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Approach of COVID-19 induced coagulopathy, from literature to the clinical practice.

Coagulopatía inducida por COVID-19, de la bibliografía a la práctica clínica

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Abstract

OBJECTIVE: To determine the clinical practice of the intentional search of COVID-19 induced coagulopathy at hospital admission and describe its incidence, thrombosis rates and mortality.

MATERIALS AND METHODS: A retrospective cohort study of adult patients with COVID-19 that required hospitalization was made from April 2020 to May 2021 in a Mexican private hospital. COVID-19 induced coagulopathy diagnosis was established if two of these criteria were met: D-dimer above 1 µg/mL, platelet count below 150 K/µL and international normalized ratio (INR) of 1.2 or higher. The population was divided according to therapy: thromboprophylaxis, anticoagulation *vs* not-to-treat. General characteristics, mortality, length of stay, and thrombosis rates were described for each group.

RESULTS: For a total of 532 patients, 116 were evaluable for COVID-19 induced coagulopathy at hospital admission; the diagnosis was confirmed in 34 of them (29.3%). The thrombosis rates and mortality were 17.6% and 32.3%, respectively. Those who received anticoagulation presented with more severe clinical and biochemical characteristics, hence the length of stay and thrombosis rates were higher in them.

CONCLUSIONS: The diagnosis of COVID-19 induced coagulopathy reached 29.3% in the evaluable population. Its search is close to 21.8% of the patients admitted.

KEYWORDS: Coagulopathy; COVID-19; Thrombosis; Anticoagulation.

Resumen

OBJETIVO: Determinar la práctica clínica de la búsqueda intencional de coagulopatía inducida por COVID-19 al ingreso hospitalario y describir su incidencia, tasas de trombosis y mortalidad.

MATERIALES Y MÉTODOS: Estudio de cohorte retrospectivo de pacientes adultos con COVID-19 que requirieron hospitalización, efectuado de abril de 2020 a mayo de 2021 en un hospital privado mexicano. El diagnóstico de coagulopatía inducida por COVID-19 se estableció si se cumplían dos de estos criterios: dímero D superior a 1 µg/mL, recuento de plaquetas inferior a 150 K/µL e índice internacional normalizado (INR) de 1.2 o superior. La población se dividió según el tratamiento: tromboprofilaxis, anticoagulación *versus* sin tratamiento. Para cada grupo se describieron las características generales, la mortalidad, la duración de la estancia hospitalaria y las tasas de trombosis.

RESULTADOS: De un total de 532 pacientes, 116 fueron evaluables para coagulopatía inducida por COVID-19 al ingreso hospitalario; el diagnóstico se confirmó en 34 de ellos (29.3%). Las tasas de trombosis y mortalidad fueron del 17.6 y 32.3%, respectivamente. Los pacientes que recibieron anticoagulación mostraron características clínicas y bioquímicas más graves, de ahí que la estancia hospitalaria y las tasas de trombosis fueran mayores en ellos.

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CONCLUSIONES: El diagnóstico de coagulopatía inducida por COVID-19 alcanzó el 29.3% en la población evaluable. Su búsqueda se acerca al 21.8% de los pacientes ingresados.

PALABRAS CLAVE: Coagulopatía; COVID-19; trombosis; anticoagulación.

BACKGROUND

It has been more than two years from the time when the early COVID-19 cases were reported; ever since, its hematological characteristics have been identified as an important feature of the disease.[1,2] The wide clinical spectrum of the severe disease includes the development of acute respiratory distress syndrome (ARDS); acute myocardial, kidney, and liver injury; cardiac arrhythmias, acute heart failure, rhabdomyolisis and coagulopathy.[3,4] The latter being of interest because of its association with poor prognosis and thrombotic complications.[5,6] It is now known that the SARS-CoV-2 virus damage the vascular endothelium and the lung alveolar epithelial cells by its interaction with the angiotensin-converting enzyme 2 (ACE2). This triggers an excessive immune response-induced cytokine storm, generating a local and systemic inflammatory response, that progress to an endotheliopathy and a hypercoagulability state, responsible for the macro- and micro-thrombosis manifestations.[7,8]

This complex mechanism between the SARS-CoV-2 virus, the endothelial cells, the inflammatory response, and the coagulation system explains the laboratory abnormalities such as: elevated D-dimer levels, thrombocytopenia, increased levels of fibrin degradation products and elevation of the activated partial thromboplastin (aPTT) and prothrombin time (PT).[9] The presence of these alterations is known as COVID-19 induced coagulopathy (CIC).[10]

