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Clinical and prognostic implications of the presence of other prothrombotic factors in patients with Antiphospholipid syndrome: A single center cohort analysis

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Clinical and prognostic implications of the presence of other prothrombotic factors in patients with Antiphospholipid syndrome: A single-center cohort analysis

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Projeto de Opção do 6º ano - DECLARAÇÃO DE INTEGRIDADE

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DESIGNAÇÃO DA ÁREA DO PROJECTO

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TÍTULO DISSERTAÇÃO/MONOGRAFIA (riscar o que não interessa)

Clinical and prognostic implications of the presence of other prothrombotic factors in patients with Antiphospholipid Syndrome: A single center cohort analysis

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É AUTORIZADA A REPRODUÇÃO INTEGRAL DESTE TRABALHO APENAS PARA EFEITOS DE INVESTIGAÇÃO, MEDIANTE DECLARAÇÃO ESCRITA DO INTERESSADO, QUE A TAL SE COMPROMETE.	☐
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DEDICATÓRIA

A entrega e apresentação de uma dissertação conferidora de grau de mestrado constitui um dos marcos de maior importância no percurso académico de qualquer estudante universitário.

A elaboração de uma tese, nomeadamente de um trabalho de investigação, como é o caso, apresenta-se-nos como um desafio. De facto, trata-se de todo um processo que se inicia com a seleção do tema, escolha de orientadores e coorientadores, progride com a definição de populações a estudar bem como métodos e recursos a utilizar, e finalmente se conclui com uma análise objetiva, franca e crítica dos achados obtidos.

Nesta caminhada tive o privilégio de trabalhar com dois distintos profissionais da área da Medicina Interna, a Dr.ª Ester Ferreira e o Dr. Gilberto Rosa, que pacientemente deram resposta às minhas inquietações e dúvidas, a *e-mails* em horário extralaboral, a telefonemas ao domingo. Pelo papel que tão bem desempenharam e de forma tão preponderante, mais do que possam imaginar, irei sempre recordá-los com particular carinho, pelo que também a eles dedico este trabalho.

Dedico ainda aos meus avós, Alexandre e Augusta, e aos meus padrinhos, Isabel e José, por sempre acreditarem em mim e nas minhas capacidades.

Por último, dedico este trabalho à pessoa sem a qual todo este percurso não teria existido. Por todos os ensinamentos e lições de vida que me transmitiu que me tornaram na pessoa que sou hoje. Refiro-me à minha querida mãe, Carla, exemplo de superação, dedicação, e empenho em todos os papéis que desempenha na minha vida.

Clinical and prognosis implications of other prothrombotic factors in Antiphospholipid syndrome patients: a single-center cohort analysis

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Main Scientific area: Autoimmune diseases

Abstract

Introduction: The development of thrombosis is multifactorial in Antiphospholipid Syndrome (APS), with other inherited and acquired risk factors influencing the thrombotic profile. While inherited thrombophilia are still rare among APS patients, some works suggest a higher prevalence of C and S Proteins deficiencies and factor V Leiden mutation in these patients compared to the general population. Nevertheless, the exact frequency and clinical implications of the presence of these prothrombotic factors in APS are still poorly characterized. Methods: All patients followed in an Autoimmune Diseases consultation with a diagnosis of APS fulfilling the Sidney revised criteria were included. Data regarding inherited thrombophilia was collected - Activated protein C resistance (APCR); Leiden V Factor mutation; C and S proteins deficiencies; Prothrombin G20210A mutation; and Antithrombin III deficiency. Results: A total of 75 patients were analysed, with 65.3% corresponding to primary APS. The mean age of the study sample was 40 ± 9.4 years and the mean duration of disease was of 6.57 years ± 4.78 years. Seventeen (22.7%) patients exhibited an inherited thrombophilia: 9 (16.1%) S protein deficiency, 5 (10.2%) APCR, 5 (8.5%) antithrombin III deficiency, 4 (7.1%) C protein deficiency, 2 (4.5%) prothrombin G20210A mutation and 1 (2.0%) Leiden V factor mutation. The presence of inherited thrombophilia did not show statistically significant association with clinical manifestations or recurrence of events. Conclusion: Although with a significant prevalence in the studied sample, the presence of inherited thrombophilia did not display a significant clinical implication. However, positive findings might have been undermined due to the reduced sample size originating an underpowered study.

Key-words

Antiphospholipid syndrome; Inherited trombophilia; Antithrombin III deficiency; C Protein deficiency; S Protein deficiency; Leiden V Factor mutation; Prothrombin G20210A mutation;

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Introduction

Antiphospholipid Syndrome (APS) is defined by the presence of venous and/or arterial thrombosis and/or obstetrical manifestations in combination with the persistent positivity of antiphospholipid antibodies (aPL) [1,2].

The development of thrombosis is multifactorial in APS, with other inherited and acquired risk factors influencing the thrombotic profile [3]. The exact prevalence and clinical implications of other prothrombotic factors are still poorly characterized. Previous data suggests that anticoagulant deficiencies are rare among APS patients but, albeit with conflicting results, some works indicate that C and S proteins deficiencies and Leiden V factor mutations are more frequent when compared to non-APS patients [4-8]. A study hints a role of Leiden V factor mutation in increased risk of arterial and venous thrombosis in APS patients [6], but further works do not confirm this association [8,4]. Regarding prothrombin G20210A mutation, available evidence does not suggest an increased prevalence nor a role as an additional thrombotic risk factor in APS [6,8,4].

APS carries significant morbidity and mortality without the appropriate management, but the recommended therapy, anticoagulation, carries itself significant morbidity and considerable change in the patient´s daily life [9].

Important questions remain unanswered on this field, namely what determines the type of APS clinical manifestation (arterial *versus* venous *versus* obstetric) and why some patients recur despite anticoagulation. Deepening the knowledge on other prothrombotic factors' influence on APS clinical spectrum is still a goal for physicians who fight to improve therapeutic regimens, outcomes and patient's quality of life.

