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Profile of parenteral anticoagulant use in patients with COVID-19 in an university hospital in Rio de Janeiro

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Abstract

Objective: To evaluate the anticoagulation prescription in the hospitalized COVID-19 patients, and the occurrence of hemorrhagic events, in those with anticoagulation usage, that developed acute respiratory distress syndrome (ARDS), requiring advanced medical support at the ICU, compared with hospitalized patients with non-requirement of advanced medical support. **Methods**: Observational descriptive study with a quantitative approach, developed at a public hospital in Rio de Janeiro city, between March 29 to October 13 of 2020. Data was analyzed and collected from the electronic clinical record from hospitalized patients with a COVID-19 diagnosis, confirmed by RT-PCR and with a minimal anticoagulation usage of 60% during the hospitalization period. The patients that met the inclusion criteria were divided in 2 groups: Group 1, patients that developed ARDS, requiring advanced medical support at the ICU or any other unit. Group 2, patients that required hospitalization with no requirement of advance medical support. **Results**: From the 421 hospitalized patients with COVID-19, a total of 281 clinical record were analyzed, from which, 218 met the study's inclusion criteria. From those, 112 (51%) were categorized within the Group 1, and 106(49%) in the Group 2. Mean general Age was 64 (p=0.053) and the majority where males (52%). The general mortality was 33.5%, where those in the group 1 were affected the most (60.7%). Regarding the anticoagulant usage, 160 patients (73.6%) used a prophylactic dosage, 47 patients (21.6%) used an intermediate dosage and 11 (5%) used a therapeutic dosage. In general, 27 patients (12.4%) had hemorrhagic events after the start the anticoagulation treatment. From those, 18 patients (66.7%) were use of prophylactic dosage, before the event, 5 patients (18.5%) were in intermediate, and 4 patients (14.8%) were in therapeutic dosage. **Conclusion**: In this study was possible to observe which dosage was the most used in hospitalized patients, in concordance with the literature evidence and with the own institution´s recommendations. The occurrence of hemorrhagic events was greater in the patients group who used the prophylactic dosage.

Key words: COVID-19; enoxaparin; hemorrhage; heparin.

Perfil de utilização de anticoagulantes parenterais em pacientes com COVID-19 em um hospital universitário no Rio de Janeiro

Resumo

Objetivo: Avaliar o perfil de prescrição de anticoagulação dos pacientes hospitalizados com COVID-19 e a ocorrência de eventos hemorrágicos em pacientes em uso de anticoagulantes, que desenvolveram doença respiratória grave necessitando de suporte clínico avançado em CTI comparados com pacientes que necessitaram de internação, porém sem suporte clínico avançado. **Métodos:** Estudo observacional descritivo com abordagem quantitativa realizado em um hospital público no rio de Janeiro, no período de 29 de março de 2020 a 13 de outubro de 2020. Foram analisados dados recuperados do prontuário e prescrição eletrônicos de pacientes hospitalizados com diagnóstico de COVID-19 confirmado por RT-PCR e que fizeram uso de anticoagulante por no mínimo 60% do tempo de internação. Os pacientes que preencheram os critérios de inclusão foram divididos em dois grupos: grupo 1, pacientes que desenvolveram doença respiratória grave necessitando de suporte clínico avançado em CTI ou em qualquer outra unidade hospitalar, em caso de ausência de leitos no CTI); grupo 2, pacientes que necessitaram de internação, porém sem suporte clínico avançado. **Resultados:** Dos 421 pacientes internados com COVID-19, 281 prontuários foram analisados e, destes, 218 preencheram os critérios de inclusão do estudo. Cento e doze (51%) pacientes foram categorizados no grupo 1 e 106 (49%) no grupo 2. A média de idade geral foi de 64 anos (p=0,053) e a maioria (52%) era do sexo masculino. A mortalidade geral deste estudo foi de 33,5%, sendo os pacientes do grupo 1 os mais afetados (60,7%). Em relação ao uso de anticoagulante, cento e sessenta (73,6%) pacientes fizeram uso de dose profilática, 47 (21,6%) pacientes de dose intermediária e 11 (5,0%) pacientes de dose terapêutica. No geral, 27 (12,4%) pacientes apresentaram eventos hemorrágicos após terem iniciado o tratamento com anticoagulante. Destes, 18 (66,7%) pacientes estavam em uso de dose profilática anteriormente ao sangramento, 5 (18,5%) pacientes em dose intermediária e 4 (14,8%) pacientes em dose terapêutica. **Conclusão:** Neste estudo, foi possível observar que a dose profilática foi a mais utilizada nos pacientes hospitalizados, condizente com as evidências da literatura e com a recomendação da própria instituição. A ocorrência de eventos hemorrágicos foi maior no grupo de pacientes que fizeram uso de anticoagulantes em dose profilática.

