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Clinical evolution of patients with COVID-19: anticoagulation impact

Evolução clínica dos pacientes com COVID-10: impacto da anticoagulação

Evolución clínica de pacientes con COVID-10: impacto de la anticoagulación

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Abstract
Coronavirus disease 19 (COVID-19) mainly targets the respiratory system and progresses to a severe form in up to 16% of in-patients, causing thromboembolic disorders, sepsis and death. In severe cases, a pro-inflammatory cytokines "storm" develops that trigger clotting pathways disorders and thromboembolism. The objective of this study was to assess the evolution of COVID-19 patients, admitted to an intensive care unit (ICU), and to observe the impacts of anticoagulation therapy in those patients with critical parameters. This was a cross-sectional study, reviewing the medical records of patients admitted to the ICU, with a confirmed diagnosis of COVID-19, in the period between March and December 2020, in a general hospital in southern Brazil. Among the 231 patients assessed, a mortality rate of 66.2% was recorded. Among the most relevant findings associated with death are the presence of heart disease and previous systemic arterial hypertension (SAH), clinical evolution with renal failure and creatinine clearance <30 and hyperbilirubinemia. Out of the 103 patients who were on anticoagulation therapy under critical parameters, 88 died. Advanced age (≥ 60 years), presence of comorbidities, complications during hospital stay, laboratory alterations and evolution with transinfectious hepatitis were associated with mortality. Anticoagulation therapy under critical parameters was associated with a higher death rate, with clinical evolution between ICU admission and fatal outcome after two weeks of infection.
Keywords: COVID-19; Evolution; Anticoagulation; Intensive Care Unit.

Resumo
A doença do coronavírus 19 (COVID-19) tem como alvo principal o sistema respiratório e evolui para forma grave em até 16% dos casos hospitalizados, com a instalação de transtornos tromboembólicos, sepse e morte. O objetivo deste estudo foi avaliar a evolução de pacientes com COVID-19, internados em unidade de terapia intensiva (UTI), observando os impactos da anticoagulação naqueles com parâmetros críticos. O objetivo deste estudo foi avaliar a evolução de pacientes com COVID-19, internados em unidade de terapia intensiva (UTI), observando os impactos da anticoagulação naqueles com parâmetros críticos. Estudo transversal, realizado com a revisão de prontuários de pacientes internados em UTI, com diagnóstico confirmado de COVID-19, no período compreendido entre março e dezembro de 2020, em um hospital geral no sul do Brasil. Dentre os 231 pacientes analisados, observou-se letalidade de 66,2%. Dentre os achados mais relevantes associados à óbito estão a presença de cardiopatia e hipertensão arterial sistêmica (HAS) prévia, evolução clínica com insuficiência renal e clearance <30 e hiperbilirrubinemia. Dos 103 pacientes internados que estavam com anticoagulação sob parâmetros críticos, 88 evoluíram com óbito. Foram

associados à mortalidade a idade avançada (≥ 60 anos), presença de comorbidades, complicações durante a internação, alterações laboratoriais e evolução com hepatite transinfecciosa. Anticoagulação sob parâmetros críticos foi associada à maior taxa de óbito, com evolução clínica entre admissão em UTI e desfecho fatal após duas semanas de infecção.
Palavras-chave: COVID-19; Evolução; Anticoagulação; Unidade de Terapia Intensiva.

