

Risk of thrombosis associated with antiphospholipid antibodies in immune thrombocytopenia: a retrospective study of 152 patients

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ET DES PROFESSIONS PARAMÉDICALES
Université Clermont Auvergne

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UFR DE MÉDECINE ET DES PROFESSIONS PARAMÉDICALES

THÈSE D'EXERCICE

pour le

DIPLÔME D'ÉTAT DE DOCTEUR EN MÉDECINE

par

FAYARD Damien, Pierre

Présentée et soutenue publiquement le 27/09/2021

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LIST OF ABBREVIATIONS

aCL : Anticardiolipin

APL : Antiphospholipid Antibodies

APS : Antiphospholipid Syndrome

ASH : American Society of Hematology

BMI : Body Mass Index

CKD-EPI : Chronic Kidney Disease - EPIdemiology

IgG, IgM : Immunoglobulin G, Immunoglobulin M

HR : Hazard Ratio

ITP : Immune Thrombocytopenic Purpura

LA : Lupus Anticoagulant

MRI : Magnetic Resonance Imaging

NSAIDs : Nonsteroidal Anti-Inflammatory Drugs

SBP : Systolic Blood Pressure

SLE : Systemic Lupus Erythematosus

TE : Thromboembolic Events

TPO-RA : Thrombopoietin Receptor Agonists

VKA : Vitamin K Antagonist

VTE : Venous Thromboembolic Event

1. Introduction

Immune Thrombocytopenic Purpura (ITP) or Immune Thrombocytopenia is an acquired autoimmune condition, defined by thrombocytopenia < 100 G/L, and caused by autoantibodies directed against platelet antigens, as well as impaired platelet production in the bone marrow (dysmegakaryopoiesis) (1).

The main complication associated with ITP is bleeding, but an increased thrombotic risk is also well established in the literature (2-6).

Antiphospholipid antibodies (APL), e.g anticardiolipin (aCL IgG and IgM), antiβ2gp1 (IgG and IgM), and lupus anticoagulant (LA), are clearly associated with an increased prevalence of thromboembolic events (TE), especially LA positivity (7-10).

Prevalence of antiphospholipid antibodies in patients with ITP varies between 20 and 40% in several cohorts (11, 12) but their implication in this thrombotic risk is unclear (13-17).

One of the main characteristics of these studies is the exclusion from the study population of the ITP associated with a connective tissue disease (13, 14, 16), even though hematologic systemic lupus erythematosus (SLE) is frequently associated with a positive antiphospholipid status (18).

Finally, most of these studies were conducted before the extended use of TPO-receptor agonists (eltrombopag and romiplostim), of which the association with an increased risk of thrombosis is yet to be determined (19-26).

An increased risk of thrombosis with TPO-RA might exist in patients with antiphospholipid syndrome (APS), or even with antiphospholipid antibodies without any former thrombotic event (18, 20).

With this new monocentric cohort, we aim to specify which role can be attributed to the positivity of antiphospholipid antibodies during ITP, in terms of both thrombotic and bleeding risks (13, 27).

2. Material and methods

2.1. Study design and participants

In this retrospective, monocentric study, we enrolled all ITP out and in-patients seen at least once in a single regional "French competence center" for auto-immune cytopenias between January 1st, 2014 and December 31st, 2019. In this center, APL serology (anticardiolipin IgG and IgM, antiβ2gp1 IgG and IgM, lupus anticoagulant) was systematically performed in all patients with ITP.

Patients were included if they had a diagnosis of ITP according to the 2011 ASH criteria (1). Patients with an associated connective tissue disorder were not excluded.

Patients under 16 years of age or with a diagnosis of ITP secondary to malignant hemopathy or neoplasm, myelodysplastic syndrome, chronic viral infection, and acute ITP were excluded from the analysis.

2.2. Data collection and definitions

Demographic data recorded included gender and age at diagnosis, last known BMI, cardiovascular risk factors (e.g diabetes, hypertension, active smoking), the presence of a connective tissue disorder. We also recorded the platelet count at diagnosis and platelet count nadir during follow-up, median duration of follow-up, antiphospholipid status, and maximal bleeding score during follow-up (28).