The aim of our study was to evaluate the presence of other prothrombotic factors and their clinical and prognostic implications, and also to verify the role of such risk factors in thrombosis recurrence. In addition we assessed for the presence of non-criteria clinical manifestations.

1. Patients and methods

A cohort analysis (with descriptive and analytical components) was conducted following approval by the Ethics Committee of Centro Hospitalar de São João.

The study included male and female Caucasian patients, with ages between 18 and 65 years, selected as a convenience sample from the Autoimmune Diseases Outpatients Clinic of the Internal Medicine Department of Centro Hospitalar de João, Porto, Portugal.

Inclusion criteria: patients with a diagnosis of "classic" APS based on the Sidney revised criteria.

A total of 75 patients have been recruited, which were characterized by revising their records as well as laboratory and complementary imaging exams.

All patients recruited strictly met the current classification criteria for APS [2]. Population characterization was performed by revising medical records as well as laboratory and imaging exams, and included in a database. Data registered comprised: (1) gender, (2) race, (3) age at diagnosis, (4) underlying autoimmune diseases, if any, (5) clinical manifestations at onset (defined as index event) and thereafter (6) clinical non-criteria manifestations, (7) laboratory profile including screening for inherited thrombophilia and immunological profile (antiphospholipid antibodies, aPL – namely β2glycoprotein1,

anticardiolipin and lupus anticoagulant, ANA; ANA pattern; anti-SSa; anti-SSb; anti-Scl70; anti-U1RNP; anti-centromere; ANCA; Rheumatoid Factor), (8) cardiovascular risk factors (hypertension; dyslipidemia; diabetes; obesity; hyperurucemia, smoking; (9) use of combined oral contraceptives (COCs), (10) therapy before and after disease onset/relapse.

2. Statistical analysis

All data and variables were in a database. Statistical analysis was performed by using SPSS 22 (IBM Analytics). In the analytical field, variables were analyzed using Chi-square and Fisher's Exact tests for categorical variables.

3. Results

General Characteristics. The study included 75 patients, 61 female (80%) and 14 male (20%), with a mean age of 40.03 $\pm$ 9.41 years old (30.61 – 49.44) and a mean disease duration of 6.57 $\pm$ 4.78 years (1.79 – 11.35). 65.3% of patients (n=49) corresponded to primary APS, with the remaining being associated with other autoimmune disease, mostly Systemic Lupus Erythematosus (SLE) – 16 patients, 21.3%. Regarding comorbidities, the most frequent cardiovascular risk factor among all analyzed variables was dyslipidemia (n=29, 38.7%). Twenty-four patients (47%) were taking COCs. Detailed information is presented in Table VII of "Attachments" section.

Concerning thrombotic events, the most frequent index event among APS-patients was venous thrombosis, present in 47 (62.7%) patients, while arterial thrombosis occurred in 13 (17.3%) patients. Deep vein thrombosis corresponded to the most significant venous event, present in 36 patients (48%), followed by cerebral venous sinus thrombosis (n=12, 16%) and pulmonary embolism (n=10, 13.3%). On the arterial side, stroke was the most significant manifestation (n=6, 8%), followed by acute myocardial infarction (n=3, 4%) and transient ischemic attack (n=2, 2.7%). Regarding female patients, 36.1% of them presented with obstetric morbidity – 24.6% suffered from unexplained fetal death after 10^{th} week of gestation; 6.6% had one or more premature births before 34 weeks and 1.6% experienced three or more embryonic pregnancy losses.

Considering recurrence of thrombotic events, it occurred in 16% (n=12) of patients with venous thrombosis being the most frequent recurrent event. Complete description of recurrence is displayed in Table I.

Analysing the group of patients with SLE-associated APS (n=16), venous thrombosis was present in 11 (68.8%) patients, while arterial thrombosis occurred in 3 (18.8%) patients and obstetric morbidity in 6 (46.2%) of patients.

Recurrent Event	*Nº of cases (%)*
Venous thrombosis	**14 (18.7%)**
Deep vein thrombosis	13 (17.3%)
Pulmonary embolism	2 (2.7%)
Cerebral venous sinus thrombosis	1 (1.3%)
Axillary vein thrombosis	1 (1.3%)
Ocular thrombosis	1 (1.3%)
Arterial thrombosis	**2 (2.6%)**
Ischemic stroke	1 (1.3%)
Transient Ischemic Attack	1 (1.3%)
Obstetric morbidity	**5 (6.7%)**
Unexplained fetal death at 10 or more gestation weeks	3 (4.0%)
One or more premature births before 34 weeks	2 (2.7%)

Table I. Event recurrence among APS-patients.

Regarding non-criteria clinical manifestations, the most common clinical entities observed were migraine (n=16, 21.3%) and thrombocytopenia (n=12, 16%). Less commonly, there were cases of renal microangiopathy (n=2, 2.7%), seizures (n=2, 2.7%), alveolar hemorrhage (n=2, 2.7%), livedo reticularis (n=1, 1.3%), memory lapses and cognitive impairment (n=1, 1.3%), and bone osteonecrosis (n=1, 1.3%). No patients displayed past events of transverse myelitis or chorea, ARDS, heart valve dysfunction or skin pseudovasculitis. Detailed data is presented in the "Attachments" section, tables III and IV.

Inherited thrombophilia and remaining immunological profile. Laboratory tests for inherited thrombophilia were not available in all patients, hence reducing the sample size in the analysis of these variables (levels of S Protein and C protein n=56, prothrombin G20210A mutation n= 44, Antithrombin III n=59, Leiden V factor n=51, and ACRP n=49). In the studied sample, 17 (22.7%) patients exhibited at least one inherited thrombophilia. The prevalence of each thrombophilia among the studied population is presented in table II.

