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RESEARCH ARTICLE OPEN ACCESS

THROMBOEMBOLIC COMPLICATIONS IN COVID-19 PATIENTS ADMITTED AT A TERTIARY HOSPITAL IN BELÉM – PARÁ

José M. C. dos Reis[1,*], Glauco S. Melo[1], Murilo O. Vasconcelos[1], Elisa M. N. Barros[1], Mariseth C. de Andrade[2], Adam S.F. Santos[3], Caio F. L. Ribeiro[3] and Karina R. Melo[3]

[1]Department of Vascular Surgery, Hospital Das Clínicas Gaspar Vianna, Bélem, Pará
[2]Department of Statistical analysis, Centro Universitário Metropolitano da Amazônia, Belém, Pará
[3]Department of Medicine, Universidade Federal do Pará, Belém, Pará

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Corresponding author:
José M. C. dos Reis

ABSTRACT

Introduction: The new severe acute respiratory syndrome coronavirus 2 has led to an unprecedented global health crisis. The high rate of thromboembolic complications in these patients is notorious, but the tools to estimate the risk of these complications are still preliminary. **Objective:** To describe the rate of thromboembolic events in patients admitted for COVID-19 in a tertiary hospital in Belém - Pará. Methodology: This is a retrospective cohort study that included data from medical records of patients admitted for COVID-19 at the Hospital das Clínicas Gaspar Vianna (HCGV), from March 1st to October 31st, 2020. The following variables were evaluated: demographic data, cardiovascular risk factors, thromboembolic complications, medications, among others. Statistical analysis using the chi-square test, p <0.001. **Results:** 203 patients were included, mostly male (61.4% *), with a mean age of 58.4 years and with previous morbidities (87.2% *). The cumulative rate of thromboembolic events was 22.2%, with deep vein thrombosis being the most common (9.4%). Mainly treated with antithrombotic drugs (91.6% *), the most used were heparins (86.7% *). **Conclusion:** Patients hospitalized for COVID-19 in a tertiary institution in the state of Pará were predominantly elderly, male and with multiple morbidities, which reflected a high cumulative rate of thromboembolic events, especially deep vein thrombosis.

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INTRODUCTION

The new severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) that causes coronavirus disease 2019 (COVID-19) has led to an unprecedented global health crisis. The mortality rate has been estimated in 15% in some countries (Worldometer, 2020). Clinical manifestations are absent or mild in a substantial number of individuals whoose test are positive for SARS-CoV2. Bilateral pneumonia is main finding in hospitalized patients and at least 5% are in serious condition, requiring advanced medical support or intensive care (Worldometer, 2020 and Zhou *et al*, 2020). Bilateral pneumonia, systemic inflammation, endothelial dysfunction, hypercoagulation, acute respiratory distress syndrome, and multiple organ failure have been described as major features of severe COVID-19 (Ruan *et al*,2020 ; Han *et al*,2020; Huang *et al*, 2020; Chen *et al*, 2020; Tang *et al*, 2020 and Varga *et al*, 2020) and signs of myocardial injury are present at least in a quarter of severe cases (Zhou *et al*, 2020 and Clerkin *et al*, 2020).