Resumen
La enfermedad por coronavirus 19 (COVID-19) tiene como objetivo principal el sistema respiratorio y progresa a forma grave hasta en un 16% de los casos hospitalizados, con instalación de trastornos tromboembólicos, sepsis y Muerte. El objetivo de este estudio fue evaluar la evolución de pacientes con COVID-19, ingresados en una unidad de cuidados intensivos (UCI), observando los impactos de la anticoagulación en aquellos con parámetros críticos. El objetivo de este estudio fue evaluar la evolución de pacientes con COVID-19, ingresados en una unidad de cuidados intensivos (UCI), observando los impactos de la anticoagulación en aquellos con parámetros críticos. Estudio transversal, realizado con la revisión de histórias clínicas de pacientes ingresados en la UTI, con diagnóstico confirmado de COVID-19, entre marzo y diciembre de 2020, en un hospital general del sur de Brasil. Entre los 231 pacientes analizados se observó una tasa de mortalidad del 66,2%. Entre los hallazgos más relevantes asociados a muerte se encuentran la presencia de cardiopatía e hipertensión arterial sistémica (HAS) previa, evolución clínica con insuficiencia renal y aclaramiento < 30 e hiperbilirrubinemia. De los 103 pacientes hospitalizados que estaban en anticoagulación bajo parámetros críticos, 88 fallecieron. La edad avanzada (≥ 60 años), la presencia de comorbilidades, las complicaciones durante la hospitalización, las alteraciones de laboratorio y la evolución con hepatitis transinfecciosa se asociaron con la mortalidad. La anticoagulación bajo parámetros críticos se asoció con una mayor tasa de mortalidad, con evolución clínica entre el ingreso en UCI y el desenlace fatal das semanas después de la infección.
Palabras clave: COVID-19; Evolución; Anticoagulación; Unidad de Cuidados Intensivos.

1. Introduction

Coronavirus disease 19 (COVID-19) emerged in late 2019 in China. It is caused by a viral infection that has as its main target the respiratory system and has generated a recent pandemic, still current, on a global scale, with high rates of morbidity and mortality (Weston, et.al., 2020). Named Severe Acute Respiratory Syndrome caused by coronavirus type 2 (SARS-COV-2) by the World Health Organization (WHO), the disease represents an important public health problem, with social and economic impact, given its high transmissibility, spreading on a massive scale following a geometric progression and developing into the severe form in up to 16% of hospitalized patients (Rico-Mesa, et.al., 2020; Guan, et.al., 2020).

The pathophysiology of COVID-19 has not yet been fully clarified, also due to the heterogeneity of the clinical conditions. The infection is characterized by signs and symptoms such as fever (98%), cough (76%) and myalgia/fatigue (44%), and may worsen with the onset of adult acute respiratory distress syndrome (ARDS) disseminated intravascular coagulation (DIC), sepsis and death. Although most patients evolve with the oligosymptomatic or asymptomatic form of the disease, studies report that advanced age and the presence of comorbidities such as systemic arterial hypertension (SAH), heart disease, diabetes mellitus, chronic obstructive pulmonary disease (COPD), neoplasms, obesity and habits such as smoking are common findings in patients who have progressed to a serious condition requiring admission in an intensive care unit (ICU) and death (Guan, et.al., 2020; Espinosa, et.al., 2020; Huang, et.al., 2020).

One of the frequent complications which is the target of research is the evolution of critically ill patients experiencing thromboembolic events. Patients admitted to the ICU exhibit risk factors common to general thrombotic complications such as older age, immobilization, obesity, sepsis, respiratory or heart failure, trauma, use of vasopressors and mechanical ventilation (Minet, et.al., 2015). In addition, studies indicate that SARS-CoV-2, alone, has factors that induce thrombus formation, since COVID-19 leads to a "stormy soar" of pro-inflammatory cytokines and, as a result of this exaggerated inflammatory response, a platelet hyperactivation occurs as well as abnormal clot formation and inhibition of physiological anticoagulant pathways, thus leading to hypercoagulability. Miesbach and colleagues reported that, in addition to factors intrinsic to the patient as well as factors specific to the current pneumonia, SARS-CoV-2 causes an increase in angiotensin II as an immunological reaction against the virus as well as increased expression of tissue factor and plasminogen inhibitor 1 which, added to the soaring pro-

inflammatory cytokines, result in hyperactivation of the coagulation cascade and increased risk of progression to disseminated intravascular coagulation (DIC) (Miesbach, et.al., 2020).