Thrombophilia	*Nº of patients (%)*	*Patients with obstetric morbidity (n=22)*
S Protein Deficiency (n=56)	9 (16.1%)	4 (18.2%)
Activated C-reactive protein (n=49)	5 (10.2%)	3 (13.6%)
Antithrombin III (n=59)	5 (8.5%)	1 (4.5%)
C Protein Deficiency (n=56)	4 (7.1%)	0
Prothrombin gene mutation (n=44)	2 (4.5%)	1 (4.5%)
Leiden V Factor (n=51)	1 (2.0%)	0

Table II. Prevalence of thrombophilia among the studied patients

Concerning the aPL profile, isolated lupus anticoagulant positivity occurred in 22 patients (29.3%), isolated anticardiolipin antibodies positivity in 14 (20%) and isolated β2glycoprotein1 antibodies positivity in 11 (14%). Double positivity for β2glycoprotein1 and antiocardiolipin antibodies occurred in 7 patients (9.3%), double positivity for β2glycoprotein1 antibodies and lupus anticoagulant also in 7 (9.3%) and double positivity for anticoagulant antibodies and lupus anticoagulant in 6 (8%). Triple

positivity occurred in 8 patients (10.7%). Persistent positivity for aPL antibodies (accounted as more than 3 positive determinations) occurred in 24 patients (32%).

Referring to the remaining immunological profile, ANA antibodies were present in 54.7% of the patients included in this study. The most frequent pattern was speckled (29.3%), followed by homogeneous (14.7%), nucleolar (9.3%) and mid-body (1.3%). Other autoantibodies usually requested as part of an autoimmune profile were almost always negative. More detailed information is presented in table V in the "Attachments" section.

Therapeutic approach. Fifty-eight patients were under oral anticoagulation (warfarine), 28 with aspirin and one taking clopidogrel. Twenty-five patients were under therapy with hydroxychloroquine. Among the 12 patients that recurred, 9 (75%) were under under oral anticoagulation.

Correlation between inherited thrombophilia, cardiovascular risk factors and clinical outcomes. The presence of inherited thrombophilia did not show statistically significant association with specific clinical manifestations or with recurrence of events. However, regarding non-criteria manifestation, a statistically significant association was found between APS-patients with C-protein deficiency and the occurrence of Raynaud phenomenon, with a p-value of 0.011 (determined using Fisher's exact test). Concerning classical cardiovascular risk factors and their influence on patients' prognosis, no statistically significant association with the type of clinical event nor with recurrence frequency was found.

We present more detailed data in "Attachments", tables VII and VIII.

Discussion

In this study APS patients were evaluated for the presence of inherited thrombophilia (namely C and S Proteins deficiencies, Leiden V factor mutation, APCR, Antithrombin III deficiency and prothrombin G20210A mutation), cardiovascular risk factors and association with other autoimmune disease. The presence of inherited thrombophilia and/or cardiovascular risk factors were not associated with increased risk for recurrence neither with the type of vascular events. Furthermore, the presence of other autoimmune disease did not display any particular clinical significance among these patients.

The literature surrounding the domain of other prothrombotic factors in APS is markedly scarce. Firstly, the rarity of these entities undermines the recruitment of large study samples. Secondly, a number of factors affects the determination of these parameters - in acute thrombotic events or in patients under oral anticoagulation, natural anticoagulant activities counting may be decreased. Our study, albeit undersized, has tried to address these matters in a coherent manner: in order to avoid misdiagnosis of inherited C or S proteins deficiencies, these parameters were determined when patients were not under anticoagulation and with appropriate separation from an acute event.

As the most striking finding of this study comes the significant prevalence of inherited thrombophilia, with 22.7% of patients displaying at least one of these parameters. Previous reports in the literature stated a prevalence of Factor V Leiden ranging from 1.3 to 13% and Prothrombin G20210A mutation ranging from 2.7% to 6.5% in APS [4,6,8]. Our values rank among these range (2% and 4.5%, respectively), but are not superior to those reported in the general population (2 to 8% for Factor V

Leiden in Caucasians and 0 to 15.9% for Prothrombin G20210A mutation in different ethnic groups) [10,6,11,12]. In our cohort, nevertheless, there was a significant prevalence of other thrombophilia, such as S Protein deficiency (16.1%), RCPA (10.2%), Antithrombin III deficiency (8.5%) and C Protein deficiency (7.1%).

In fact, no association was found between the presence of hereditary thrombophilia and specific thrombotic manifestations or recurrent events. Although these findings should be analyzed with care due to the reduced sample size, they add strength to the hypothesis that the presence of hereditary thrombophilia do not significantly increase the thrombotic risk of APS patients, and that no specific therapeutic measure needs to be contemplated in these patients.

Inherited thrombophilia are also linked to adverse pregnancy outcomes [13]. Studies have suggested that pregnant women with antithrombin III deficiency have a higher incidence of obstetric morbidity when compared to women without thrombophilia [14,15]. In the present work no statistically significant association was found regarding these outcomes.

In our study, we also evaluate the prevalence and potential associations with typical cardiovascular risk factors in criteria and non-criteria manifestations and event recurrence. A statistically significant association was not found, as in previous works, suggesting that they might not play a major role in thrombotic events of APS-patients [1,16].

Considering non-criteria manifestations, our study showed a prevalence of 16% of thrombocytopenia, a less prominent value than previous studies had reported. Other manifestations (neurological, renal, cutaneous) occurred in similar frequencies, being in line with previous works, suggesting that the presence of hereditary thrombophilia did not change the presence of these involvements [1,16-18]

Study Limitations

We present a single center, retrospective study with the inherent limitations of this type of study design. Additionally, the limited number of the study sample undermines the study power.