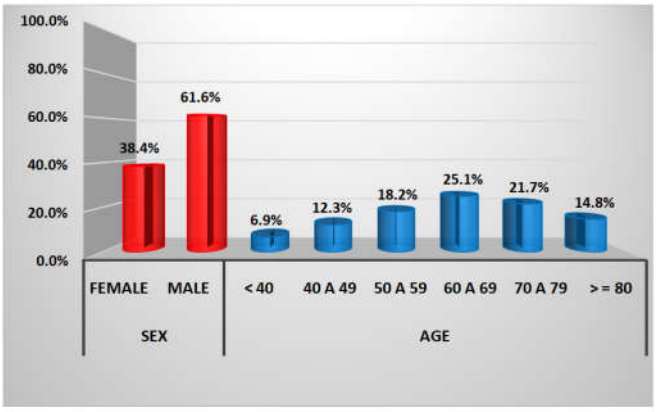
It has been postulated that high mortality observed among patients with COVID-19 may be partially due to unrecognized pulmonary embolism (PE) and *in situ* pulmonary thrombosis. Risk estimative for arterial complications and, in particular, venous thromboembolic complications are still preliminary and depend on strategies for early diagnostic and prevention (Klok *et al*, 2020 and Cui *et al*, 2020). COVID-19 may predispose to venous and arterial thromboembolic diseases due to inflammatory process, hypoxia, immobilization and intravascular coagulation (Han *et al*, 2020; Huang *et al* 2020; Chen *et al*, 2020 and Tang *et al*, 2020). Thus, accurate knowledge about incidence of thrombotic complications in patients with COVID-19 is important for decision making regarding the intensity of thromboprophylaxis, especially in patients admitted in intensive care unit (ICU), and also will help to optimize diagnostic strategies and guide randomized clinical trials on prevention of this complication. Therefore, the aim of this study was to describe rates and characteristics of venous and arterial thromboembolic complications in patients who were admitted at a tertiary hospital in Belém - Pará, along the first outbreak in the country.

METHODS

All data of this research were studied according to Declaration of Helsinki preceps and the Nuremberg Code, respecting Research involving Human beings norms (Brazilian Resolution n.466 of 2012) of the National Health Council and after obtaining the necessary authorizations. The study project was submitted and aproved by Research Ethics Committee of the Hospital Das Clínicas Gaspar Viana (Protocol number 4.241.661). This is a retrospective cohort study, based on medical records of every patient hospitalized at HCGV from March 1st to October 31, 2020, with high clinical suspicion or laboratory confirmation of infection by COVID-19. Patients whose medical records do not indicate infection by COVID-19 were excluded. To characterize the epidemiologic profile, the analyzed variables were: demographic data, pre-existing cardiovascular risk factors, previous thromboembolic phenomena, thromboembolic complications after COVID-19, use of medications (such as antiplatelet or anticoagulants), results of laboratory and image tests, according to research protocol (supplement data A). Data were tabulated at Excel program and subjected to statistical analysis using the chi-square test, and $p<0.001$ was considered statically significant.

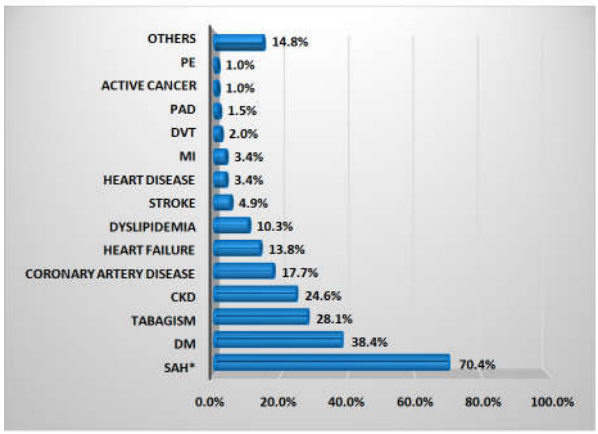
RESULTS

A total of 203 patients were included in the present study, of which 83%* were laboratory confirmed. The majority of patients were male (61.4%)*, with a mean age of 58.4 years old (Table 1).



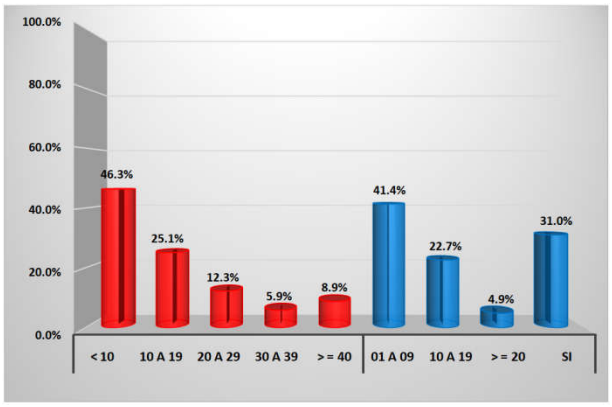
Source: research protocol.