Palavras-chave: COVID-19; hemorragia; heparina de baixo peso molecular; heparina.

Introduction

In December 2019, the first COVID-19 case was identified, such was the name given to the disease caused by the new SARS-CoV-2 coronavirus, in the city of Wuhan, China. The disease spread rapidly through several countries and, in March 2020, the World Health Organization (WHO) decreed the Pandemic state.[1]

In Brazil, on February 26th, 2020, the first COVID-19 case was confirmed in the country.[2] According to the WHO, by August 27th, 2021, more than 214,468,601 cases and more than 4,470,969 million deaths were confirmed in the world, with Brazil accounting for approximately 13% of the deaths.[3]

In addition to the variety of respiratory clinical manifestations, countless previous reports have related COVID-19 to coagulopathies, with venous and arterial thrombotic complications being the most frequent.[4,5] In view of this fact, a number of studies showed, through the autopsy of these patients, a high frequency of thromboembolic phenomena, even in patients who did not present thrombotic complications during hospitalization.[6-8] Although the pathophysiology of this phenomenon has not yet been elucidated, COVID-19 is believed to be associated with disseminated intravascular coagulation, endothelial damage, cytokine-induced systemic inflammatory response, antiphospholipid antibody syndrome, vascular stasis and thrombosis in various organs.[9,10]

Due to the hypercoagulability state, there are coagulation and inflammation parameters that require attention and that have been related to a worse prognosis, such as high D-dimer and C-reactive protein (CRP), prolonged prothrombin time (PPT), lymphopenia, thrombocytopenia and leukocytosis.[11]

In this scenario, early introduction of the anticoagulant therapy in COVID-19 has been increasingly discussed, aiming at reducing thromboembolic outcomes and even mortality.[12,13] However, there is still no consensus about the risk stratification of venous thromboembolism (VTE), as well as about dose and duration of the treatment in hospitalized patients. In addition to that, the clinical decision regarding anticoagulant therapy must involve evaluating the benefits and risks of hemorrhagic outcome.[14]

A number of reports evidenced that critically-ill patients presented high mortality, greater need for vasopressor therapy and a higher chance of having cardiac and renal complications during hospitalization.[15,16] From this perspective, it is believed that patients who developed severe respiratory disease, requiring advanced clinical support in an intensive care unit (ICU), are more likely to present worse outcomes and higher coagulation and inflammation parameters.

In order to contribute new information about the treatment of COVID-19, in particular, in relation to the thromboprophylaxis scheme for critical and non-critical patients, the study objective was to analyze the anticoagulation prescription profile of hospitalized patients diagnosed with COVID-19 and the occurrence of hemorrhagic events in patients using anticoagulants who developed severe respiratory disease requiring advanced clinical support in the ICU and to compare them with those who required hospitalization, although without advanced clinical support.

Methods

A descriptive, longitudinal and observational study with a quantitative approach, conducted from March 29th, 2020, to October 13th, 2020, in the Clementino Fraga Filho University Hospital (*Hospital Universitário Clementino Fraga Filho*, HUCFF). This hospital is the assistance branch of the Federal University of Rio de Janeiro (*Universidade Federal do Rio de Janeiro*, UFRJ), linked to the Ministry of Education and to the Unified Health System (*Sistema Único de Saúde*, SUS) and currently has 303 beds and 12 operating rooms.[17]

The study population consisted of patients aged 18 years old or over; hospitalized at the HUCFF in an Intensive Care Unit (ICU) and in specific wards for the treatment of COVID-19; and with confirmed diagnosis by reverse transcription followed by polymerase chain reaction (RT-PCR). The patients included were those who were hospitalized for more than 24 hours and who used anticoagulants, unfractionated heparin (UFH) or low molecular weight heparin (LMWH) for at least 60% of the hospital stay. The choice of a minimum time of 60% for the use of anticoagulants was due to the fact that this is an unknown disease, which is still surrounded by uncertainties regarding the risks and benefits of using anticoagulants. It was for this reason that it was decided to be more flexible and not only include patients using anticoagulants during the entire hospitalization time.