Conclusion

Although with a significant prevalence in the studied sample, the presence of inherited thrombophilia displayed no categorical or particular clinical significance. These findings suggest that clinical manifestations in APS are mainly due to the APS itself, and that the presence of inherited thrombophilia do not significantly change the disease course.

However, future research is needed, with larger study populations and ideally a prospective design, in order to categorically clarify the role of concomitant inherited thrombophilia on APS and the need to adjust treatment goals in this particular population.

Compliance with ethical standards

Conflict of interest

The authors declare that they have no conflict of interest.

Ethical approval

All procedures performed were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its amendments and comparable ethical standards

Research involving human and animal participants

This article does not contain any studies with animals performed by any of the authors.

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Attachments

Table III. Non clinical vascular manifestations of APS

Vascular Manifestations	*Nº of patients (%)*
Superficial Vein Thrombosis (n=75)	7 (9.3%)
Cutaneous Ulcers/Necrosis (n=75)	5 (6.7%)
Raynaud Phenomenon (n=75)	4 (5.3%)
Livedo Reticularis (n=75)	1 (1.3%)
Alveolar hemorrhage (n=75)	0
Skin Pseudovasculitis (n=75)	0

Table IV. Non clinical neurological manifestations of APS

Neurological Manifestations	*Nº of patients (%)*
Migraine (n=75)	16 (21.3%)
Seizures (n=75)	2 (6.7%)
Memory lapses (n=75)	1 (1.3%)
Cognitive impairment (n=75)	1 (1.3%)
Transverse myelitis (n=75)	0
Chorea (n=75)	0

Table V. Immunological profile of APS-patients

Other antibodies	*Nº of patients (%)*
ANA (n=75)	41 (54.7%)
Anti-SSa (n=71)	6 (8.5%)
Rheumatoid Factor (n=61)	3 (4.9%)
Anti-SSb (n=71)	2 (2.8%)
Anti-RNP (n=71)	1 (1.4%)
ANCA (n=71)	1 (1.4%)
Anti-centromere (n=71)	0
Anti-Scl70 (n=71)	0

Table VI. Prevalence of cardiovascular risk factor s among APS-patients

Cardiovascular Risk Factor	*Nº of cases (%)*
Dyslipidemia (n=75)	29 (38.7%)
Obesity (n=75)	19 (25.3%)
Arterial Hypertension (n=75)	15 (20%)
Smoker (n=75)	12 (16%)
Hyperuricemia (n=75)	3 (4%)
Diabetes (n=75)	3 (4%)

Table VII. Thrombotic events among APS-patients with thrombophilia

Trombophilia / *Clinical event*	*Presence of one Thrombophilia (n=17)*	*Antithrombin Deficiency (n=4)*	*C-Protein Deficiency (n=4)*	*S-Protein Deficiency (n=9)*	*Leiden V Factor (n=1)*	*RCPA (n=5)*	*Prothrombin Gene Mutation (n=2)*
Arterial Thrombosis	n=2 p=0.720	n=0	n=1 p=1	n=2 p=1	n=0	n=0	n=0
Venous Thrombosis	n=12 p=0.572	n=3 p=1	n=3 p=1	n=5 p=0.707	n=1 p=1	n=4 p=1	n=1 p=0.508
Obstetric morbidity	n=4 p=0.763	n=1 p=1	n=0	n=3 p=0.668	n=0	n=0	n=1 p=0.296
Recurrence of thrombotic events	n=2 p=0.723	n=0	n=0	n=3 p=0-312	n=0	n=1 p=0.554	n=0

Table VIII. Non criteria clinical events among APS-patients with thrombophilia

Trombophilia / *Clinical event*	*Antithrombin Deficiency (n=4)*	*C-Protein Deficiency (n=4)*	*S-Protein Deficiency (n=9)*		*Leiden V Factor (n=1)*	*RCPA (n=5)*	*Prothrombin Gene Mutation (n=2)*
Vascular	*SVT*	0	0	1	0	1	0
	Livedo reticularis	0	0	0	0	0	0
	Raynaud	0	2	1	0	1	0
	Cutaneous ulcers/necrosis	0	0	1	0	0	0
Hematological	*Thrombocytopenia*	1	1	1	0	1	0
Cardiac	*Valvular dysfunction*	0	0	0	0	0	0
Neurological	*seizures*	0	0	0	0	0	0
	Migraines	1	1	2	1	3	0
Pulmonar	*Pulmonary Hypertension*	1	0	1	0	0	0
Renal	*microangiopathy*	1	0	1	0	1	0

ANEXOS

Journal of Thrombosis and Thrombolysis: Instructions for Authors

TYPES OF PAPERS

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Brief Communication
Rapid Report
Most manuscripts should be a maximum of 2500 words with 3 figures and 2 tables. All other tables and figures will appear in an online supplement. A brief communication should be no more than 1500 words with 1-2 figures and a single table. A rapid report represents the ideal format for novel observations that may signal a sea change in the field with further investigation and validation. It can be up to 1000 words with 1-2 figures.
Please provide a brief structured abstract followed by 4 to 5 key points captured in a bullet format. The last bullet should be implications for future directions.
Manuscripts should fall under one of the following sections:

Clinical Trials and Methods

This section is dedicated to clinical research that includes human subjects. Phase 1-4 trials will be considered. Planned or ongoing clinical trials with background, hypothesis being tested and methods being employed will also be considered.

Fundamental and Translational Science: Research Models and Platforms

This section focuses on research being performed at the bench (basic or fundamental science) or in the context of translating prior observations to patient care (the bedside). New research methods, including simulations, modeling and in silica experiments are also welcomed..

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This section is designed to highlight the development of new drugs for use in heart and vascular disease and devices that could be used for diagnostic or treatment purposes.

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This section will feature brief and focused reviews that clinicians can refer to for day-to-day decision making. Reviews submitted to this section must have clear and practical clinical focus, with emphasis on patient care/management. Reviews should be approximately 1,500-2,000 words in length with 2 tables, 2 figures and a maximum of 10 references.