Table 1. Distribution of COVID 19 patients addmited to HCGV, according to age and sex



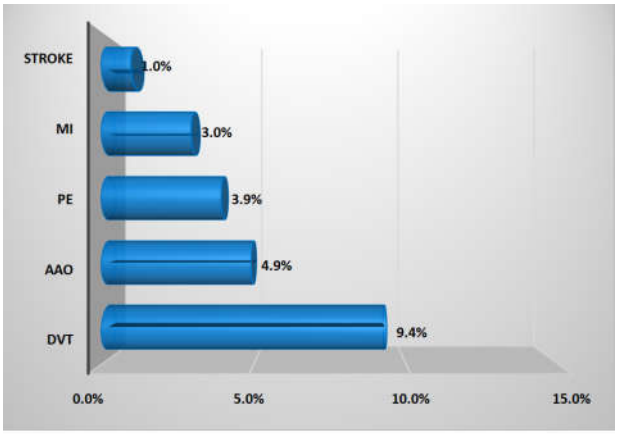
Legend: PE: Pulmonary embolism; PAD: Occlusive Peripheral Arterial Disease; DVT: Deep Venous Trombosis; MI: myocardial infarction; CKD:Chronic kidney failure; DM: Diabetes Mellitus; SAH: Systemic arterial hypertension. Source: research protocol, chi-squared test, *p<0,001

Table 2. Previous comorbidities in COVID 19 patients addmited to HCGV



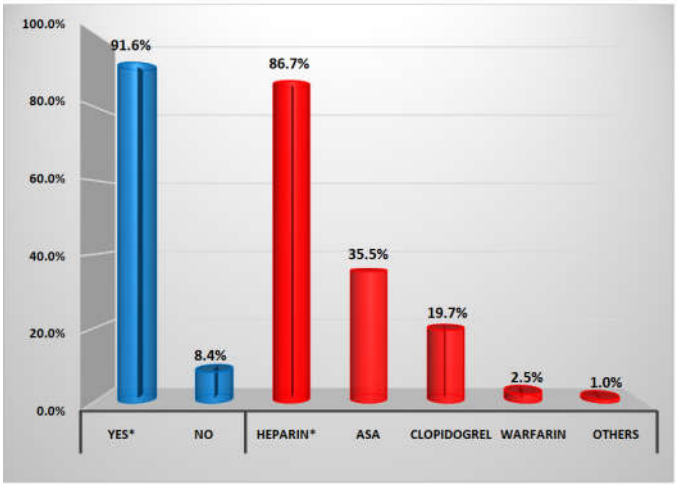
Source: Research protocol.

Table 3. COVID 19 patients hospitalization period at HCGV (red column) and lengh of time from begining of symptons to hospital admission (blue column)



Legend: MI: myocardial infarction; PE: Pulmonary embolism; AAO: *Acute arterial occlusion*; DVT: Deep Venous Trombosis. Source: Research protocol

Table 4. Thromboembolic complications at COVID 19 patients addmited to HCGV



Legend: ASA: Acetylsalicylic acid. Source: Research protocol.

Table 5. Percentage of COVID 19 patients admitted at HCGV that were submitted to clinical antithrombotic treatment (blue column), and most used drugs for this purpose (red column)

Most patients admitted had previous comorbidities (87.2%*), the most prevalent were: systemic arterial hypertension (70.4%*); Diabetes mellitus (38.4%); smoking (28.1%) and chronic renal failure (24.6%) (Table 2). The mean time from symptoms to hospitalization was 8.7 days, with a mean hospital stay of 15.6 days (Table 3). Furthermore, the cumulative rate of thromboembolic events was 22.2% and most common were, respectively, deep vein thrombosis (9.4%); acute arterial occlusion (4.9%) and pulmonary

thromboembolism (3.9%) (Table 4). Most patients underwent antithrombotic drug treatment (91.6%*), the main one being heparins (86.7%*), followed by acetylsalicylic acid and clopidogrel (Table 4); Whereas surgical treatment was performed in 7.9% of cases, with thromboembolectomy being the most frequently performed vascular procedure (50%), followed by coronary angioplasty (25%), amputation (12,5%) and myocardial revascularization (12,5%). About laboratory results, we could evidence that most patients presented high levels of D-dimer (38,5%) and Lactate dehydrogenase (49,8%) during the course of hospitalization, but normal coagulogram (61,1%).