Due to the high rate of venous thromboembolism (VTE) as a complication of SARS-CoV-2 infection, prophylactic anticoagulation treatment for infected patients has become a consensus. Prophylaxis is recommended in mild to moderate cases where patients present risk factors for thrombus formation, provided there are no contraindications (Zhai, et.al., 2020). Risk factors can be calculated with the risk assessment methodology (RAM) using the PADUA or IMPROVE RAM score for clinical patients, when there is a high to moderate risk for VTE (Darzi, et.al., 2020). In surgical patients, the calculation is guided by the evaluation of CAPRINI RAM (Cronin, et.al., 2019). There is also a consensus that all critically ill patients should be considered high-risk patients for thrombotic complications, and therefore thromboprophylaxis should be indicated, either with medication or by intermittent pneumatic compression (IPC) in case of contraindication of pharmacological therapy (Zhai, et.al., 2020).

Most studies enhance the importance of anticoagulation in SARS-CoV-2 infection, but little is known about mechanisms that interrupt the domino effect of hypercoagulability and DIC. Therefore, studies in this area are required for an improved approach and clinical outcome. Thus, this study aimed to analyze the evolution of patients with COVID-19, admitted to an intensive care unit (ICU), in a general hospital in southern Brazil, observing the impact of anticoagulation in critically ill patients and associating it with the clinical outcome.

2. Methodology

This study was approved by the *Comitê de Ética em Pesquisa* (CEP, Research Ethics Committee) of the *Universidade do Sul de Santa Catarina* (UNISUL), in compliance with the precepts of Resolution 466/2012 of the National Health Council, under Opinion No. 4,632,402, dated April 2021.

This was an epidemiological study with observational design, analytical cross-sectional type, carried out by reviewing the medical records of patients admitted to an intensive care unit (ICU), with a confirmed diagnosis of COVID-19, during the period between March and December 2020, in a general hospital in southern Brazil.

Data were collected between April and July 2021. Patients admitted to adult and pediatric ICUs, with a confirmed diagnosis of COVID-19 obtained with the real-time polymerase chain reaction test (RT-PCR) or viral antigen test, or even by epidemiological linkage at medical judgment according to the clinical condition and imaging exams presented. The sample was of the census type, totaling 247 patients.

Demographic data such as age, gender and race were included as variables of interest to the study, as well as habits such as smoking and alcohol consumption, presence of comorbidities and previous history of acute myocardial infarction (AMI) in the last year or of cerebrovascular accident (CVA) in the last two years, with a time limit proposed after analysis of the literature in relation to care with thromboprophylaxis (Touzé, et.al., 2005). Among the complications during ICU stay, renal failure, coagulopathy, blood pressure >180/110 and liver failure were considered. Such complications were verified from laboratory and clinical tests performed at admission and periodically during hospitalization. Limiting reference values were those established by the clinical analysis laboratory used by the hospital. Renal function was assessed from the association of serum creatinine >1.5 with glomerular filtration rate (GFR) and oliguria. Patients exhibiting GFR <60 ml/min/1.73^2 without previous kidney disease, were considered as acute renal failure (ARF) patients; if GFR <30 ml/min/1.73^2 patients were considered with severe ARF. On the other hand, in those patients with chronic renal failure (CRF), an acute CRF was claimed if a drop of ≥ 25% in GFR occurred (Levey, et.al., 2015). Liver damage was considered as absolute alanine aminotransferase (ALT) values >56 U/L and aspartate aminotransferase (AST) >40 U/L, presence of serum albumin <3.5 and hyperbilirubinemia>1.1. Coagulation disorders were recorded in the presence of platelets number <50,000 (Williamson, et.al.,

2013), active bleeding and absolute D-dimer values>0.5, prothrombin time>16.5 seconds and activated partial thromboplastin time >38.1 seconds. Hemodynamic changes were also observed, through blood pressure values (looking for peaks >180/110 mmHg in measurements performed every 6 hours) and thromboembolic and cardiac events recorded from the evolution of specialists in each medical area (AMI or stroke during hospitalization).