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Early Career Scientific Contributions will contain original investigations, images, and reviews written by individuals in residency or fellowship training positions. Case reports that include unique features, multimedia formats or imaging, will also be considered. Submissions should be accompanied by a cover letter from the training director certifying that the corresponding author is in training.

Education, Training, Networking and Career Development Series

This section will include original investigations, concise review articles, and brief scientific or editorial communications dedicated to training, education, and career development. Submissions are welcomed that highlight relevant issues at all stages of ones' career as well as topics for continuing education in thrombotic, hemostatic, and vascular diseases.

Vascular Medicine

This section is dedicated to the burgeoning field of vascular conditions, disorders or diseases affecting the cerebrovascular, peripheral arterial vascular, venous, lymphatic and microvascular circulatory beds.

National and International Meeting Highlights

Highlights of the high-impact research presented at major Cardiology and Hematology Meetings (ie. AHA, ACC, ESC, ASH, and ISTH). A highlight summary can be up to 1,200 words with 2-3 tables and 2-3 figures.

Fundamental and Translational Science Translator

This section will provide an interpretation or translation of fundamental scientific constructs in the context of their potential impact or contribution to clinical practice, patient care and future patient-centered research.

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This section is dedicated to comparing and contrasting guidelines in the disciplines of thrombosis and hemostasis from varying writing groups, societies, foundations and governing bodies in the United States and abroad. The overall goal is to provide clarity and context for practicing clinicians. Submissions should summarize guidelines and key points in specific practice areas employing the best available evidence.

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Please provide an abstract of 150 to 250 words. The abstract should not contain any undefined abbreviations or unspecified references.

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- Use the equation editor or MathType for equations.
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Reference citations in the text should be identified by numbers in square brackets. Some examples:

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- Book chapter

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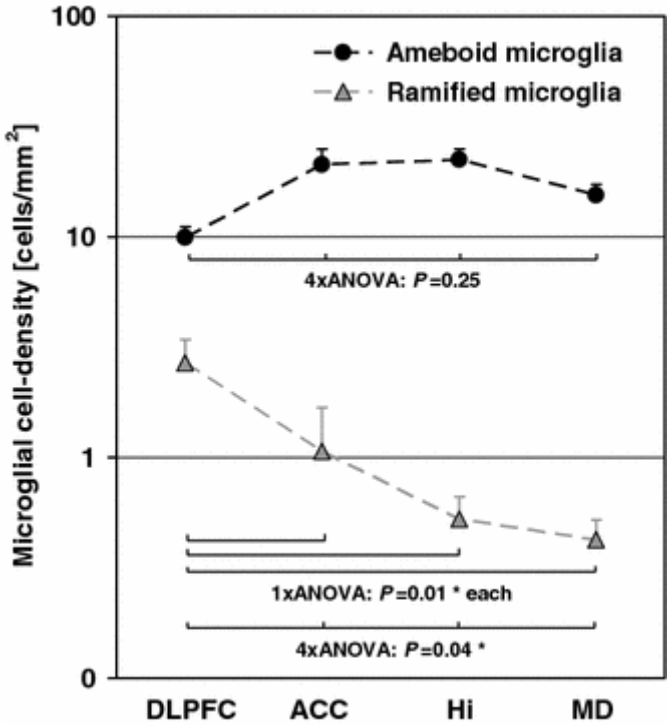

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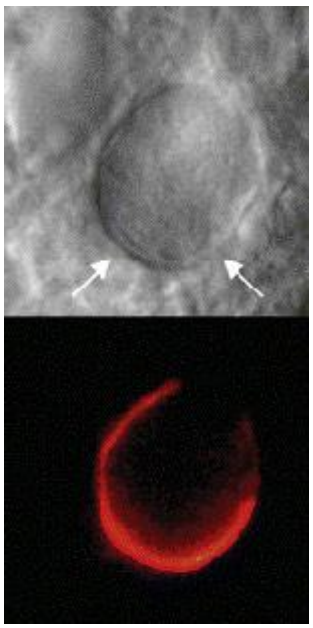

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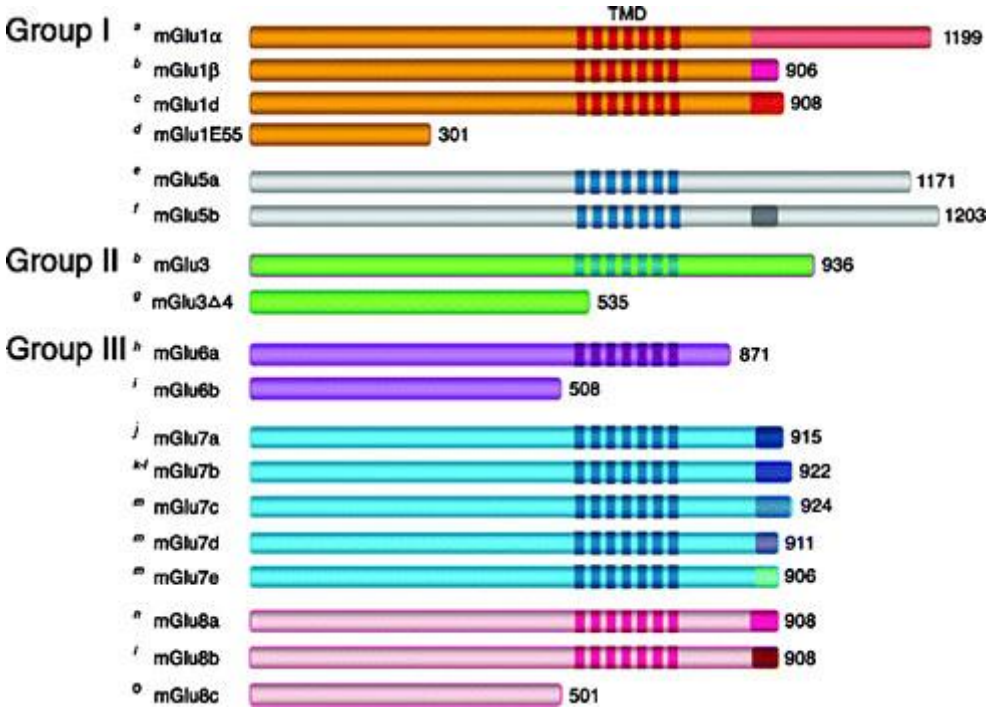

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Tomei conhecimento. Nada a opor.

