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Assessment of the incidence of venous thromboembolism in patients with Covid-19 admitted to an intensive care unit

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Abstract

Objective: To assess the incidence of venous thromboembolism (VTE) in patients hospitalized in an intensive care unit (ICU) due to Covid-19, its relationship with D-dimer levels and other possible associated factors. **Method:** A cross-sectional and retrospective study, carried out in a public university hospital, between April and June 2021. The sample consisted of patients ≥ 15 years old with positive reverse transcription polymerase chain reaction (RT-PCR) for Sars-CoV-2, excluding pregnant and postpartum women who had ICU admission. Data were collected and tabulated in the Microsoft Office Excel ® program and analyzed using the R Studio® software. Continuous variables were expressed as mean and standard deviation, and categorical variables were expressed as absolute (n) and relative (%) frequencies, and analyzed by Chi-square, a confidence level <0.05 was adopted. **Results:** The study consisted of 144 patients (61.1% male), with a mean length of stay in the ICU of 14.2±10.3 days. The incidence of deep vein thrombosis (DVT) in these patients was 19% and 5% for pulmonary thromboembolism (PTE). Regarding the D-dimer test, it was noted that the group with the presence of DVT+PTE had a higher median. In total, 31.2% patients were anticoagulated. There was a statistically significant relationship between the performance of hemodialysis and the clinical outcome of death (p<0.05). **Conclusion:** It is concluded that 21% of the evaluated patients had VTE during their stay in the ICU. The study contributed to characterizing the profile of patients with Covid-19 admitted to the ICU who developed VTE, with the purpose of presenting consistent data that will allow improving the planning of the health care process.

Keywords: Covid-19; venous thromboembolism; d-dimer; venous thrombosis.

Avaliação da incidência de tromboembolismo venoso em pacientes com Covid-19 internados em uma unidade de terapia intensiva

Resumo

Objetivo: Avaliar a incidência de tromboembolismo venoso (TEV) em pacientes hospitalizados em uma unidade de terapia intensiva (UTI), em decorrência da Covid-19, sua relação com os níveis de D-dímero e outros possíveis fatores associados. **Método:** Estudo transversal e retrospectivo, realizado em um hospital público universitário, entre abril e junho de 2021. A amostra foi composta por pacientes ≥ 15 anos com reação da transcriptase reversa seguida pela reação em cadeia da polimerase (RT-PCR) positivo para Sars-CoV-2, excluindo-se gestantes e puérperas que tiveram internamento na UTI. Os dados foram coletados e tabulados no programa Microsoft Office Excel ® e analisados com auxílio do software R Studio®. As variáveis contínuas foram expressas por média e desvio padrão, e as variáveis categóricas foram expostas em frequência absoluta (n) e relativa (%), e analisadas por Qui-quadrado, adotou-se um nível de confiança <0,05. **Resultados:** O estudo foi composto por 144 pacientes (61,1% do sexo masculino), com tempo de internamento médio de 14,2±10,3 dias na UTI. A incidência de trombose venosa profunda (TVP) nesses pacientes foi de 19% e 5% para tromboembolismo pulmonar (TEP). Com relação ao exame D-dímero, notou-se que o grupo com presença de TVP+TEP apresentou maior mediana. No total 31,2% pacientes foram anticoagulados. Notou-se uma relação estatística significativa entre a realização de hemodiálise e o desfecho clínico para óbito(p<0,05). **Conclusão:** Conclui-se que 21% dos pacientes avaliados tiveram TEV durante o internamento na UTI. O estudo contribuiu para caracterizar o perfil dos pacientes com Covid-19 internados na UTI que desenvolveram TEV, com propósito de apresentar dados consistentes que permitirão melhorar o planejamento do processo de assistência à saúde.

Palavras-chave: Covid-19; tromboembolismo venoso; d-dímero, trombose venosa.