Response to corticotherapy (complete response, partial response, and no response, according to the ASH 2011 criteria), and use of TPO-RA were also collected.

For patients with at least one episode of arterial or venous thromboembolic event (VTE), delay between ITP diagnosis and thrombosis was recorded, as well as platelet count at the time of the event (when available), and thrombotic risk factors (e.g for arterial thromboses: age, active smoking, dyslipidemia, diabetes, hypertension; for venous thromboses: active cancer, central venous catheter, recent surgery (<3 months), immobilization (bed rest) > 3 days, sepsis, splenectomy, estroprogestative contraception, pregnancy or post-partum, BMI>30, known thrombophilia (apart from APS), and a previous venous event) (29, 30).

Thromboembolic events had to be objectively confirmed (e.g ultrasonography, computed tomography, or MRI).

For patients with at least one bleeding episode with a Khellaf score greater than or equal to 8, classic bleeding risk factors were recorded (e.g medication such as NSAIDs, platelet aggregation inhibitors, VKA, direct anticoagulants, heparin) ; cranial trauma or previous ischemic stroke for cranial hemorrhage ; hepatic failure defined by a factor V <60% ; chronic kidney disease defined by a CKD-EPI < 30 mL/minute ; uncontrolled hypertension defined by ~~a~~ SBP > 160 mmHg ; chronic alcoholic intoxication defined by more than 30g of pure alcohol per day for a man, 20g/day for a woman ; recent surgery at the bleeding site) (31).

2.3. Laboratory techniques for APL detection

APL positivity (LA, and/or anticardiolipin IgG and/or IgM, and/or antiβ2gp1 IgG and/or IgM) was confirmed at 12 weeks in most of our cases, according to “Sydney” guidelines (32).

Lupus anticoagulant positivity was defined by the International Society on Thrombosis and Haemostasis (33).

Detection of anticardiolipin and antiβ2gp1 antibodies was performed using a chemiluminescent technique (HemosIL AcuStar (WERFEN)).

Cut-off values were determined according to a Fontana study (34). We considered positivity for anticardiolipin and antiβ2gp1 when values were equal to or greater than twice the upper limit.

2.4. Statistical analysis

Continuous data were expressed as mean and standard deviation or median and extreme values. The assumption of normality was assessed with the Shapiro-Wilk test. Comparisons between groups (i.e., APL-negative vs. APL-positive) were carried out, for quantitative data, using Student t-test or non-parametric Mann-Whitney test, when the assumptions of t-test were not met. The homoscedasticity was studied using Fisher-Snedecor test. For categorical data, chi-squared or Fisher's exact test were applied. Thrombosis free survival was treated as censored data and estimates were constructed using the Kaplan-Meier method. The log-rank test was used for univariate analysis to test the prognostic value of patient characteristics for the occurrence of event (i.e., thrombosis). Cox proportional hazards regression was used to investigate associated prognostic factors in multivariable analyses. Hence, no specific statistical strategy approach, such as stepwise, was conducted. The covariates were chosen with caution due to sample size according to the univariate results and to clinical relevance (35). Particular attention was paid to multicollinearity. The proportional-hazard hypothesis was verified using Schoenfeld's test and plotting residuals. Results were expressed as hazard-ratio (HR) with a confidence interval of 95%. Statistical analysis was performed using Stata

software version 15 (StataCorp, College Station, US). Statistical tests were two-sided with a type-I error set at 5%.

3. Results

3.1. Patients characteristics

We included 152 patients, of whom 91 (59.8%) were female, with a mean age at ITP diagnosis of 50,5 years. They were followed for a mean period of 105 months, representing 1331 patient-years. Patients characteristics according to the APL status are detailed in table I: 25/152 (16,4%) patients were positive for at least 1 APL. There was no significant difference between the two groups, except for the association with a connective tissue disease which was significantly higher in the APL+ group (44% vs 17,4%), and the percentage of patients treated with corticosteroids which was higher in the APL-negative group (81% vs 60%).