In-hospital anticoagulation was analyzed using four factors: type, dose, duration and adequacy. All anticoagulants used during hospital stay were considered. We also included in the study the daily anticoagulation therapy used prior to admission, the type and whether dual platelet antiaggregation therapy was used. The impact of drug anticoagulation was evaluated based on the patient's clinical condition and laboratory parameters. Patients' critical parameters were considered those of patients with active bleeding (absolute contraindication for anticoagulation) and/or two or more of the following findings: prothrombin time >16.5s, severe thrombocytopenia (< 50,000/mm^3) and renal failure with creatinine clearance <30 ml/min/1.73^2 (Williamson, et.al., 2013; Zhou, et.al., 2020; Tang, et.al., 2020).

Out of the 247 initial patients, 16 were excluded from the study due to transfer to other hospitals, making the analysis of the clinical outcome unfeasible. Thus, 231 participants were included in the survey.

The database was organized in Excel and analyzed using the SPSS v.21 software (IBM, Armonk, New York, USA). Quantitative variables were described using mean, median and standard deviation measurements. Qualitative variables were described using absolute and percentage frequencies. To compare the independent variables and the outcome, Pearson's chi-square test or Fisher's exact test was used for qualitative variables, and the Wilcoxon-Mann-Whitney U test was used to compare medians. The level of statistical significance adopted was 5%.

3. Results

During the study period, 231 in-patients with COVID-19 admitted in the ICU at the study site were included; 58.4% were male and the mean age was 59.1 (SD ±19.8) years; the age range was 0 to 96 years. Table 1 presents the demographic, laboratory and clinical characteristics of the study participants.

Table 1 – Demographic, laboratory, and clinical characteristics of critically ill patients with COVID-19 and their association with outcome.

	Total	**Hospital discharge**	**Death**	**p-value**
		n (%)		
Age				**<0,001**
0-19	13 (5,6)	12 (92,3)	1 (7,7)	
20-59	87 (37,7)	45 (51,7)	42 (48,3)	
≥60	131 (56,7)	21 (16,0)	110 (84,4)	
Sex				0,495
Male	135 (58,4)	48 (35,6)	87 (64,4)	
Female	96 (41,6)	30 (31,3)	66 (68,8)	
Race				0,335
White	211 (91,3)	74 (35,1)	137 (64,9)	
Non-white	17 (7,4)	4 (23,5)	13 (76,5)	
Social habits				
Alcoholism	4 (1,6)	0	4 (100,0)	0,188†
Smoking	14 (5,7)	2 (14,3)	12 (85,7)	0,090

Comorbidities				
Systemic arterial hypertension	130 (56,3)	35 (26,9)	95 (73,1)	**0,004**
Diabetes mellitus	62 (26,8)	16 (25,8)	46 (74,2)	0,075
Heart disease	59 (25,5)	10 (16,9)	49 (83,1)	**0,001**
Vascular disease	15 (6,5)	3 (20,0)	12 (80,0)	0,208†
Kidney disease	16 (6,9)	1 (6,3)	15 (93,8)	**0,013†**
Respiratory disease	41 (17,7)	12 (29,3)	29 (70,7)	0,396
Obesity	58 (25,1)	24 (41,4)	34 (58,6)	0,212
Neoplasm	12 (5,2)	1 (8,3)	11 (91,7)	**0,040†**
Morbid past history				
Acute myocardial infarction	15 (6,5)	2 (13,3)	13 (86,7)	0,074
Cerebrovascular accident	6 (2,6)	1 (16,7)	5 (83,3)	0,347†
Complications in hospitalization				
Renal failure	139 (60,1)	15 (10,7)	124 (89,2)	**<0,001**
Coagulopathy	20 (8,7)	3 (15,0)	17 (85,0)	0,062
Active bleeding	5 (2,2)	1 (20,0)	4 (80,0)	0,448†
Blood pressure >180/110	124 (53,7)	44 (35,5)	80 (64,5)	0,552
Albumin <3.5	30 (13,0)	10 (33,3)	20 (66,7)	0,413†
Hyperbilirubinemia on admission	12 (5,2)	3 (25,0)	9 (75,0)	0,473†
Hyperbilirubinemia in evolution	49 (21,2)	8 (16,3)	41 (83,7)	**0,028**
Glomerular filtration rate <30 ml/min/1.73^2	138 (59,7)	15 (10,9)	123 (89,1)	**<0,001**
Clinical outcome				
Hospital discharge	78 (33,8)	-	-	-
Death	153 (66,2)	-	-	-