The diagnosis of CIC has gain significance because of its prognosis and therapeutic value.[11] It is established by the International Society on Thrombosis and Haemostasis that all patients with COVID-19 must be tested for coagulation markers at the time of diagnosis, guiding the decision for hospital admission on those with D-dimer markedly raised, prothrombin time prolonged, platelet count below 100 x 10^9/L and fibrinogen levels below 2 g/L. Also, they suggest that all patients who required hospital admission must be treated with low molecular weight heparin (LMWH) at thromboprophylaxis doses in the absence of any contraindications.[12] The American Society of Hematology agree with this suggestion an remark that there's no benefit using higher doses or anticoagulation.[13] Besides this data, there has been many clinical trials to determine whether thromboprophylaxis vs anticoagulation vs none-to-them is the most appropriate treatment.[14]

At our institution, some clinicians seek for the diagnosis of CIC at hospital admission and initiate early thromboprophylaxis and some prefers the intermediate-to-therapeutic full dose-anticoagulation. In this study, we describe the tendency by the clinical physicians regarding the

diagnosis and therapeutics of CIC in a third level hospital at the north of Mexico. The objective of this study is to determine the adherence to the established by the international guidelines and describe our population.

MATERIALS AND METHODS

A single-center retrospective cohort study of adult patients diagnosed with COVID-19 that were admitted to our institution from April 2020 to May 2021. Those who required extracorporeal membrane oxygenation support during the hospital stay, were pregnant at admission or had incomplete medical file were excluded. The population was divided into three groups according to the therapy employed: early thromboprophylaxis, early full dose anticoagulation or none-to-them.

Sociodemographic, clinical, and biochemical characteristics were described for each group. The sociodemographic characteristics collected included gender, age, body mass index (BMI), and the following comorbidities: diabetes mellitus type 2, hypertension, coronary artery disease, atrial fibrillation, heart failure, end-stage kidney disease, liver disease, cancer, asthma, chronic obstructive disease, cerebrovascular disease, overweight, obesity, and current smoking status. The clinical characteristics at hospital admission included were days from illness onset, symptoms such as: dyspnea, respiratory distress, cough and fever; vital signs such as: heart rate, respiratory rate, systolic blood pressure, temperature, and oxygen saturation as determined by pulse oximetry. The biochemical characteristics gathered were hemoglobin, hematocrit, white blood cells, neutrophils absolute count, lymphocytes absolute count, platelets, glucose, creatinine, blood urea nitrogen (BUN), triglycerides, total cholesterol, aspartate aminotransferase, alanine aminotransferase, lactic dehydrogenase, ferritin, c-reactive protein (CRP), interleukin-6 (IL-6), prothrombin time (PT), activated partial thromboplastin time (aPTT), international normalized ratio (INR), d-dimer, fibrinogen, pro brain natriuretic peptide (ProBNP), creatine phosphokinase-MB (CPK-MB), myoglobin, and procalcitonin.

The primary outcome was to determine the intentional search of CIC at hospital admission by identifying the percentage of patients that had record of coagulation tests, complete blood count, and D-dimer levels at the first 24 hours of hospitalization in their clinical files to describe the level of adherence to the International Guidelines recommendations in the total population.[12,13] The incidence of CIC was determined in the population that had this laboratory set at hospital admission. The diagnosis of CIC was established if two of these criteria were met: D-dimer level above 1 µg/mL, platelet count below 150 K/µL and an International Normalized Ratio (INR) of 1.2 or higher. Mortality and thrombosis rate was determined on those with CIC diagnosed.

The diagnosis of thrombosis was determined by an existing Doppler vascular ultrasound and/or computed tomography angiography (CTA) compatible with the diagnosis of deep venous thrombosis, pulmonary thromboembolism, acute ischemic stroke, acute myocardial infarction or acute mesenteric ischemia reported in their clinical files.

Early thromboprophylaxis and full-dose anticoagulation was considered if the therapy was initiate in the first 24 hours of hospital stay. Those who received enoxaparin at doses of 0.5 mg/kg per day or 0.5 mg/kg twice a day, fondaparinux 2.5 mg per day, rivaroxaban 10 mg per day or apixaban 2.5 mg twice a day were included in the thromboprophylaxis group. In the full-dose anticoagulation were included those who received enoxaparin 1 mg/kg twice a day or higher, fondaparinux 5 mg per day or higher, rivaroxaban 15 mg twice a day or apixaban 5 mg

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twice a day or higher. Those who did not had this medication on the first 24 hours of admission were included in the none-to-them group. We review all dosages individually considering each patient's weight and age to guarantee its correct categorization. For each group, mortality, length of stay and thrombosis rate were determined.