Thirty-one patients had an associated connective tissue disease: SLE (7 in the APL+ group, 2 in the APL- group), Gougerot-Sjögren syndrome (4 in the APL- group), Evans syndrome (2 in the APL+ group, 9 in the APL- group), dermatomyositis (1 in the APL- group), systemic sclerosis (1 in the APL+ group), rheumatoid arthritis (3 in the APL- group), primary biliary cirrhosis (2 in the APL- group).

Only a few patients underwent splenectomy, without any significant difference between APL-positive and APL-negative patients.

3.2. Description of thromboembolic events

Among our population, 18 patients developed 20 thromboembolic events (12 arterial events and 8 venous events). One patient developed a catastrophic antiphospholipid syndrome 108 months after the diagnosis of ITP. One patient developed obstetrical APS, which we

considered to be an arterial event. For every patient, clinical and biological characteristics at baseline and at the time of the thrombotic event are shown in table II.

The incidence rate of TE events in the whole ITP population was 1.5/100 patient-years, and for the APL-positive group 3.2/100 patient-years, versus 0.92/100 patient-years for the APL-negative group.

TE events were observed in 8/25 (32%) APL-positive patients, and in 10/127 (8%) APL-negative patients (HR 5.94; CI95% 2.22-15.9); this difference was statistically significant (table III). We compared the thrombosis-free survival of APL-positive patients with APL-negative patients by using a Kaplan-Meier test (fig.1): after 10 years of follow-up, survival rate was 68% in the APL-positive group versus 94% in the APL-negative group, a difference that was statistically significant.

When comparing the different APL, LA positivity and aCL positivity were both associated with thrombotic events in univariate analysis, but antiβ2gp1 positivity was not. However, in a multivariate model, only aCL positivity seemed independently associated with thrombosis. This result is to be considered with caution, because of the high degree of multicollinearity between aCL and LA positivity.

We also separated the thromboembolic events between arterial (12 patients) and venous events (7 patients); the difference between the two groups remained significant on both arterial and venous events in univariate analysis (table III).

A multivariate analysis adjusted on confounding factors (connective tissue disease, smoking status, diabetes, and high blood pressure for arterial events; connective tissue disease,

splenectomy, and smoking status for venous events) showed that the difference between the two groups was still significant for arterial events, but not for venous events (table IV).

When we compared the 18 patients with thrombosis according to their APL status, there was no significant difference between the two groups, regarding mean age, mean platelet count at the time of thrombosis, or response to corticosteroids (data not shown, cf table II).

4. Discussion

We found higher incidence of thrombosis in patients with APL, especially arterial events. The global incidence of thrombosis in our cohort was 11.8%, which is slightly higher than what is reported in the literature (2, 36).

LA and aCL positivity were both associated with thrombotic events, confirming what was already shown in previous studies (13, 15, 17), but we failed to demonstrate that each APL was independent from the other.

In our study, the prevalence of APL was 16.4%, which was slightly less than usually described in the literature (11, 13, 14).

One of the innovative points of this study is the inclusion of patients treated with TPO-RA (35% of our patients), who were absent from previous studies because their widespread use in ITP is quite recent, and most of these studies date back to the early 2010s. We showed that the prescription of TPO-RA was not associated with an increased risk of thrombosis in our cohort, but they tended to be less prescribed in APL-positive patients, which is the population that might have an increased risk of thrombosis when receiving such treatment (18).

Our study has several limitations, the first one being its retrospective nature which predisposes to selection and misclassification biases. However, we tried to avoid these biases

by systematically excluding every patient with incomplete and/or uncertain data and including only those who had a regular follow-up. The second major limitation is due to the small number of thrombotic events, which did not allow statistical significance on several analyses.

We must also consider the higher prevalence of connective tissue disease among APL-positive patients, which can be considered as a bias since SLE and rheumatoid arthritis are independently associated with a higher risk of venous thrombosis (37-38). However, in our multivariate analysis, the thrombotic risk associated with APL was independent from the SLE status (cf table IV).