Introduction

SARS-CoV-2 is a member of the betacoronavirus family responsible for the COVID-19 disease (Corona Virus Disease 2019), identified in patients with atypical pneumonia characterized by fever, dry cough and progressive dyspnea[1]. It has single-stranded RNA with typical structural proteins, involving the envelope (E protein), membrane (M), nucleocapsid (N) and spike (S) proteins, responsible for the viral infection. The S protein present on its surface binds to human ACE-2 (angiotensin-converting enzyme 2) receptors, a transmembrane protein, which, in turn, transfer its genetic material into the cell and soon after that begin their replication process[2-4].

Regarding the complications related to COVID-19, despite respiratory compromise being the main characteristic of the disease, some studies evidence the presence of clotting disorders associated with elevation of several biomarkers, with circulating D-dimer among them. Although the pathological effect of SARS-CoV-2 on the coagulation system is not well understood, it is clear that the release of several pro-inflammatory cytokines, cellular damage to the vascular endothelium and platelet activation may play an important role in the process[5].

Viral infection is closely related to severe pulmonary manifestations such acute respiratory distress syndrome (ARDS) due to its diffuse pulmonary or extrapulmonary inflammation, pulmonary thromboembolism (PTE), due to the erratic location of a thrombus in the pulmonary arteries and, mainly, coagulopathies for being a significant negative prognosis in the patient's condition, in most cases. In addition, Systemic Arterial Hypertension (SAH) and Diabetes Mellitus (DM) are a risk factor in aged patients; when untreated, they can lead to changes in coagulation and the immune system and to production of inflammatory cytokines[6].

It is known that the coagulation and hemostasis process maintains blood flow integrity. However, severe acute infection by SARS-CoV-2 results in hypercoagulability because it infects the endothelial cells that express angiogestin 2, mainly myocardial and lung cells. This damage can activate the tissue factor that produces thrombin from prothrombin by the action of the activated X factor. In addition to that, circulating platelets aggregate and form a phospholipid surface for the adhesion of components of the coagulation cascade, generating a large amount of thrombin, thus playing the role of exacerbated procoagulation. Consequently, a "cytokine storm" develops due to the sharing between immune response and coagulation regulation pathways releasing interleukins and tumor necrosis factor-α (TNF-α), together with expression of the tissue factor and of the Von Willebrand factor in endothelial cells[7].

From that point, venous thromboembolism occurs due to the formation of a clot inside a deep vein, most of the times located in the region of the lower limbs. In addition to that, erratic locations of the thrombo favor pulmonary thromboembolic complications as a result of tropism due to Type 2 pneumocytes, in the infection by COVID-19[6].

Thus, biomarkers such as D-dimer, a protein fragment released into circulation when a blood clot breaks down as a result of normal body processes or with the use of fibrinolytic medications, are sometimes associated with the presence of deep vein thrombosis or pulmonary embolism[8].

The occurrence of bleeding raises the hypothesis of a possible correlation with urea elevation in the acute renal failure presented by many patients, resulting from an important COVID-19 complication. It is known that uremia alters the platelet function, probably due to the accumulation of non-excreted metabolites, compromising adhesion and aggregation, as well as platelet activation[9].

This study aimed at evaluating the incidence of deep vein thrombosis and pulmonary thromboembolism in patients diagnosed with COVID-19 and hospitalized in an Intensive Care Unit, as well as at correlating with changes in laboratory tests, drug prescription and clinical outcome.

Methods

This is a retrospective, cross-sectional and descriptive study, carried out from April to June 2021 by consulting the Tasy® electronic medical record management system of adult patients (≥ 15 years old) with a confirmed COVID-19 diagnosis, through "real-time reverse transcription polymerase chain reaction" (RT-PCR) trials of samples collected through nasopharyngeal swabs, and admitted to the Intensive Care Unit (ICU) of a university hospital, excluding pregnant and postpartum women.

The study evaluated the following variables: age, gender, race, ICU hospitalization time, ward and mechanical ventilation, previous comorbidities, undergoing hemodialysis, number of hemodialysis sessions, diagnosis of deep vein thrombosis and/or pulmonary thromboembolism, days of anticoagulation with low molecular weight heparin (1 mg/kg every 12 hours) and dose adjustment due to acute renal failure, reports of bleeding in the oral and nasal cavities when introducing catheters and/or drains in medical records, prescription of antifibrinolytics, anticoagulants and clinical outcome.