SPSS® Statistics software platform was used for all statistical analyses. Continuous variables were summarized as median and its interquartile range for the three groups. Categorical variables summarized as count and percentage. To compare the variables included between the three groups the Kruskal-Wallis test was used for continuous variables and χ^2 test was used for categorical variables.

RESULTS

From April 2020 to May 2021 a total of 581 patients were admitted to the hospital with the diagnosis of COVID-19. We excluded 49 patients because they presented one of the following conditions: extracorporeal membrane oxygenation support during the hospital stay, pregnancy at admission, incomplete medical file or were younger than 18 years old. We included a total of 532 patients.

The search for CIC diagnosis at hospital admission were done in 116 patients (21.8%), with an incidence reported in 29.3% (n = 34). The mortality was 32.3% (n = 11) and thrombosis rate reached 17.6% (n = 6) of those affected with CIC.

Male sex predominates in the total population (67.6%). The median age was 49 years (IQR 32-65). The most frequent comorbidities were overweight (44%), followed by obesity (40.1%), systemic arterial hypertension (27.8%), type 2 diabetes mellitus (21.6%) and current smoking status (12.4%).

The preferred therapy at admission were the use of early thromboprophylaxis in 410 patients (77%) followed by neither thromboprophylaxis nor anticoagulation in 71 cases (13.3%), and full dose anticoagulation in 51 of the total population (9.5%). **Table 1** shows the prevalence of every clinical condition presented within each group of the population.

According to the clinical characteristics at hospital admission, the group that receive early thromboprophylaxis or anticoagulation had higher rates of severity conditions or symptoms (3), such as: more days of active disease before the hospital admission ($p < 0.001$), dyspnea ($p < 0.001$), and higher grade of hypoxemia ($p < 0.001$). The clinical characteristics are reported for each group in **Table 2**.

The statistically significant difference was present in the serum levels of lactic dehydrogenase (LDH) and C-reactive protein (CRP), both were higher in the early thromboprophylaxis and anticoagulation groups ($p = 0.011$ and $p = 0.005$, respectively). No statistically significant difference was reported in the coagulation parameters. The biochemical characteristics for each group are shown in **Table 3**.

Those who received full-dose anticoagulation had longer lengths of stay with a median of 10 days (IQR 6-19). The thrombosis rate was higher in this group with an incidence of 11.8% (n = 6). There was no difference in mortality. **Table 4** shows the difference for length of stay, thrombosis rate and mortality for each group.

DISCUSSION

The level of adherence to the recommendations by the International Guidelines in the diagnosis of CIC at the time of hospital admission reaches 21.8% in our population. To establish the diagnosis, we used the biochemical definition by Toshiaki Iba et al.[15] Within this population, the incidence of CIC was reported in 29.3%, with a mortality of 32.3% and a thrombosis rate of

Table 1. Demographic characteristics of the cohort

Total (n = 532)	No treatment N = 71 (13.3%)	Thromboprophylaxis N = 410 (77%)	Therapeutic anticoagulation n = 51 (9.5%)	p value
Men	38 (53.5%)	282 (68.8%)	40 (78.4%)	**0.009**
Age	49 (32-65)	51 (41-63)	55 (46-64)	0.125
Body mass index	27.7 (24.8-31)	28.7 (26.4-32.6)	30.2 (27.5-34.6)	0.170
Comorbidities				
Type 2 diabetes	8 (11.3%)	91 (22.2%)	16 (31.4%)	**0.024**
Hypertension	22 (31%)	109 (26.6%)	17 (33.3%)	0.487
Coronary artery disease	9 (12.7%)	27 (6.6%)	4 (7.8%)	0.198
Atrial fibrillation	3 (4.2%)	8 (2%)	3 (5.9%)	0.170
Heart failure	1 (1.4%)	4 (1%)		0.720
End-stage kidney disease	6 (8.5%)	12 (2.9%)	3 (5.9%)	0.066
Liver disease	2 (2.8%)	3 (0.7%)		0.186
Cancer	3 (4.2%)	12 (2.9%)	2 (3.9%)	0.808
Asthma	2 (2.8%)	3 (0.7%)	1 (2%)	0.258
Chronic obstructive pulmonary disease		5 (1.2%)		0.472
Cerebrovascular disease	6 (8.5%)	10 (2.4%)	2 (3.9%)	**0.035**
Overweight	32 (45.1%)	187 (45.6%)	16 (31.4%)	0.153
Obesity	22 (31%)	168 (41%)	28 (54.9%)	**0.030**
Current smoking	6 (8.5%)	55 (13.4%)	5 (9.8%)	0.422

Values are median (Interquartile range) or n (%), unless otherwise indicated.
* χ^2 test used for categorical variables. Kruskal-Wallis test used for continuous variables.