Patients who were still hospitalized at the end of data collection were excluded, as well as those who did not use anticoagulants during hospitalization, those using oral anticoagulants during hospitalization, and those who used anticoagulants for less than 60% of their hospital stay.

At the beginning of the Pandemic, the electronic medical record of that hospital included a sign that allowed searching for patients who were hospitalized with laboratory-confirmed, suspected or discarded cases of COVID-19. From that starting point, the names and medical record numbers of the patients with a confirmed diagnosis were consecutively introduced in an online Google drive spreadsheet.

After meeting the inclusion criteria, the study target population was divided into two groups: Group 1, patients who developed severe respiratory disease requiring advanced clinical support in the ICU or any other hospital unit (in case of lack of beds in the ICU); and Group 2, patients who required hospitalization, although without advanced clinical support (Table 1). Due to the reduced work schedule established for the Pharmacy residents, aiming to reduce circulation of people in the hospital, it was not possible to daily analyze the hospitalized patients diagnosed with COVID-19. Inclusion of new patients took place on specific days of the week according to the monthly schedule issued by the Pharmacy Sector management, characterizing a convenience sample.

The variables analyzed were collected from the analysis of electronic medical records and prescriptions, which included demographic data (age and gender); previous treatment with anticoagulants; doses of anticoagulants used during hospitalization; admission laboratory tests; hospitalization outcome (discharge or death); occurrence of hemorrhagic events during hospitalization; and number of hospitalization days.

The LMWH and UFH dosage regimens were classified as follows: prophylactic – LMWH 40 mg or 20 mg once a day or UFH 5,000 IU two or three times a day; therapy- LMWH 1 mg/kg twice a day and, in this study, there were no patients using a therapeutic UFH dose;

and intermediate – doses that do not fit the descriptions above, both for UFH and for LMWH. [18] For patients with kidney disease, the cases were analyzed individually so that it was possible to classify the doses as prophylactic, intermediate or therapeutic.

The hemorrhagic events were classified as major or minor. According to the classification defined by the International Society on Thrombosis and Haemostasis (ISHT), major hemorrhagic events were those in which there was intracranial bleeding and/or reduction in the hemoglobin value of 2 g/dL in relation to the previous value and/or the need for blood transfusion. The other hemorrhagic events were categorized as minor.[19]

The categorical variables were described based on their occurrence frequency, both absolute and relative, and the numerical variables through their median and interquartile range (IQR). A bivariate analysis was performed to assess the statistically significant differences between the clinical-demographic characteristics of the different groups analyzed. The Chi-square test was used to assess statistically significant differences between the distribution of the categorical variables, and the Mann-Whitney test was employed for the numerical variables. All the analyses were performed in SPSS Statistics®, version 23, adopting a p-value<0.05 as statistical significance level.

The research followed the current ethical principles of Resolution No. 466/12 of the National Health Council (*Conselho Nacional de Saúde*, CNS), being approved by the Research Ethics Committee of HUCFF, with CAAE No. 34020720.2.0000.5257 and favorable opinion number 4,176,292.

Results

In total, 421 patients diagnosed with COVID-19 were hospitalized, eligible for the study; of which, 281 had their medical records analyzed, given the restrictions in the team's work schedule due to the pandemic. Of these, 218 (76%) met the inclusion criteria. A total of 112 (51%) and 106 (49%) patients were categorized in Groups 1 and 2, respectively (Figure 1).