In addition to that, laboratory test results for D-dimer (reference value < 500 ng/mL), troponin (< 19 ng/mL) and brain natriuretic peptide (< 469 ng/mL) at hospital admission were collected. For C-reactive protein (CRP), creatinine and urea, the results of the first and last collection procedures were considered. In order to identify platelet disorders, the hemograms collected during the study period were evaluated.

To detect patients with a diagnosis of deep venous thrombosis, the results of the ultrasound Doppler examinations of the deep venous system of the lower/upper limbs were consulted and, to identify patients with a diagnosis of pulmonary thromboembolism, angiotomography reports were consulted.

To verify the drug prescription, a filter was established according to the study period and an analysis of the anticoagulation need and time was performed, as well as of dose adjustment. In addition to that, the prescription of procoagulants, heparin antidotes and thrombolytics was tracked.

The data were typed in spreadsheet format into Microsoft Office Excel® 2010,where descriptive statistics of absolute and relative frequencies (for the qualitative variables) and graphical representations were developed.

In order to assess possible significant relationships between the outcome and the other observed qualitative factors or presence of DVT, PTE, both or their absence, χ^2 (Chi-square) tests were performed.

p-value<0.05 was considered statistically significant. The statistical analysis was performed in the R Studio® software (R Core Team, 2020).

The study was approved by the Committee of Ethics in Research with Human Beings of the State University of Western Paraná, based on opinion No. 4,953,327.

Results

During the period under study, 167 patients were hospitalized in the COVID-19 ICU No. 2 and, of these, 159 tested positive for SARS-CoV-2 and 15 were excluded because they were pregnant or puerperal women. Therefore, the sample was comprised by 144 patients aged > 15 years old, with 61.1% (88) males. Nearly 91.7% (132) of the patients required mechanical ventilation for a mean of 14 days, with a standard deviation of ±10. In relation to the hospitalization time, it was noticed that the ICU hospitalization time was nearly 14.2 days (±10.3),with 3.9 days in the ward (±6.6).

Regarding the age, gender, previous morbidities and race variables, Table 1 emphasizes that the proportion of patients aged less than 65 years old was higher (76.4%). However, when the clinical outcome was evaluated, it was observed that only 50.9% of them were discharged. In turn, among the patients aged at least 65 years old, this percentage dropped to 41.2%. According to the Chi-square test, this relationship is not significant (p-value>0.05), as can also be observed in relation to gender, race and presence or absence of previous comorbidities. The absence of statistical significance can be related to the number of patients evaluated and to the multiple association of factors that exerts an impact on the bivariate assessment.

Table 1. Characterization of the patients evaluated according to clinical outcome.

Variables	n (%)	Outcome		p-value[1]
		Discharge	Death	
Age (years old)				0.426
<65	110 (76.4)	56 (50.9)	54 (49.1)	
≥ 65	34 (23.6)	14 (41.2)	20 (58.8)	
Gender				0.143
Female	56 (38.9)	32 (57.1)	24 (42.9)	
Male	88 (61.1)	38 (43.2)	50 (56.8)	
Presence of comorbidities				0.455
Yes	106 (73.6)	54 (50.9)	52 (49.1)	
No	38 (26.4)	16 (42.1)	22 (57.9)	
Race				0.518
Asian	4 (2.8)	2 (50.0)	2 (50.0)	
White	112 (77.8)	52 (46.4)	60 (53.6)	
Black	4 (2.8)	3 (75.0)	1 (25.0)	
Brown	22 (15.3)	13 (59.1)	9 (40.9)	
Total	144 (100.0)	70 (48.6)	74 (51.4)	

[1]Chi-square test.

It was observed that 73.6% (106) of the patients included in the study presented some previous comorbidity, as well as that 29.2% (31) had only one disease, 33.0% (35) had two, 20.8% (22) had three and 17.0% (18), four or more. Systemic Arterial Hypertension (SAH) was the most common with 47.2%, followed by Type 2 Diabetes *Mellitus* with 28.5% and by obesity with 25.0%.