12 de Março de 2018

A Coordenadora da Unidade de Investigação

(Prof.ª Doutora Ana Azevedo)

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(Dr. António Oliveira e Silva)

Diretor Clínico | Enfermeira Diretora | Vogal Executivo | Vogal Executivo

(Prof. Dr. José Artur Paiva) | (Enf.ª Manuela Sarmento) | (Dr. Luís Pinto Guerra) | (Dr. Eduardo G. Matos)

06/2018

Exmo. Senhor

Presidente do Conselho de Administração do

Centro Hospitalar de S. João – EPE

Assunto: Pedido de autorização para realização de estudo/projecto de investigação

Nome do Investigador Principal: Mariana Ribas Laranjeira

Título do projecto de investigação: Clinical and prognostic implications of other prothrombotic factors in Antiphospholipid syndrome-patients: a single-center cohor analysis

Pretendendo realizar no(s) Serviço(s) de Medicina Interna do Centro Hospitalar de S. João – EPE o estudo/projecto de investigação em epígrafe, solicito a V. Exa., na qualidade de Investigador/Promotor, autorização para a sua efectivação.

Para o efeito, anexa toda a documentação referida no dossier da Comissão de Ética do Centro Hospitalar de S. João respeitante a estudos/projectos de investigação, à qual endereçou pedido de apreciação e parecer.

Com os melhores cumprimentos.

Porto, 24 / Outubro / 2017

O INVESTIGADOR/PROMOTOR

Mariana Laranjeira

Comissão de Ética para a Saúde do HSJ
Parecer

Projecto de investigação: "Clinical and prognosis implications of other prothrombotic factors in Antiphospholipid syndrome patients: a single center cohort analysis".

Promotor:

- Sociedade Portuguesa do Acidente Vascular Cerebral.

Concepção e pertinência do estudo

- Trata-se de um estudo retrospetivoa realizar no âmbito da tese de Mestrado Integrado em Medicina na Faculdade de Medicina da Universidade do Porto (FMUP), que tem como objectivo principal, a avaliação de outros factores protrombóticos em doentes com síndrome antifosfolipídico, e as suas implicaçõesclínicas e prognósticas.
- Tem ainda outros objectivos que são pertinentes e adequados aos objectivos do estudo.
- O estudo incluirá 80 doentes com síndrome antifosfolipídico seguidos nas consultas de Doenças Autoimunes do Serviço de Medicina Interna, de Trombofilia do Serviço de Imunohemoterapia e da Consulta de Obstetrícia do Centro Hospitalar de S. João. No entanto, no protocolo submetido à CES não está explícito se todos os doentes são seguidos na consulta de Medicina Interna; *caso sejam seguidos exclusivamente nas consultas de Imunohemoterapia ou da Obstetrícia, terá que ser pedida autorização aos respectivos Diretores de Serviço*.
- Serão consultados os processos clínicos e colhidos dados clínicos, laboratoriais e imagiológicos, todos eles pertinentes e adequados aos objectivos do estudo. Todos os critérios e variáveis a estudar estão bem descritos no protocolo do estudo submetido à CES.
- O protocolo de estudo, os critérios de inclusão e de exclusão estão suficientemente detalhados e não levantam quaisquer questões do foro ético.
- O estudo é importante, pertinente e muito bem fundamentado.
- A Investigadora Principal, Mariana Laranjeiro, estudante do 6º ano do curso de Medicina da FMUP (tendo como elo de ligação o Dr. Gil Rosa, e como orientadora da Tese, a Dra. Ester Ferreira, Médica especialista de Medicina

Interna, do Centro Hospitalar de S. João EPE dispõe das competências técnicas e científicas para a realização do estudo.

- O estudo será realizado no Serviço de Medicina Interna do Centro Hospitalar de S. João EPE que dispõem das condições necessárias para a realização do estudo. O estudo está autorizado pelo Diretor de Serviço, Dr. Jorge Almeida.
-

– **Beneficio/Risco**

Dado a natureza retrospectiva do estudo não existirão riscos, incómodos ou benefícios acrescidos pela participação do doente neste tipo de estudo.

– **Respeito pela liberdade e autonomia do sujeito do ensaio**

- Dado a natureza retrospectiva do estudo, não é necessária a obtenção do consentimento informado.

– **Confidencialidade dos dados**

A confidencialidade dos dados está garantida.

– **Indemnização por danos**

Não aplicável.

– **Continuação do tratamento**

Não aplicável.

- Propriedade dos dados

Não aplicável.

Conclusão

Em face da análise do protocolo do estudo "Clinical and prognosis implications of other prothrombotic factors in Antiphospholipid syndrome patients: a single center cohort analysis", proponho a sua aprovação pela CES do HSJ/FMUP, depois de obtida as resposta à questão em sublinhado e em itálico.