The mean age was 64 years old (p=0.053), most of the patients (52%) were male, and their mean hospitalization time was 19 days. Table 1 presents the stratification corresponding to the patients from Groups 1 and 2 in relation to their demographic and clinical characteristics. Analyzing the age and gender variables, there was a small superiority of mean age (p=0.053) and a significant predominance of men among the patients in Group 1 (p= 0.015) when compared to the patients in Group 2. In relation to mortality, 73 (33.5%) patients evolved to death. There was a significant difference in the mortality outcome (p=0.001), where Group 1 was the most affected, with 68 (60.7%) patients.

The evaluation of the admission laboratory tests showed that the coagulation parameters analyzed, such as the International Normalized Ratio (INR), PPT and activated Partial Thromboplastin Time (aPTT) did not present significant differences (p=0.201; p=0.538; p=0.442, respectively) between the groups analyzed. The analysis of the inflammatory parameters did not evidence statistically significant differences in relation to lymphocytes and PCR (p=0.478 and p=0.182, respectively) in the groups analyzed. The only inflammatory parameter analyzed was leukocytes, for which the patients in Group 1 presented a mean of 9,863,000/mm³, while those in Group 2 had a mean of 7,400,000/mm³.

Regarding the characterization of the anticoagulant dosage regimen used by the two groups analyzed, 160 (73.4%) patients used a prophylactic dose; 47 (21.6), an intermediate dose; and 11 (5%), a therapeutic dose, with no statistically significant correlation between the groups analyzed. Of the eleven patients treated with the therapeutic dose, seven (63.6%) already presented clinical indication prior to hospitalization. Analyzing the anticoagulation profile, there was no significant difference between the dosage regimens in relation to the discharge and death outcomes (p=0.093), nor in relation to the frequency of these regimens used between the two groups (p=0.113).

A total of 27 (12.4%) patients presented hemorrhagic events after having initiated treatment with anticoagulants during their hospitalization. Of these, 18 (66.7%) patients were using the prophylactic dose prior to bleeding, 5 (18.5%) patients were in use of the intermediate dose, and 4 (14.8%) patients were receiving the therapeutic dose Most of the hemorrhagic events occurred in Group 1, in 25 (92.6%) patients; and, in Group 2, only 2 (7.4%) patients presented the event, with a statistical difference (p=0.001).

Regarding characterization of the type of bleeding, 14 (52%) events were considered as major and 13 (48%) as minor. No significant difference was found in relation to the different anticoagulation dosage regimes and to the occurrence of hemorrhagic events (p=0.851).

Figure 1. Study diagram.

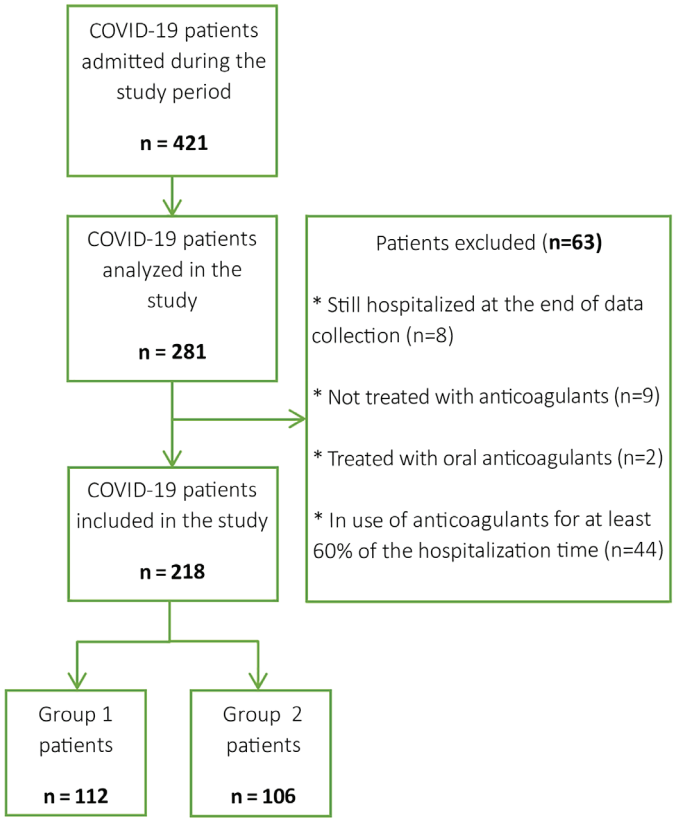

Table 1. Demographic and clinical characteristics stratified by Group 1 and Group 2 patients.