There were also more smokers in the APL-positive group (28% vs 12.5%), an association already suggested in some studies (39-40) and that could have artificially increased the thrombotic risk in APL-positive patients; but this association was not found in the multivariate analysis.

5. Conclusion

Our results showed that APL positivity during ITP was associated with a higher risk of thrombosis, irrespective of other traditional risk factors. On the other hand, the frequency and severity of bleeding events was not influenced by APL status. Therefore, our suggestion would be to perform APL serology in every ITP patient, to determine a category of patients with a higher risk of thrombotic event. In this population, thromboprophylaxis with aspirin could be discussed, provided the platelet count is greater than 50 G/L. Further large-scale prospective studies are required to address these questions and provide guidelines on how to manage these high-risk patients.

Le Doyen de l'UFR de Médecine, **Le Président du Jury,**



A Clermont-Ferrand, le 29 Juillet 21



Table I. Baseline characteristics of the population according to APL status

	APL-positive (n=25)	**APL-negative (n=127)**	**p-value**
Demographic and clinical characteristics			
Mean age at diagnosis (years) (+/- SD, years)	46.9 (+/-19.8)	51.2 (+/- 20.4)	0.34
Female sex, *n* (%)	15 (60)	76 (59.8)	0.99
BMI (kg/m²), median (extreme)	24.5 (18-35)	25 (17-42)	0.38
Follow-up (months), median (extreme)	90 (23-558)	69 (13-378)	0.38
Bleeding event, *n* (%)	13 (52)	80 (63)	0.31
Khellaf score > 8 °, *n* (%)	5 (38.5)	31 (38.7)	0.98
Associated connective tissue disease	10 (40)	21 (16.5)	**0.008**
Cardiovascular risk factors, *n* (%)			
Active smoking at last follow-up	7 (28)	16 (12.5)	0.07
Diabetes	3 (12)	19 (15)	0.70
High blood pressure	8 (32)	44 (34.6)	0.80
Biological features			
Platelet count at diagnosis (G/L), mean (+/- SD)	44.4 (+/-29.4)	41 (+/-31.7)	0.65
Platelet nadir (G/L), mean (+/- SD)	26.2 (+/-23.4)	21.3 (+/-23)	0.19
Lupus anticoagulant, *n* (%)	14 (56)	--	
Anticardiolipin (IgG and/or IgM), *n* (%)	16 (64)	--	
Antiβ2gp1 (IgG and/or IgM), *n* (%)	17 (68)	--	
Triple positivity, *n* (%)	7 (28)	--	
Treatment characteristics			
Any treatment, *n* (%)	18 (72)	104 (81.8)	0.26
Corticosteroids, *n* (%)	15 (60)	103 (81.1)	**0.02**
TPO-R agonists, *n* (%)	5 (20)	49 (38.6)	0.08
Corticosteroid efficacy*, *n* (%)	13 (86.7)	76 (73.8)	0.35
Splenectomy, *n* (%)	2 (8)	9 (7.1)	1.00

° among the 93 bleeding events

* including partial response (platelet count ≥ 30G/L and at least 2-fold increase the baseline count and absence of bleeding) and complete response (platelet count ≥ 100 G/L and absence of bleeding)