It was found that 94.4% (136) of the patients underwent the D-dimer examination at admission. In general, the mean value was 18 times above the reference value (9,575.7±15,341.8 ng/ml), with variability of the results higher than the mean.

Figure 1 shows that the dispersion graph referring to age does not present any clear trend or relationship between these factors. In addition to that, when observing the result according to the outcome, there are cases of patients both discharged from the hospital and who evolved to death, presenting D-dimer results considered high.

Figure 1. Relationship between the D-dimer test and the patients' age according to clinical outcome.

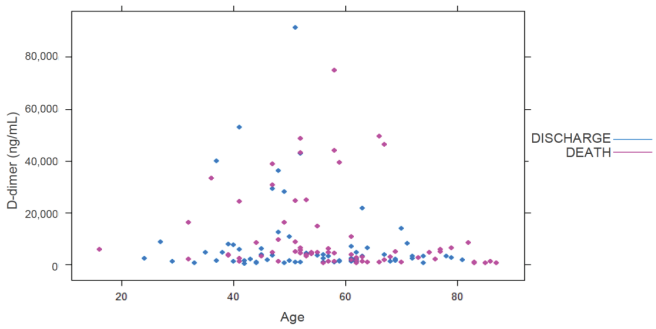
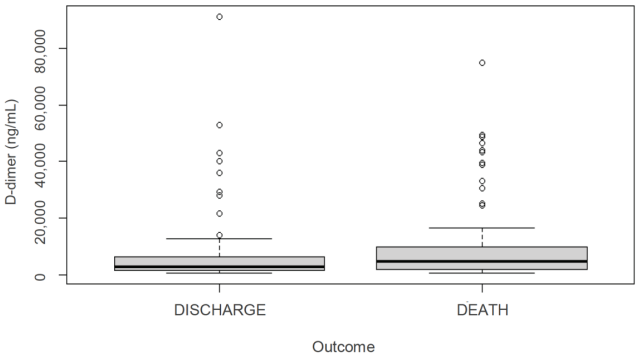


Figure 2 allows seeing several cases considered statistically divergent from the others, in both groups. The mean D-dimer values between the groups with discharge and death as outcomes were 8,046.5 (±14,983,9) and 11,060.6 (±15,646.9) ng/ml, respectively.

Figure 2. Relationship between the D-dimer test and clinical outcomes: discharge and death.



It was noticed that 36.1% (52) of the patients underwent hemodialysis sessions with a mean of 3.6 sessions/patient; and a statistically significant relationship was identified between hemodialysis and the clinical outcome of death (p-value<0.0001). Among those that underwent hemodialysis, 17.3% (9) were discharged from the hospital, whereas in the group that did not undergo such procedure, 87.1% (61) of the patients were discharged.

Among the exams performed to screen thrombotic complications, it was identified that 49.3% (71) of the patients were subjected to Eco-Doppler. A total of 27 deep venous thrombosis cases were detected, with 19% incidence; of these, 44.4% (12) were discharged from the hospital with a prescription of direct oral anticoagulant (DOAC).

It was observed that 42.2% (61) of the patients were subjected to an ecocardiogram during their hospitalization and that 52.4% (32) presented pulmonary hypertension. In addition, 14.6% (21) were subjected to angiotomographies, which identified 7 cases of pulmonary thromboembolism, with 5% incidence. Nearly 71.4% (5) were discharged with a DOAC prescription. In total, 57.1% (4) patients with PTE were concomitantly diagnosed with DVT.

When evaluating the results referring to the laboratory tests, Table 2 allows seeing the difference between the mean values according to presence or absence of PTE and DVT. However, as the number of patients with each condition is extremely different, it is not suitable to perform any statistical inference.

Table 2. Laboratory characteristics of the sample.