Variables	n	Total	Group 1 patients	Group 2 patients	P-Value
Age (years old) mean (IQR)	218	63.5 (55.0-73.0)	65.0 (57.0-77.0)	62.0 (54.0-71.0)	0.053
Gender n(%)	218				0.015
Female		105 (48.2)	45 (40.2)	60 (56.6)	
Male		113 (51.8)	67 (59.8)	46 (43.4)	
Medications n (%)					
Previous anticoagulant	218	16 (7.3)	7 (6.3)	9 (8.5)	0.526
Anticoagulant doses n (%)	218				0.113
Prophylactic		160 (73.4)	78 (69.6)	82 (77.4)	
Intermediate		47 (21.6)	30 (26.8)	17 (16.0)	
Therapeutic		11 (5.0)	4 (3.6)	7 (6.6)	
Laboratory at admission mean (IQR)					
INR	180	1.1 (1.0-1.1)	1.2 (1.0-1.2)	1.11 (1.0-1.1)	0.201
PPT (s)	180	13.7 (11.5-13.1)	13.3 (11.5-13.5)	14.22 11.5-12.70	0.538
aPTT (s)	178	28.3 (25.0-28.4)	27.8 (25.0-28.6)	28.84 (25.0-28.1)	0.442
Leukocytes (thousand/mm³)	216	7,900.0 (5,800.0-10,250.0)	9,863.0 (6,100.0-12,400.0)	7,400 (5,400.0-9,200.0)	0.008
Lymphocytes (thousand/mm³)	216	1,002.0 (695.0-1.487.0)	960.0 (625.0-1.482.0)	1,012 (754.0-1.500.0)	0.478
CRP (mg/L)	216	108.0 (43.5 -191.8)	112.3 48.2-208.1)	100.0 (42.2-176.8)	0.182
D-dimer (ng/ml)	54	6,553.1 (988.7-8,367.7)	8,784.1 (1,289.0-10,887.0)	1,254.25 (703.0-1,477.0)	0.018
Outcomes					
Mortality n (%)	218	73 (33.5)	68 (60.7)	5 (4.7)	0.001
Hemorrhagic events n (%)	262	27 (12.4)	25 (22.3)	2 (1.9)	0.001
Hospitalization days mean (IQR)	218	19.2 (8.0-22.0)	25.0 (11.0-29.0)	13.0 (7.0-13.0)	0.001

Key: INR – International Normalized Ratio; PPT – Prothrombin Time; aPTT – Activated Partial Thromboplastin Time; IQR: interquartile range.

Discussion

In line with the recently published guideline on anticoagulation for thromboprophylaxis in patients with COVID-19 and the document with suggestions regarding the use of anticoagulants in these patients published on the HUCFF website, which recommend anticoagulation with a prophylactic dose in relation to intermediate doses and with a therapeutic dose in patients without confirmation or suspicion of VTE, the prophylactic dose was the most frequently used in this current study in the two groups analyzed, followed by the intermediate and therapeutic doses. The intermediate dose presented a relatively high frequency, which can be explained by the concern about the occurrence of VTE in the studied population and the higher risk of bleeding resulting from the use of the therapeutic dose, even in the face of uncertainty in the use of these doses and the reduction in the risk of all-cause mortality. [14,20]

The findings of this study showed that the rate of adherence to thromboprophylaxis was high, considering a public Brazilian university hospital in a developing country, which had to quickly structure itself for emergency care in the midst of the pandemic.

A retrospective study conducted at five hospitals in New York indicated that most of the bleeding events occurred in the group of patients on a therapeutic dose.[6] In the present study, it was not possible to state that the incidence of bleeding events occurred significantly in a given anticoagulation dosage regimen. However, it was noticed that the highest frequency of bleeding events occurred in Group 1, in which the more critical patients were allocated. In this context, more studies are needed to assess the risk and benefit of choosing the anticoagulant dose and the possibility of bleeding in critically-ill patients with COVID-19.