Table II. Description of 18 patients with thromboembolic events

Pt	Age at TE (years)	Sex	Plt at diagnosis	LA	aCL	aβ2gp1	Treatment	Response to CS	Thrombotic risk factors	Type of TE	Months after ITP diagnosis	Plt
1	68	M	2	-	-	-	CS + IVIg + ELT	CR	Age	NSTEMI	83	259
2	74	M	80	-	-	-	CS + D + RTX	CR	HL, past smoking, age	Stroke	31	45
3	24	F	68	-	-	-	CS + RTX	CR	COCP	DVT (iliac)	65	140
4	81	F	35	-	+	-	0	-	Obesity	PE	0	35
5	53	M	17	-	-	-	CS + IVIg + D + ELT + RTX	CR	HL, age, past smoking, TPO-RA	TIA	5	43
6	87	M	4	+	-	-	CT + D + ELT	CR	Age, TPO-RA	STEMI	8	135
7	30	F	70	+	+	+	CS	CR	0	Obstetrical APS (fetal death)	1	69
8	54	M	17	-	-	-	CS + D +RTX + splenectomy + ELT + IVIg	CR	5 days after splenectomy	DVT (splenic vein)	226	ND
9	26	F	81	+	+	+	0	-	0	Stroke	13	56
10	74	M	41	-	+	-	CT + D + ELT + RPM	CR	Age	Stroke	56	46
11	67	M	60	-	-	-	CS	CR	Age, HL	TIA	232	88
12	28	F	16	+	+	+	0	-	Post-partum (<1 month), obesity (IMC 31)	CAPS (STEMI, spleen and kidney infarction, cerebral venous thrombosis)	105	278
13	66	M	70	-	-	-	CS	NR	Age, HL	STEMI	106	ND
14	47	M	48	+	-	-	CS + IVIg + RTX	PR	0	PE	101	35
15	55	M	45	+	+	-	RTX	-	Age, past smoking	Stroke	26	ND
16	86	M	92	-	-	-	CS + IVIg + ELT	NR	0	PE	0	37

17	67	M	50	-	-	-	CS + IVIg + RPM + RTX + D + ELT + MMF	NR	Age, past smoking, TPO-RA	TIA	80	355
18	66	F	3	-	-	-	CT + IVIg + D + RTX + Vincristine + splenectomy + ELT + RPM	NR	Obesity (IMC 37), splenectomy	DVT PE	15 26	166 1

aβ2gp1 : anti-bêta2-gp1 IgG and/or IgM; aCL : anticardiolipin IgG and/or IgM; COCP : combined oral contraceptive pill; CR : complete response; CS : corticosteroids; D : dapsone; ELT : eltrombopag; HL : hyperlipidemia; IVIg : intravenous immunoglobulins; LA : lupus anticoagulant; MMF : mycophenolate mofetil; NR : no response; Plt : platelet count; PR : partial response; Pt : patient; RPM : romiplostim; RTX : rituximab; TE : thromboembolic event; TIA : transient ischemic attack

Table III. Association between thromboembolic events and APL status

	APL-positive (n=25)	APL-negative (n=127)	HR (CI 95%)	p-value
Any thromboembolic event (n=18 patients), *n* (%)	8 (32)	10 (7.9)	5.94 (2.22-15.9)	**<0.001**
Venous thromboembolic event (n=7 patients), *n* (%)	3 (12)	4 (3.1)	5.89 (1.19-29.3)	**0.03**
Arterial thromboembolic event* (n=12 patients), *n* (%)	6 (24)	6 (4.7)	7.24 (2.21-23.8)	**0.001**

* total of VTE + ATE = 19 because one patient presented with CAPS and both arterial and venous thrombosis (myocardial, splenic, kidney infarction, and cerebral venous sinus thrombosis); we also included obstetrical APS (n=1) in arterial events