Table 2. Clinical characteristics at hospital admission

Total (n = 532)	No treatment N = 71 (13.3%)	Thromboprophylaxis N = 410 (77%)	Therapeutic anticoagulation n = 51 (9.5%)	p value
Das from illness onset	6 (2-10)	8 (7-10)	10 (7-13)	**< 0.001**
Dyspnea	27 (38%)	302 (73.7%)	37 (72.5%)	**< 0.001**
Respiratory distress	11 (15.5%)	76 (18.6%)	16 (31.4%)	0.063
Cough	35 (49.3%)	310 (75.6%)	39 (76.5%)	**< 0.001**
Fever	33 (46.5%)	335 (81.7%)	38 (74.5%)	**< 0.001**
Heart rate	86 (76-99)	95 (83-109)	93 (80-105)	**0.016**
Respiratory rate	20 (18-24)	23 (20-26)	23 (21-28)	**0.016**
Systolic blood pressure	122 (111-141)	128 (117-143)	130 (120-151)	0.780
Temperature	36.6 (36-37.4)	37.2 (36.7-38)	37.3 (36.6-37.7)	**< 0.001**
Oxygen saturation	96 (92-98)	92 (88-95)	91 (85-94)	**< 0.001**

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* χ^2 test used for categorical variables. Kruskal-Wallis test used for continuous variables.

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Table 3. Biochemical characteristics at hospital admission

Total (n = 532)	No treatment N = 71 (13.3%)	Thromboprophylaxis N = 410 (77%)	Therapeutic anticoagulation n = 51 (9.5%)	p value
Hemoglobin, g/L	13.6 (12.3-15.1)	14.3 (13.4-15.3)	14.1 (13.2-15.3)	0.167
Hematocrit, %	39.9 (36.2-44.5)	41.3 (38.8-44.1)	41.1(38.3-44.3)	0.497
White blood cells, x10^9/L	7.92 (6.04-11.01)	8.30 (5.88-11.42)	9.33 (6.18-12.73)	0.504
Neutrophils, x10^9/L	5.56 (4.16-8.69)	6.87 (4.26-9.73)	7.68 (4.48-11.29)	0.160
Lymphocytes, x10^9/L	1.17(0.81-1.62)	0.91 (0.65-1.17)	0.91 (0.66-1.29)	0.13
Platelet, x10^9/L	237 (178-294)	209 (166-272)	218 (174-278)	0.179
Glucose, mg/dL	110 (98-128)	119 (104-147)	123 (110-174)	0.054
Creatinine, mg/dL	0.81 (0.68-1.2)	0.85 (0.7-1.01)	0.89 (0.72-1.08)	0.451
BUN, mg/dL	14 (9.3-23)	14.8 (10.9-19.1)	15.4 (12.6-20.7)	0.536
Triglycerides, mg/dL	121 (93-179)	129 (100-168)	130 (100-168)	0.537
Cholesterol, mg/dL	145 (121-175)	135 (115-161)	132 (112-154)	0.606
AST, U/L	26 (20-54)	41 (29-62)	41 (28-75)	0.095
ALT, U/L	28 (17-59)	40 (27-67)	39 (26-62)	0.119
LDH, U/L	289 (195-472)	393 (294-562)	419 (312-652)	**0.011**
Ferritin, ng/mL	499.7 (78.9-2118)	1092 (529.5-1848)	1320 (879.7-1960)	0.118
CRP, mg/L	59.03 (25.35-121.93)	91.52 (51.85-156.36)	115.6 (64.81-191.97)	**0.005**
IL-6, pg/mL	33.48 (7.71-79.6)	57.61 (27.94-111.1)	85.34 (37.38-145.35)	0.220
PT, s	12.4 (11.2-13.2)	13 (12.3-14.1)	14.2 (12.9-15)	0.110
aPTT, s	27.8 (24.9-32.1)	30.1 (27.1-32)	29.5 (27.9-33.5)	0.493
INR	1.09 (0.98-1.16)	1.15 (1.07-1.25)	1.25 (1.16-1.31)	0.67
D-dimer, mg/mL	0.5 (0.3-0.8)	0.69 (0.37-1.56)	0.34 (0.26-1.91)	0.56
Fibrinogen, mg/dL	447 (447-447)	672 (551-729)	841 (598-911)	0.279
ProBNP, pg/mL	130 (81-891)	180 (64-499)	134 (90-375)	0.877
T Troponin, ng/mL	14.7 (5-15.5)	6 (5-10.9)	7.7 (5-12.7)	0.185
CPK-MB, ng/mL	1.17 (0.94-1.34)	1.24 (0.69-1.94)	1.44 (0.91-1.90)	0.641
Myoglobin, ng/mL	39.7 (35-49)	54.3 (27-116)	51.3 (32.4-78.8)	0.119
Procalcitonin, ng/mL	0.25 (0.7-0.34)	0.15 (0.1-0.3)	0.1 (0.3-0.25)	0.682