Laboratory tests	**Total**	**Hospital discharge**	**Death**	**p***
		Median (SD)		
Admission				
LDH	386,5 (60,0)	356,0 (15,7)	409,0 (88,8)	**0,040**
D-dimer	1,8 (0,3)	0,8 (0,5)	2,4 (0,4)	**0,022**
Ferritin	834,0 (130,6)	706,5 (117,3)	861,5 (182,7)	0,547
PT	13,8 (0,2)	13,6 (0,3)	14,1 (0,2)	**0,008**
aPTT	36,2 (3,1)	36,2 (3,0)	37,3 (1,0)	**0,024**
AST	42,0 (11,4)	41,0 (4,0)	43,0 (16,6)	0,629
ALT	34,0 (11,3)	42,0 (5,0)	32 (16,3)	**0,028**
Evolution				
LDH	560,0 (232,1)	484,0 (25,0)	610 (348,3)	**<0,001**
D-dimer	2,4 (0,6)	1,3 (0,8)	4,4 (0,8)	0,066
Ferritin	909,0 (184,0)	628,3 (140,9)	1239,5 (272,2)	**0,028**
PT	16,2 (0,3)	15,2 (0,4)	16,9 (0,5)	**<0,001**
aPTT	45,9 (3,7)	45,8 (3,7)	58,2 (2,8)	**<0,001**
AST	89,0 (80,5)	67,0 (9,2)	100,5 (115,3)	**0,001**
ALT	74,5 (25,9)	72,0 (14,8)	75,5 (36,7)	0,590

†Fisher exact proof. * Wilcoxon-Mann-Whitney U test. Source: Hospital Nossa Senhora da Conceição, Tubarão, Santa Catarina, Brazil.

As for anticoagulation therapy performed in an in-hospital setting, the drugs used were acetylsalicylic acid (ASA), cilostazol, low molecular weight heparin (LMWH) at doses of 20mg, 40mg, 60mg or 80mg, clopidogrel, fondaparinux, novel oral anticoagulants (NOACs) and unfractionated heparin (UFH) every 8 hours or every 12 hours. Among the main findings, it was observed that out of the 57 patients who used LMWH at a dose of 20mg, 47 (87.7%) died (p <0.001) and out of the 58 patients who used UFH every 8 hours, 47 (81%) died (p = 0.007). The other anticoagulants were not statistically significant in relation to the clinical outcome. Anticoagulation characteristics and clinical outcome are shown in Table 2.

Table 2 – Anticoagulation characteristics and clinical outcome of critically ill patients with COVID-19.

	Total	**Hospital discharge**	**Death**	**p**
		n (%)		
Anticoagulation dose				
Full anticoagulation	76 (33,0)	28 (36,8)	48 (63,2)	0,448
Prophylactic anticoagulation	150 (55,2)	46 (30,7)	104 (69,3)	0,216
Duration of anticoagulation				**<0,001**
< 2 weeks	92 (40,7)	17 (18,5)	75 (81,5)	
2 to 4 weeks	89 (39,4)	32 (36,0)	57 (64,0)	
>4 weeks	42 (18,6)	21 (50,0)	21 (50,0)	
Anticoagulation and clinical parameter				**<0,001**
Severe	128 (55,4)	63 (49,2)	65 (50,8)	
Critical	103 (44,5)	15 (14,6)	88 (85,4)	
Previous anticoagulation				**0,002**
Single	41 (17,7)	9 (22,0)	32 (78,0)	
Duo	11 (4,8)	62 (41,9)	86 (58,1)	

Source: Hospital Nossa Senhora da Conceição, Tubarão, Santa Catarina, Brazil.