DISCUSSION

The study describes demographic characteristics of patients hospitalized for COVID 19 in a tertiary institution in the state of Pará, and our findings are in accordance with other studies that demonstrated a high prevalence of elderly (Table 1), most of whom already had previous morbidities (Table 2), and systemic arterial hypertension (SAH) was one of the most common one (Aggarwal *et al*, 2020 and Padmaprakash *et al* 2021). Chronic diseases share several standard features with infectious disorders, such as proinflammatory state, and attenuation of innate immune response, leading to secondary immunodeficiencies (Chovancová *et al*, 2019),which may make individuals more susceptible to COVID 19 complications (Yang *et al*, 2020)and increase the need for hospital care. Furthermore, a high risk of thromboembolic complications was observed (cumulative rate of 22.2%), mainly venous events, which has already been observed in literature (Klok *et al*, 2020; Lodigiani *et al*, 2020 and Middeldorp *et al*, 2020) , however, the most commonly reported complication in other centers was pulmonary thromboembolism, which differs from the present study, that showed the occurrence of deep vein thrombosis as the most prevalent (Table 4). Such divergence can be explained by high rate of critically ill patients admitted to Intensive Care Unit in such analyses, while the present study mainly involved patients admitted to medical ward; and it has been postulated that the risk for venous thromboembolism (VTE) and arterial thrombosis ranged from 15% to 30% in critically ill patients while approximately only 7% was found in those admitted to medical wards(Chan *et al*, 2020) . Overall, it is known that VTE related to current or recent hospitalization are much more common than among people residing in the community(Heit *et al*, 2016), therefore the elevated hospital stay for COVID19 found in our study (Table 3) can also influence the high rates of VTE found. Thromboembolic complications are the hallmark of COVID-19, the new coronavirus SARS-CoV-2 elicits an acute inflammatory effect with hypercoagulability, platelet activation, and endothelial dysfunction (Iba *et al*, 2020 and Gómez-Mesa *et al*, 2021)that can cause death even in asymptomatic cases. The coagulopathy associated with COVID-19, is characterized by, among other things, the high levels of D-dimer, witch is a breakdown product of crosslinked fibrina and correlate with disease severity and predict the risk of thrombosis, the need for ventilatory support, and mortality (Chan and Weitz, 2020), and it is important to notice that our study found high levels of this marker in almost 40% of patients. Therefore, it is justified why most patients were submitted to antithrombotic drug treatment (Table 5), beeing heparins the most common used, because in addition to its anticoagulant properties, heparins have along-established history of anti-inflammatory activity, with demonstrated reductions in IL-6 and IL-8, as well as a reduction in human pulmonary microvascular endothelial cell damagesecondary to lipopolysaccharide induced nuclear factor κB signalinginvolved in sepsis (Ali and Spinler, 2021). We acknowledge limitations to our study. This was a retrospective analysis conducted at a large university hospital, therefore possibly not reflecting the demographic characteristics, management strategies and complications found at other non-academic institutions. Therefore larger studies including various institutions at Pará are needed to correctly evaluate the incidence of thrombotic events in COVID 19 patients and also to evaluate prevention strategies.

CONCLUSION

Patients hospitalized for COVID-19 in a tertiary institution in the state of Pará were predominantly elderly, male, with multiple comorbidities and prolonged hospitalization, which reflected in a high cumulative rate of thromboembolic events, particularly deep vein thrombosis.

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