BUN: blood urea nitrogen; AST: aspartate aminotransferase; ALT: alanine aminotransferase; LDH: lactic dehydrogenase; CRP: C-reactive protein; IL-6: interleukin-6; PT: prothrombin time; aPTT: activated partial thromboplastin time; INR: international normalized ratio; ProBNP: probrain natriuretic peptide; CPK-MB: creatine phosphokinase-MB.
Values are median (interquartile range), n (%), or n/N (%), unless otherwise indicated.
* χ^2 test used for categorical variables. Kruskal-Wallis test used for continuous variables.

17.6%. The presence of CIC has been previously related with its high mortality due to the development of ARDS,[16] in our population this condition was the main cause of dead in a 71% of the total deaths. The thrombosis rate within our population with CIC diagnosis approximates to the previously reported by other authors. Klok et al. found an incidence of thrombosis complication of 31% in the COVID-19 patients admitted to the intensive care unit.[17] Similarly,

Al-Samkari et al. reported an overall thrombotic complication rate of 18.1% in the critically ill patients.[18] We don't make the distinction of the severity of the disease in our population, but we reported higher presence of severity symptoms and biochemical factors associated in the group that received full-dose anticoagulation, the same group that had higher mortality and thrombosis rates within our population. **Table 4**

Obesity, type 2 diabetes mellitus and systemic arterial hypertension was previously reported as the most prevalence comorbidities in the Mexican population, these data were consistence in our study population.[19,20]

In our total population thrombosis rate was reported in the 4.62%, whether the diagnosis of CIC was established at admission or not. We believe that this low rate of thrombosis, compared with the reported by Klok et al. and Al-Samkari et al., was determined by the early initiation of thromboprophylaxis in most of our population (n = 410), but because of the character of the present study we cannot associated this relation. It is remarkable that the thrombosis diagnosis definition was made according to the presence of a thrombus detected by an imaging diagnostic method, as Doppler ultrasound of lower extremities, computed tomography, angiography for pulmonary embolism or by interventional angiography.[17,18]

The clinical physicians of our institute preferred the initiation of early thromboprophylaxis over full-dose anticoagulation or none-to-them, this shows a level of adherence of 77% to the recommendations by the International Guidelines regarding the preferred treatment at admission.[13,14] We assumed that the decision of full-dose anticoagulation was taken according to the severity factors presented in much higher proportions in this population (**Tables 2 and 3**). Currently, the evidence supports the use of prophylactic doses over full-dose or intermediate-anticoagulation.[21,22,23]

We found that the level of adherence to the intentional search of CIC at the time of hospital admission is closed to 22% in our population. In those whom CIC diagnosis was investigated, the reported incidence was 29.3%. We believe the incidence of CIC can be higher if there were more adherence to the recommendations by the International Guidelines. The high mortality and thrombosis rates associated with this condition must warn our clinical physicians to commit to the intentional investigation of this diagnosis.

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Table 4. Outcome stratified by the therapeutic received

Total (n = 532)	No treatment N = 71 (13.3%)	Thromboprophylaxis N = 410 (77%)	Therapeutic anticoagulation n = 51 (9.5%)	p value
Length of stay	5 (2-10)	9 (6-16)	10 (6-19)	0.002
Thrombotic event	5 (7%)	14 (3.4%)	6 (11.8%)	0.018
Mortality	9 (13%)	56 (13.9%)	11 (22%)	0.287

Values are median (interquartile range), n (%), or n/N (%), unless otherwise indicated.
* χ^2 test used for categorical variables. Kruskal-Wallis test used for continuous variables.

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