Test (Reference value)	**Presence of DVT** (23)		**Presence of PTE** (3)		**Presence of DVT and PTE** (4)		**Absence of DVT and PTE** (114)	
D-dimer (> 500)	16,309±19,257		33,995±49,739.6		30,166.8±21,383		6,736.9±10,782	
Troponin (19 ng/mL)	96.3±141.1		264±330		140.7±145.8		437.9±1,491.8	
ProBNP (469 pg/mL)	6,709±12,600		997.3±146.41		2,452±3,354		5,249±10,460.6	
	Initial	Final	Initial	Final	Initial	Final	Initial	Final
PCR (From 0.0 to 0.9 mg/dL)	15.8±11.5	14±12.9	11.9±8.2	7.7±7.9	14.2±17.7	4.8±1.9	12.8±9.3	13.5±14.5
Creatinine (From 0.7 to 1.2 mg/dL)	2.8±2.8	3±2.9	1.3±0.5	1.1±0.5	2.3±2.3	2.7±2.1	3.0±3.2	2.8±2.7
Urea (From 19 to 43 mg/dL)	96.9±75	118.5±109	69.3±31	123.3±157	75.0±66	74.7±64	103.7±126	112.1±82

In relation to the PCR, Creatinine and Urea tests, it is observed that there is no clear trend in the relationship between the result in the patients' first and last dosage. The mean PCR results were 13.3 mg/dL (±9.8) in the first dosage and 13.2 (±14.0) in the last whereas mean creatinine presented 2.9 mg/dL (±3.1) in the first dosage and 2.8 (±2.7) in the last. In relation to the mean urea value, the results were 101 mg/dL (±117.0) in the first dosage and 112 (±87.4) in the last.

Among the laboratory alterations evaluated, it was evidenced that 20.14% (29) of the patients included in the study had some thrombocytopenia episode during hospitalization and that 44.8% (13) had platelet counts below 50,000/mm^3. It was identified that 63.9% (92) of the individuals had reports of bleeding in their medical charts and that 34.8% (32) were anticoagulated with enoxaparin.

In this sample, it was observed that 31.2% (45) of the patients were anticoagulated for a mean period of 11.9 days and that 0.69% (1) had the Alteplase thrombolytic prescribed. However, this period and percentage of incidence were different according to presence or absence of PTE and DVT (Table 3). Nearly 8.3% (9) of the patients underwent dose adjustment due to their renal function. Regarding management of bleeding, 6.2% (9) of the patients were prescribed antifibrinolytics/anticoagulant antagonists. When assessing the situation of patients on anticoagulation or not in relation to the group with presence of DVT, PTE, DVT+PTE or absence of both, a significant association between these factors was evidenced (p-value<0.0001). Among the patients with DVT, nearly 82.6% were anticoagulated; in turn, in the group with no DVT or PTE, the highest percentage corresponded to not anticoagulated patients (83.3%).

In all, 51.4% (74) of the patients evolved to death and 48.6% (70) were discharged to the ward. Nearly 12.2% (9) had confirmed brain death and 5.4% (4) did not finish the protocol due to serious clinical conditions. It was observed that 16.2% (12) of the patients that evolved to death had hemorrhagic strokes.

Discussion

According to a study carried out in China, the most prevalent comorbidity among the patients who required ICU hospitalization was Diabetes *Mellitus*[10]. In another study, also developed in China, among the 39% of the patients who recovered, the most common pre-existing chronic disease was Systemic Arterial Hypertension with 48% of the population[11], data similar to those obtained in this study.

In a study carried out in Italy on COVID-19, higher prevalence of DVT was also observed in male patients, representing 57.6%, and in hypertensive patients (63.3%)[12]. In another study, preponderance of men with a high prevalence of obesity and other chronic medical comorbidities was observed, especially cardiovascular diseases, hypertension and Diabetes *Mellitus*[13].

A correlation was observed with severity of the disease in patients with elevated D-dimer levels in this study. It is known that it is a reticulated fibrin degradation product indicating increased thrombin generation and fibrin dissolution by plasmin. However, high D-dimer levels are common in severely-ill individuals with a number of infectious/inflammatory diseases, and do not always imply an increased risk of thrombosis[14].