Porto, 12 de janeiro de 2018

O Relator

Prof. Manuel Vaz Silva

Foi entregue a declaração em falta

21/02/18

7. SEGURO

a. *Este estudo/projecto de investigação prevê intervenção clínica que implique a existência de um seguro para os participantes?*

SIM ☐ (Se sim, junte, por favor, cópia da Apólice de Seguro respectiva)

NÃO ☐

NÃO APLICÁVEL ☑

8. TERMO DE RESPONSABILIDADE

Eu, Mariana Ribas Laranjeira,

abaixo-assinado, na qualidade de Investigador Principal, declaro por minha honra que as informações prestadas neste questionário são verdadeiras. Mais declaro que, durante o estudo, serão respeitadas as recomendações constantes da Declaração de Helsínquia (com as emendas de Tóquio 1975, Veneza 1983, Hong-Kong 1989, Somerset West 1996 e Edimburgo 2000) e da Organização Mundial da Saúde, no que se refere à experimentação que envolve seres humanos. Aceito, também, a recomendação da CES de que o recrutamento para este estudo se fará junto de doentes que não tenham participado em outro estudo no decurso do actual internamento ou da mesma consulta.

Porto, 24 / Outubro / 2017

Mariana Laranjeira

O Investigador Principal

PARECER DA COMISSÃO DE ÉTICA PARA A SAÚDE DO CENTRO HOSPITALAR DE S. JOÃO

emitido na reunião plenária da CES de ___/___/___

12/01/18

A Comissão de Ética para a Saúde, tendo aprovado o parecer [illegible] aguarda que o Investigador [illegible] esclareça as questões nele [illegible] que possa emitir parecer definitivo.

Centro Hospitalar São João.

CONSIDERADOS QUE FORAM COMO SATISFATÓRIOS OS ESCLARECIMENTOS PRESTADOS PELO(A) INVESTIGADOR(A), A CES APROVA POR UNANIMIDADE O PARECER DO RELATOR, PELO QUE NADA TEM A OPOR À REALIZAÇÃO DESTE PROJETO DE INVESTIGAÇÃO.

21/02/18

RESPONSÁVEL PELO ACESSO À INFORMAÇÃO

SÃO JOÃO

Pedido de Reutilização de Registos Clínicos para Investigação e Desenvolvimento (I&D)

Número do Pedido
1 8 1 0 1 2 4 3 1 0
(A preencher pelo Gabinete de Apoio ao RAI)

Exmo. Senhor
Responsável pelo Acesso à Informação
(Artigo 9.º da Lei n.º 26/2016, de 22 de agosto)
Dr. Rui de Vasconcellos Guimarães

SÃO JOÃO

AUTORIZADO
RAI - Responsável pelo Acesso à Informação do Centro Hospitalar de São João (Art. 9º, Lei 26/2016, de 22/8)
2/12/2018
VASCONCELLOS GUIMARÃES
Administrador Hospitalar

1. Identificação do(s) Investigador(es) *Preenchimento Obrigatório*

1.1. Investigador Principal

Nome Marisa Ribas Laranjeira
Contacto telefónico 916 912 112 153 101
Endereço eletrónico maribaslaranjeira @ gmail.com

1.2. Investigador(es) Associado(s)

Número Total: 2

Nome Gilberto Carlos Pires da Rosa
Contacto telefónico
Endereço eletrónico Gilbertopiresrosa @ gmail.com

Nome Estefânia Maria Morgado Ferreira
Contacto telefónico
Endereço eletrónico estefferreira28 @ gmail.com

Nome
Contacto telefónico
Endereço eletrónico @

1.3. Afiliação Institucional do Investigador Principal

1.3.1. Grupo Profissional

☐ Médico(a) ☐ Enfermeiro(a) ☐ Docente ☒ Estudante
☐ Outro. Qual?

1.3.2. Documento de identificação pessoal ou profissional

☒ Cartão de Cidadão ☐ Bilhete de Identidade ☐ Célula Profissional
☐ Cartão de Docente ☐ Cartão de Estudante ☐ Outro. Qual?

Número de Documento 14161107138

2. Enquadramento e Identificação do Trabalho de Investigação e Desenvolvimento *Preenchimento Obrigatório*

2.1. Enquadramento da investigação

☒ Trabalho académico de investigação e desenvolvimento:
- ☐ Não conferidor de grau
- ☐ Conferidor de grau: ☐ Licenciatura ☒ Mestrado ☐ Doutoramento

☐ Projeto de investigação e desenvolvimento

RAI-IM002-0

2.2. Entidade(s) que tutela(m) a investigação

[X] Centro Hospitalar de São João

Serviço: Medicina Interna

[X] Universidade do Porto

Faculdade / Instituto: Faculdade de Medicina da Universidade do Porto

[ ] Outra Instituição. *Qual?*

Há alguma parceria entre instituições?

[X] Não [ ] Sim. Qual(is)?

2.3. Orientador *Se Aplicável*

Contacto telefónico | | | | | | | | | | | | |

Endereço eletrónico esfefevereiro28 @ gmail.com

2.4. Título provisório

Clinical and prognostic implications of the presence of other pathrombotic factors in patients with Antiphospholipid syndrome: A single centre cohort analysis.

Deverá posteriormente indicar o título definitivo para emissão do Certificado de Reutilização pelo RAI – DAta REuse Certificate for Research – DARE através dos contactos disponíveis no fim deste formulário.

2.5. Acesso requerido

[ ] Ficheiro

Descrição do património informacional a que pretende ter acesso, identificando a informação a obter, i.e. nome, morada, diagnóstico, idade, códigos dos distritos, entre outros.

[ ] Consulta de processos clínicos em ambiente papel:

[ ] Bloco [ ] Consulta Externa [ ] Hospital de Dia [ ] Internamento [ ] MCDT [ ] Urgência

Deverá anexar ficheiro(s) contendo a identificação do pretendido, i.e. números de processos, episódios, números de utente, entre outros.

Anexar ficheiro – tamanho de envio

[X] Consulta de registos clínicos eletrónicos

Especificar os Sistemas de Informação:

Data previsível de fim de utilização das credenciais de acesso | | | | - | | - | |

[ ] Outro Acesso. Qual?