Overall mortality was 33.5%, similar to what was observed in a retrospective study conducted with more than 250,000 patients hospitalized in five Brazilian macro-regions.[21] The patients in Group 1 presented high mortality (60.7%), similar to that reported in many studies in different parts of the world such as Asia, Europe and North America.[22,23] This rate can be explained by the characteristics of the patients treated at the HUCFF, who have multiple comorbidities and high social and economic vulnerability, which leads to difficulty accessing the health system.[24] It is important to emphasize that the HUCFF was a reference center for the hospitalization of COVID-19 patients, receiving patients in an advanced stage of the disease transferred from basic health units throughout the state of Rio de Janeiro, by means of the state bed regulation system.

This study presents some limitations. The search for new patients admitted with a positive diagnosis of the disease was not carried out daily due to the rigid scheduling scheme at the beginning of the pandemic to reduce circulation of people in the HUCFF and, therefore, it was not possible to analyze the total number of patients with COVID-19 admitted to the hospital during the study period. As this is an observational study where medical records were analyzed, some information relevant to the study may not have been documented by the medical team, such as previous anticoagulant use and hemorrhagic events during hospitalization. In addition to that, due to the lack of reagent for D-dimer analysis at different times during the pandemic period, it was not possible to obtain the value of this inflammatory parameter for all the patients, only for 54 (24.7%). Consequently, we cannot know for certain if this marker was used as a factor for the choice of the thromboprophylaxis dosage regime. There was also certain difficulty assessing the thromboembolic events since, due to the infectious-contagious nature of COVID-19, the use of imaging

methods to confirm these events was limited.

Conclusion

COVID-19 has been imposing many challenges for the health systems worldwide since, up to the present day, there is no consensus about the drug treatment for these patients. In this study, it was possible to observe that the prophylactic dose was the most frequently used in hospitalized patients, consistent with the evidence in the literature and with the recommendation by the institution itself. Occurrence of hemorrhagic events was higher in the group of patients who made use of anticoagulants at the prophylactic dose. These facts are similar to findings in the literature, up to the present day, and reinforce that the decision on the anticoagulant dose should be individualized and that the prophylactic dose should be suggested given the risk of bleeding.

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Collaborators

MNP and AFP: Conception of the project, data collection, analysis and interpretation. SCJ, CAT and ICV: Writing of the article and critical review relevant to the intellectual content.

Conflict of interest statement

The authors declare no conflicts of interest in relation to this article.