4. Discussion

The assessment of COVID-19 patients' evolution indicated that advanced age and the presence of previous diseases associated with viral infection imply an unfavorable outcome, with a greater need for ICU admission and an increased risk of up to 2.4 times of death outcome (Espinosa, et.al., 2020; Huang, et.al., 2020; Zhou, et.al., 2020, Li, et.al., 2020; Li, et.al., 2020), a condition that was also observed in the present study. Out of the 247 patients assessed, 153 (66.2%) died. Findings that were common in fatal cases were advanced age (≥60 years), systemic arterial hypertension, neoplasia, chronic kidney disease, and heart disease. The presence of comorbidities is common in the elderly and studies report that in these patients the risk of unfavorable evolution is greater; some scholars consider comorbidities an independent predictor of mortality with a twofold increased risk of hospitalization, disease severity and death (Salazar, et.al., 2020; Zhang, et.al., 2021; Ruan, et.al., 2020; Petrilli, et.al., 2020).

The link between viral infection, previous heart disease and higher mortality can be explained by the influence of the angiotensin-converting enzyme 2 present in cardiac and vascular cells and by the direct invasion of the SARS-CoV-2 virus of the cardiomyocytes, causing lesions. Indirectly, cardiac injury occurs as a result of severe hypoxia and inflammatory storm caused by the respiratory infection, leading to myocarditis, arrhythmias and death (Goha, et.al., 2020). It is worth mentioning that 17.7% of the patients assessed in the present study were on previous anticoagulation therapy, worsening the prognosis because, in addition to the deficit caused by the virus, studies report that the presence of cardiac injury causes a greater predisposition for coagulation disorders, increasing the risk of thromboembolic events. Shi et al, after evaluating 416 in-patients with and without cardiac injury, observed a mortality rate almost 12 times higher when there is an associated cardiac

injury (51.2% vs. 4.5%) and also reported that these patients exhibited a shorter evolution of symptoms and hospital admission, in addition to a higher risk of outcome with complications (Shi, et.al., 2020).

In the present study we also observed a lethality rate of 83.7% in the presence of hyperbilirubinemia during ICU admission due to COVID-19. It is not yet known whether the liver injuries in these patients are a result of the medications used to treat the respiratory infection or a direct liver injury by the virus and canalicular cells. Studies report that angiotensin-converting enzyme 2, in addition to being present in lung cells, is also expressed in bile ducts (higher prevalence) and hepatocytes, which may explain the pathophysiology of COVID-19 on the liver; however, the possibility of drug hepatitis should not be excluded (Xiaoqiang et.al., 2020).

A meta-analysis published in November 2020 indicated that critically ill patients have higher alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels than non-critically ill patients and that elevated AST alone is associated with higher mortality. In addition, almost half of the studies evaluated reported that critically ill patients have high levels of serum bilirubin (>17 mmol/L) and indirect markers for liver damage increased by up to 7 times in severe conditions (Wong, et.al., 2020). Such findings enhance the impact of transinfectious hepatitis on the outcome of death, since the liver, which is directly associated with the depuration and coagulation system, when it is insufficient, fails to remove inflammatory toxins from the body and causes clotting alterations, increasing hemodynamic instability and risk of bleeding and/or thromboembolic events.

It is also common to observe a higher incidence of acute renal failure (ARF) in COVID-19 critical conditions. This can be explained by the fact that SARS-CoV-2 causes direct damage to renal structures, which, added to indirect mechanisms - such as a hyperinflammatory and hypoxic state, low oral intake, hemodynamic changes and immune system imbalance -, increase the risk of ARF, with or without proteinuria, during the infection (Ertuğlu, et.al., 2020; Kudose, et.al., 2020; Puelles, et.al., 2020). Our study showed that 60.1% of patients reviewed developed ARF during hospitalization and, out of these, 89.2% died. Chan et al. reported a higher overall mortality rate in patients who developed this complication compared to those without injury, and in the association between ARF and ICU admission, the percentage of death was 6 times higher. Findings common to non-survivors were elevation of serum albumin and serum creatinine, in addition to the presence of proteinuria and hematuria that increase the risk of mortality (Chan, et.al., 2021; Cheng, et.al., 2020).