2.3. Pareceres e Autorizações

[X] Autorização da Hierarquia

[ ] Protocolo Científico Aprovado [1]

[ ] Parecer da Comissão de Ética para a Saúde (CES) [1]

[ ] Parecer do Centro de Epidemiologia Hospitalar [1]

Deverá anexar ficheiro(s) contendo cópia dos documentos referentes às opções selecionadas.

Anexar ficheiro – tamanho de envio

[1] Obrigatório se aplicável

3. Observações *Preenchimento Facultativo*

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4. Aceitação dos Termos e Condições da Reutilização

Cumulativamente com as obrigações decorrentes da lei já citada *(n.º 2 e 3 do artigo 21 e o n.º 1 e 2 do artigo 12, ambos da Lei n.º 26/2016, de 22 de agosto)* ao submeter o presente pedido concordo e fico ainda vinculado aos seguintes termos e condições:

- Comprometo-me a manter confidencial toda a informação à qual vou ter acesso;
- Não vou elaborar registos, susceptíveis de identificar ou tornar identificável a identidade das pessoas a quem os mesmos dizem respeito;
- Não vou elaborar, nem ficar na posse, de cópias de bases de dados utilizadas na recolha de informação;
- Comprometo-me a obter junto da Comissão Nacional de Proteção de Dados (CNPD) as necessárias autorizações, para eventuais bases de dados que venha a conceber e utilizar no âmbito da presente investigação;
- Comprometo-me a devolver ao Centro Hospitalar de São João, na pessoa do seu Diretor Clínico, as bases de dados e o resultado da investigação;
- Comprometo-me a ocultar os elementos de identificação da(s) pessoa(s) a quem os registos digam respeito, em futuras e eventuais publicações de resultados;
- Comprometo-me a consultar os processos clínicos nas instalações que me forem indicadas para o efeito;
- Comprometo-me a obter os necessários pareceres, quer da Comissão de Ética do Hospital, quer do Centro de Epidemiologia Hospitalar, sempre que necessário;
- Comprometo-me a citar as fontes sempre que publicitar o trabalho de investigação independentemente de requerer a Certidão de Reutilização (DAta REuse Certificate for Research – DARE);
- Tomei conhecimento, que a violação de qualquer dos compromissos aqui assumidos, resultará no apuramento de responsabilidades disciplinares, civis e penais e ainda, à impossibilidade futura de aceder a informação de saúde para fins de investigação.

5. Decisão do investigador sobre requerer a DAta REuse Certificate for Research – DARE *Preenchimento Obrigatório*

☒ Pretendo desde já requerer a Certidão de Reutilização (DARE) cujo sentido, valor e significado consultei em *http://portal-chsj.min-saude.pt/pages/710.*

☐ Não pretendo requerer a Certidão de Reutilização (DARE) cujo sentido, valor e significado consultei em *http://portal-chsj.min-saude.pt/pages/710.*

6. Assinatura

Nota 1: Se o presente pedido for submetido eletronicamente ou faz assinatura digital qualificada; ou posteriormente vem ao Centro Hospitalar de São João exibir o seu documento de identificação pessoal, ou no âmbito do seu espaço de liberdade e como manifestação expressa do seu consentimento envia cópia do referido documento, neste caso, concluído o processo ser-lhe-á devolvida ou eliminada a cópia do documento de identificação pessoal, conforme as indicações que dê.
Nota 2: Se o presente pedido for entregue presencialmente, assina e exibe o documento de identificação a quem recebe o pedido.

Data 2018 - 01 - 15

Mariana Ribas Laranjeira

Investigador Principal

Em caso de dúvida no preenchimento contacte através dos endereços eletrónicos
rai.reutilizacao.id@chsj.min-saude.pt **ou** ruiguimaraes@chsj.min-saude.pt
ou pelos números de telemóvel 962 204 194 **ou** 918 880 299

SUBMETER

AGRADECIMENTOS

Gostaria de agradecer aos Departamentos de Medicina Interna e de Imunohemoterapia do Centro Hospitalar de São João, representados nas pessoas do Dr. Jorge Almeida e da Dra Maria do Carmo Koch, respetivamente, por terem possibilitado a realização deste trabalho.

Do mesmo modo, tecer um agradecimento ao Dr. Luís Nogueira Silva, por me ter orientado na realização da análise estatística dos dados recolhidos.

Agradeço ainda a todos os Especialistas e Internos de Formação Especifica que integram o Grupo de Doenças Autoimunes, liderado pelo Dr Carlos Dias, pois foi a sua conjunta dedicação e empenho nos cuidados prestados a estes doentes que tornou possível este trabalho. Em particular agradeço à Dra Ester e ao Dr Gilberto por toda a entrega na orientação deste projeto.

Deixo também uma palavra de reconhecimento, em especial a duas amigas e colegas de curso, Marta Pinto e Ana Meireles, que não só me acompanharam inúmeras vezes no decorrer da investigação, mas também me motivaram e estimularam a fazer este caminho com positivismo e confiança. A todos os demais amigos, igualmente agradeço pelo interesse demonstrado no tema a cuja explanação procedo neste trabalho, para muitos desconhecido até terem iniciado o estudo para a Prova Nacional de Seriação ou até ao momento em que uma entusiástica amiga os aborda e orgulhosamente dá a conhecer.

Igualmente, agradeço aos meus avós e aos meus padrinhos.

Por último, não poderia perder a oportunidade de lhe agradecer por todo o esforço, todo o carinho, amor e ânimo que sempre me deu. Louvá-la por, apesar dos obstáculos que se interpuseram, possibilitar a concretização do sonho que era tornar-me médica. Agradeço ainda por me ter mostrado na primeira pessoa, no exercício da sua profissão, o quão importante é que, aliada às competências científicas, adquiramos uma visão humanizada da medicina. Obrigada Mãe!