References

1. World Health Organization. Coronavirus disease (COVID-19) outbreak. Available in: <https://www.who.int>. Accessed on: 11 Sep 2020.
2. Governo do Brasil. Brasil confirma primeiro caso do novo coravírus. Available in: < https://www.gov.br/pt-br/noticias/saude-e-vigilancia-sanitaria/2020/02/brasil-confirma-primeiro-caso-do-novo-coronavirus>. Accessed on: 11 Sep 2020.
3. World Health Organization. WHO Coronavirus Disease (COVID-19) Dashboard. Available: < https://covid19.who.int>. Accessed on: 02 Jan 2021.
4. Khnider L, Gendron N, Goudot G, *et al*. Curative anticoagulation prevents endothelial lesion in COVID-19 patients. J Thromb Haemost. 2020;18(9):2391-2399. DOI: 10.1111/jth.14968.
5. Costanzo L, Palumbo FP, Ardita G, *et al*. Coagulopathy, Thromboembolic complications, and the use of heparina in COVID-19 pneumonia. J Vasc Surg Venous Lymphat Disord. 2020;8(5):711-716. DOI: 10.1016/j.jvsv.2020.05.018.
6. Nadkarni GN, Lala A, Bagiella E, *et al*. Anticoagulation, Bleeding, Mortality, and pathology in Hospitalized Patients with COVID-19. J Am Coll Cardiol. 2020;76(16):1815-1826. DOI: 10.1016/j.jacc.2020.08.041.
7. Fox HE, Akmatbekov A, Harbert J, *et al*. Pulmonary and cardiac pathology in African American patients with COVID-19: na autopsy series from New Orleans. Lancet Respir Med. 2020;8(7):681-686. DOI: 10.1016/S2213-2600(20)30243-5.
8. Wichmann D, Sperhake JP, Tgehetmann ML, *et al*. Autopsy Findings and Venous Thromboembolism in Patients With COVID-19. Annals Intern Med. 2020;17(4):268-277. DOI: 10.7326/M20-2003.
9. Chibane S, Gibeau G, Poulin F, *et al*. Hyperacute multi-organ thromboembolic storm in COVID-19: a case report. J Thromb Thrombolysis. 2020; 1-4. DOI: 10.1007/s11239-020-02173-w.
10. Rico-mesa JS, Rosas D, Ahmadian-Tehrani A, *et al*. The Role of Anticoagulation in COVID-19-Induced Hypercoagulability. Curr Cardiol Rep. 2020;22(7):53. DOI: 10.1007/s11886-020-01328-8.
11. Martín-Rojas RM, Pérez-Rus G, Delgado-Pinos VE, *et al*. COVID-19 coagulopathy: An in-depth analysis of the coagulation system. Eur J Haematol. 2020;105(6):741-750. DOI: https://doi.org/10.1111/ejh.13501.
12. Tang N, Bai H, Chen X, *et al*. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost. 2020;18(5):1094-1099. DOI: 10.1111/jth.14817.
13. Cohoon KP, Mahé G, Tafur AJ, *et al*. Emergence of institucional antithrombotic protocols for coronavirus 2019. Res Pract Thromb Haemost. 2020;4(4):510-517. DOI: 10.1002/rth2.12358.
14. Cuker A, Tseng EK, Nieuwlaat R, *et al*. American Society of Hematology 2021 guidelines in the use of anticoagulation for thromboprophylaxis in patients with COVID-19. 2021;5(3):872-888. DOI: https://doi.org/10.1182/bloodadvances.2020003763.
15. Bhatraju PK, Ghassemieh BJ, Nichols M, *et al*. COVID-19 in critically ill patients in the Seattle Region – Case Series. N Engl J Med. 2020;382(21):2012-2022. DOI: 10.1056/NEJMoa2004500.
16. Goyal P, Choi JJ, Pinheiro LC, *et al*. Clinical Characteristics of Covid-19 in New York City. N Engl J Med. 2020;382(24):2372-2374. DOI: 10.1056/NEJMc2010419.
17. Hospital Universitário Clementino Fraga Filho. Available: <http://www.hucff.ufrj.br/institucional/profissionais>. Accessed on: 06 Feb. 2020.
18. Spyropoulos AC, Levy JH, Ageno Walter, *et al*. Scientific and Standardization Committee Communication: Clinical Guidance on the Diagnosis, Prevention and Treatment of Venous Thromboembolism in Hospitalized Patients with COVID-19. J Thromb Haemost. 2020;18(8):1859-1865. DOI: 10.1111/jth.14929.
19. Schulman S, Kearon C. Definition of major bleeding in clinical investigation of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost. 2005;3(4):692-694. DOI: 10.1111/j.1538-7836.2005.01204.x.

20. Hospital Universitário Clementino Fraga Filho. Available in : <http://download.hucff.ufrj.br/DIVULGACOES/2020/COVID_SITE/anticoagulantes%20Covid%20HUCFF.docx.pdf>. Accessed on: 17 Mar 2021.

21. Ranzani OT, Bastos LSL, Gelli JGM, *et al*. Characterisation of the first 250 000 hospital admissions for COVID-19 in Brazil: a retrospective analysis of Nationwide data. 2021;9(2):1-12. DOI: https://doi.org/10.1016/S2213-2600(20)30560-9.

22. Armstrong RA, Kane AD, Cook TM. Outcomes from intensive care in patients with COVID-19: a systematic review and meta-analysis of observational studies. Anaesthetists. 2020;75(10):1340-1349. DOI: 10.1111/anae.15201.

23. Bhatraju PK, Ghassemieh BJ, Nichols M, *et al*. COVID-19 in critically ill patients in the Seattle Region – Case Series. N Engl J Med. 2020;382(21):2012-2022. DOI: 10.1056/NEJMoa2004500.

24. Rendon AFV, Volschan IS, Pereira MN, *et al*. Marginalization, Vulnerability and Economic Dynamic in COVID-19. Int. J. Cardiovasc. Sci. 2021;34(3):319-323. DOI: 10.36660/ijcs.20210029.