(2-10)	5,7±4(4-24)	0,9
Mechanical Ventilation (yes/no)	8(66,7)	56(76,7)	0,45
vasoconstrictor drugs (yes/no)	9(75.00)	56(76,71)	0,89
CRRT(yes/no)	6(50,00)	28(38,86)	0,45
Blood Tranfusion (yes/no)	6(50,00)	21(21,77)	0,14
Patient survival at 28 days	9/12(75%)	44/73(60%)	0,16

*Quantitative characteristics are reported as mean ± standard deviation and interquartile range.
Qualitative characteristics are reported as number N and percentage (%)

TABLE 4. The comparison of epidemiological characteristics after distinguishing patients into subgroups based on the presence or absence of VTE.

Co morbidities	Patients with VTE	Patients without VTE	p value
Diabetes Mellitus	6(50.00)	55 (75,34)	0,07
Chronic Kidney Disease	12(100,00)	70 (95,89)	0,47
Heart Failure	10(83,33)	61(83,56)	0,98
Coronary artery disease	10(83,33)	64(87,67)	0,68
Cancer	10(83,33)	66(90,41)	0,46

TABLE 5. Unadjusted logistic regression analysis for the association of baseline characteristics and hospitalisation procedures with the occurrence of VTE in patients with COVID-19

Characteristics	OR (95% CI)	P-Value
Age	0.996(0.957/ 1.04)	0.856
Apache score	0.954(0.868/ 1.05)	0.338
Sofa score	1.01(0.856/ 1.2)	0.891
CRRT total lengh of stay (d)	1.05(0.975/1.12)	0.204
Triglycerides	1(0.995/1)	0.852
D-Dimers	1.09(0.975/ 1.21)	0.134
Fibrinogen	0.997 (0.993/1)	0.138
Ferritin on admission	1 (0.999/ 1)	0.42
C-reactive protein on admission	.992(0.947/ 1.04)	0.743
Total days of mechanical ventilation	1.02(1/ 1.05)	0.0235
Total days of vasoconstrictor administration	1.03(1/ 1.05)	0.0352
Blood transfusion	2.48 (0.717/ 8.56)	0.152
Plasma transfusion	4.71 (1.13/ 19.7)	0.034
Sex	.852(0.234/3.1)	0.808
Diabetes	.327(0.0937/ 1.14)	0.08
Coronary artery disease	.984(0.191/ 5.07)	0.984
Atrial Fibrillation	.703(0.132/ 3.74)	0.679
Cancer	.53(0.0963/ 2.92)	0.466
CRRT (yes/no)	1.61(0.472/ 5.48)	0.448
Mechanical ventilation (yes/no)	.911(0.221/ 3.75)	0.897
Vasoconstrictors (yes/no)	.607(0.163/ 2.27)	0.458
Mortality at 28 days	0.404(0.101-1.62)	0.2
Abbreviations: VTE, venous thromboembolism; OR, odds ratio (95% CI)		

TABLE 6. Unadjusted and adjusted logistic regression analysis for the association of plasma transfusion with the occurrence of VTE in patients hospitalised for COVID-19

	Unadjusted			**Model 1**			**Model 2**		
	OR	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**
Blood Trans-fusion	4.71	1.13-19.7	0.034	4.82	1.139-20.4	0.033	4.07	.926-17.851	0.063

Model 1: adjusted for age and sex

Model 2: adjusted for CRRT days

Model 3: adjusted for ApacheScore OR=4.79, 95% CI 1.13-20.38, P=0.034

Abbreviations: VTE, venous thromboembolism; OR, odds ratio (95% CI)

TABLE 7. Unadjusted and adjusted logistic regression analysis for the association of the duration of mechanical ventilation with the occurrence of VTE in patients hospitalised for COVID-19

	Unadjusted			**Model 1**			**Model 2**		
	OR	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**
Total days of Mechani-cal Ventila-tion	1.02	1/ 1.05	0.024	1.024	1.004/ 1.045	0.022	1.028	.9989/ 1.0569	0.059

Model 1: adjusted for age and sex

Model 2: adjusted for CRRT days

Model 3: adjusted for ApacheScore OR=1.026, 95% CI 1.004-1.05, P=0.022

Abbreviations: VTE, venous thromboembolism; OR, odds ratio ,95% CI.