With onset of the pandemic, an increase in the incidence of thromboembolic events was reported in parallel[15]. In a study comparing the pulmonary pathology of seven individuals who died due to COVID-19, a severe endothelial lesion was observed, with generalized thrombosis, microangiopathy and alveolar capillary microthrombi, as well as increased angiogenesis, all significantly more prominent in the lungs of these patients when compared to the lungs of controls who died due to influenza or to other causes[16].

In a retrospective study conducted with 449 patients with severe COVID-19, enoxaparin (from 40 to 60 mg once a day), it proved to be associated with improved survival when compared to no pharmacological prophylaxis, especially in those with elevated D-dimer[17]. This led to the use of low molecular weight heparin in addition to the indications currently reported in the international guidelines[18].

Table 3. Relationship between treatment and outcomes according to the DVT, PTE, DVT+PTE, and Absence of DVT+PTE groups

	DVT (23)	**PTE** (3)	**DVT+PTE** (4)	**Absence of DVT+PTE** (114)	**p-value**
Anticoagulated patients From 1 mg kg 12/12h)	19 (82.6)	3 (100.0)	4 (100.0)	19 (16.7)	<0.0001
Not anticoagulated patients	4 (14.8)	0 (0)	0 (0)	95 (83.3)	
Days on anticoagulation	11.2±13.7	19.0±16.6	20.7±7.5	1.2±4.4	---
Dose adjustment due to renal function	7 (30.4)	0 (0.0)	2 (50.0)	48 (42.1)	0.3539
Thrombocytopenia (< 50,000)	7 (30.4)	0 (0.0)	2 (50.0)	20 (17.5)	0.1742
Report of bleeding	16 (69.5)	3 (100.0)	2 (50.0)	71 (62.3)	0.4791
Outcome: death	14 (60.9)	1 (33.3)	1 (25.0)	58 (50.9)	0.5038
Hemorrhagic stroke	2 (8.7)	0 (0.0)	0 (0.0)	10 (8.8)	0.9892

Results expressed as mean ± standard deviation or as absolute and percentage frequencies in between parenthesis.

Reduction of the enoxaparin dose based on antifactor Xa activity or renal function reduces the risk of bleeding. Laboratory monitoring of antifactor Xa by chromogenic assay in anticoagulated patients with low molecular weight heparin, in the presence of renal failure, obesity and COVID-19 due to changes in the standard hemostasis parameters in this particular pathology and, in view of high rates of thrombotic events, for management of anticoagulant treatment with dose adaptation[19]. Antifactor Xa monitoring is recommended by the Anticoagulation Forum four hours after the subcutaneous injection and has a pre-established therapeutic range of 0.3 – 0.7 IU/ml[20].

Adopting monitoring for anticoagulant treatment through anti-Xa measurement in COVID-19 patients, due to changes in the standard hemostasis parameters, can be a measure to ensure efficacy and safety of the anticoagulant therapy.

In a study conducted in a French ICU with patients severely infected by SARS-CoV-2, 15 brain computed tomography and 10 brain magnetic resonance imaging exams were performed in 25 individuals because of pathological neurological tests, and 4 showed hemorrhagic complications or ischemic stroke[15].

The main limitation of this study was that the sample was relatively small. In addition to that, a systematic and standardized evaluation of the thromboembolic events was not performed, and the imaging tests were performed based on the evolution of the clinical or laboratory parameters. Another important factor to note would be the need for a comparative study with non-COVID-19 patients admitted to the ICU in a period similar to the one evaluated.

Conclusion

It is concluded that the study indicates 21% incidence of clinically relevant VTE associated with the SARS-CoV-2 infection. The incidence values for DVT and PTE were 19% and 5%, respectively. The patients who underwent hemodialysis during hospitalization had a significantly higher mortality rate than the others. Thus, the need for further studies is noted to evaluate a possible relationship between COVID-19 and the incidence of venous thromboembolism.

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Collaborators

Groll, SV: data collection; interpretation of the study; writing of the article or relevant critical review of the intellectual content; approval of the final version. Santos, A: data analysis and interpretation; approval of the final version. Caldeira, LF and Sanches, AC: relevant critical review of the intellectual content; approval of the final version.

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Conflict of interest statement

There are no conflicts of interest to declare.

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