The cardiac, hepatic and renal systems have as some of their functions, the carriage of the flow of oxygen and nutrients, the balance of the coagulation system and purification of inflammatory and harmful toxins of the body and the maintenance of blood viscosity and hemodynamic stability. The insufficiency of these systems, added to the hyperinflammatory state caused by SARS-CoV-2, trigger changes that cause a fatal prothrombotic state in critically ill patients.

It is known that SARS-CoV-2 infection and its evolution into the severe form does not follow a common profile or pattern and, due to the individually characterized involvement, the follow-up with laboratory tests must be carried out periodically. The present study observed that high levels of lactic dehydrogenase (LDH), D-dimer, prothrombin time (PT), activated partial thromboplastin time (aPTT) and alanine aminotransferase (ALT) at admission determined a worse prognosis. During evolution, altered levels of LDH, ferritin, PT, aPTT and aspartate aminotransferase (AST) were associated with a higher death rate. It is important to emphasize that altered D-dimer values are associated with thromboembolic events and raised PT, in addition to thrombocytopenia, in infectious conditions, increasing the risk of disseminated intravascular coagulation, which is part of the criteria of the International Society on Thrombosis and Hemostasis (ISTH) (Asakura, et.al., 2016). Studies also enhance that D-dimer values greater than 1 μg/mL, lactate dehydrogenase >245, serum ferritin >300, and prothrombin time >16 during admission, in addition to elevated leukocytosis, AST and ALT, are associated with worse clinical outcome (Huang, et.al., 2020; Zhou, et.al., 2020; Li, et.al., 2021; Li, et.al., 2020).

Due to the coagulopathy developed by COVID-19, the ISTH recommends serial assessments of D-dimer, PT and platelet count for risk stratification and management definition. Furthermore, it suggests that all in-patients except those with active bleeding and platelet counts below 25 × 10 9/mm3 should receive prophylactic doses of low molecular weight heparin (LMWH) throughout their hospital stay, regardless of renal clearance or raised PT (Thachil, et.al., 2020).

However, in the present study it was observed that, among the 153 fatal cases recorded, 85.4% of the patients were on anticoagulation therapy in view of active bleeding, thrombocytopenia <50,000/mm3, renal clearance <30 ml/min/1,73^2 and/or PT >16 .5 seconds and 81.5% died within 2 weeks from hospital admission. Coagulation disorders induced by COVID-19 are usually subtle, causing little or no PT and aPTT rise, in addition to mild thrombocytopenia, but at the same time, they induce an increase in D-dimer and serum fibrinogen levels, which may be one of the explanations of hypercoagulability domino effect without associated bleeding events (Hadid, et.al., 2021). However, as severe SARS-CoV-2 infection plus prophylactic heparinization can lead to more intense changes in these markers, it is not known whether maintenance of anticoagulation therapy at intermediate doses is associated or not with poor outcomes, since increased values of PT are associated with higher mortality and COVID-19-induced thrombocytopenia, even with hyperfibrinogenemia, can lead to hemodynamic instability and death (Iba, et.al., 2017).

Regarding the type of anticoagulation, out of the 57 patients who used low molecular weight heparin at a dose of 20mg, 47 (87.7%) died (p <0.001) and out of the 58 patients who used unfractionated heparin every 8 hours, 47 (81%) died (p = 0.007). It is worth mentioning that the use of these drugs at such doses was due to changes during hospital stay; it was not a fixed therapy since admission, and the adjustments made were due to the hemodynamic instability after anticoagulation at higher doses, which also predicts a worse outcome. In this case, the claim that the use of anticoagulants in low doses is responsible for lethality is not valid.

Due to the instability experienced by critically ill patients, there is still no consensus on the ideal doses of heparin and the literature shows little agreement. The International Society of Thrombosis and Hemostasis recommends not using fondaparinux or the novel oral anticoagulants (NOACs) in these patients, giving preference to prophylactic/intermediate doses of heparin or mechanical thromboprophylaxis (Spyropoulos, et.al., 2020). On the other hand, experts from the American College of Chest Physicians (CHEST) claim that thromboprophylaxis should be used in a standard dose; they do not recommend an intermediate dose, with preference for low molecular weight heparin in relation to unfractionated heparin and suggest that NOACs or fondaparinux should be the 3rd choice of anticoagulation therapy in these patients. In addition, they did not recommend the use of antiplatelet agents for the prevention of venous thromboembolism or mechanical prophylaxis in addition to drug prophylaxis (Spyropoulos, et.al., 2020).

Studies show that heparin in prophylactic doses offers benefits in relation to other forms of anticoagulation, since it has antiviral and anti-inflammatory action, but on the other hand, it reduces physiological events that protect the alveoli, and the cost/benefit of higher doses in COVID-19 infection is not known (Hippensteel, et.al., 2020). In critically ill patients with high pulmonary involvement and no signs of bleeding, prophylactic doses of low-molecular-weight heparin are recommended and, in the presence of severe acute renal failure (renal clearance <30), the use of unfractionated heparin at a dose of 5000 IU, three times a day proved to be a therapeutic alternative (McBane, et.al., 2020).

Since patients admitted to the ICU have greater thrombogenesis, thromboprophylaxis is mandatory, either with medication or by intermittent pneumatic compression. Even under thrombosis prophylaxis, patients with COVID-19 in the ICU have a 31% higher risk of developing this complication, reinforcing the general prothrombotic state of these patients (Klok, et.al., 2020). In the association of thromboprophylaxis with high levels of D-dimer, it was observed that the higher the levels of this marker, the greater the thrombogenesis. Heparinization in the presence of D-dimer greater than 3.0 μg/ml reduced mortality by 20% in critically ill patients (Tang, et.al., 2020).

5. Conclusion

A lot has been learned about the pathophysiology of COVID-19 and its association with hypercoagulability; however, the findings regarding effective mechanisms that interrupt this domino effect are still uncertain. The present study showed that low doses of heparin are associated with higher mortality, but it should be emphasized that the initial thromboprophylaxis of these patients was performed at higher doses and its reduction was due to laboratory and hemodynamic alterations, reiterating the need for anticoagulation in critical patients, with dose management still to be defined based on new studies on the topic.

This work is relevant because it addresses a recent and not yet fully clarified issue, presenting unique information on the effects of anticoagulation therapy under critical parameters, on clinical outcome. One of the main limitations of this study was the absence of D-dimer values during admission and evolution of patients, since the protocol of the selected hospital does not include this variable as a periodic examination to be requested. In addition, the excess of studies on COVID-19 made it difficult to discuss the subject, increasing the risk of inducing bias.

This study observed that most ICU patients were male, and the mean age was 59.1 (SD 19.8) years. Common findings for non-survivors were advanced age (≥ 60 years) and the presence of comorbidities such as systemic arterial hypertension, heart disease, chronic kidney disease and neoplasia. Among the complications during hospitalization, mortality was associated with evolution with severe acute renal failure and hyperbilirubinemia, in addition to high levels of lactic dehydrogenase, prothrombin time, activated partial thromboplastin time, aspartate aminotransferase and renal clearance < 30 ml/min /1,73^2. A total of 19.8% of the patients exhibited hepatic alterations and, out of these, 83.7% died. Critical anticoagulation was associated with a higher death rate, with clinical evolution between ICU admission and fatal outcome two weeks after infection. A total of 17.7% of the patients were on previous anticoagulation, with dual therapy in 4.8 of the patients analyzed and out of these, 78% died. The other variables did not show statistical significance in relation to the outcome.

Further clinical studies are needed to elucidate the pathophysiology of COVID-19 and the management of the disease and its complications.

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