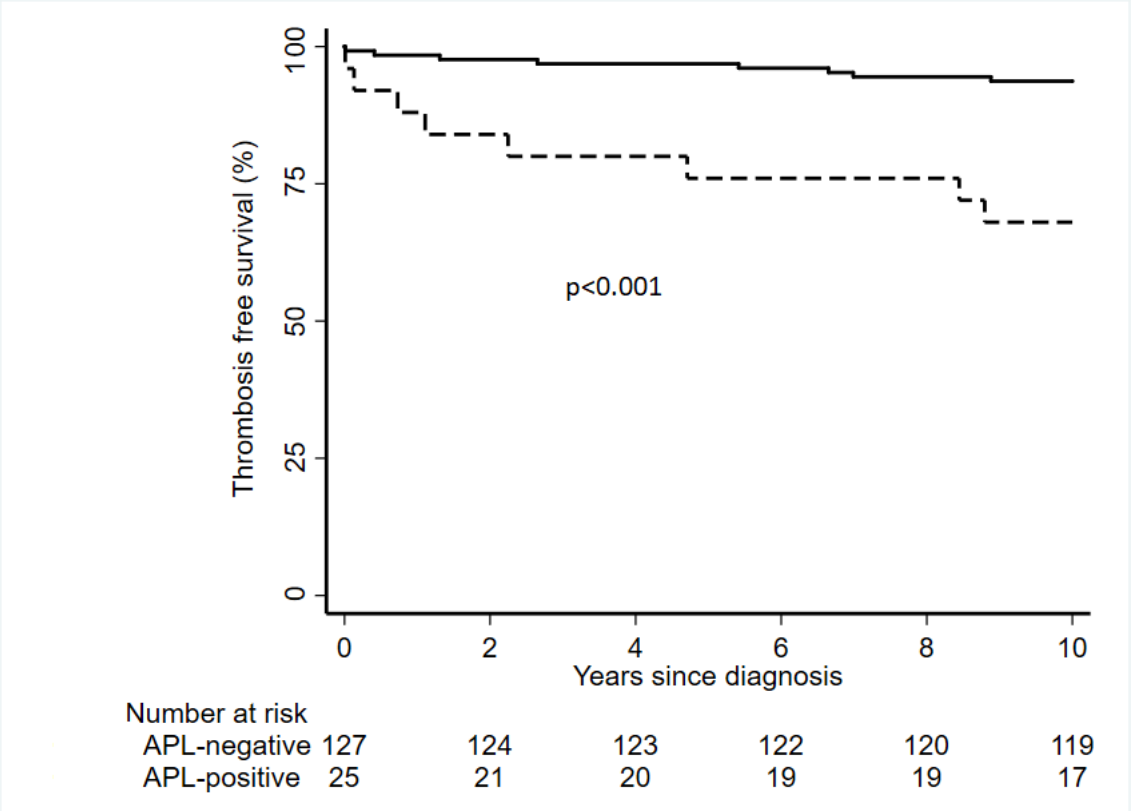


Figure 1. Thrombosis-free survival according to APL status in our ITP cohort

Table IV. Multivariate analysis for independent factors associated with thrombosis

A. All thrombotic events

Variables	HR (95% CI)	Beta coefficient	P-value
APL positivity	7.15 (2.52-20.24)	3.71	**<0.0001**
Connective tissue disease	0.82 (0.23-2.84)	-0.31	0.75
Active smoking	1.08 (0.28-4.21)	0.12	0.91
Diabetes	1.12 (0.27-4.71)	0.16	0.87
High blood pressure	1.12 (0.35-3.56)	0.19	0.85
TPO-RA	1.97 (0.66-5.84)	1.22	0.223

B. Arterial events

Variables	HR (95% CI)	Beta coefficient	P-value
APL positivity	7.86 (2.25-27.50)	3.23	**0.001**
Connective tissue disease	0.85 (0.19-3.73)	-0.21	0.83
Active smoking	0.84 (0.16-4.27)	-0.21	0.83
Diabetes	1.42 (0.26-7.68)	0.41	0.68
High blood pressure	1.05 (0.25-4.34)	0.07	0.95

C. Venous events

Variables	HR (95% CI)	Beta coefficient	P-value
APL positivity	4.90 (0.86-27.8)	1.79	0.07
Connective tissue disease	1.00 (0.15-6.48)	0.00	1.00
Splenectomy	2.81 (0.30-26.25)	0.91	0.36
Active smoking	2.24 (0.35-14.28)	0.86	0.39

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(Conseil national de l'ordre des médecins)

SERMENT D'HIPPOCRATE

Au moment d'être admis(e) à exercer la médecine, je promets et je jure d'être fidèle aux lois de l'honneur et de la probité.

Mon premier souci sera de rétablir, de préserver ou de promouvoir la santé dans tous ses éléments, physiques et mentaux, individuels et sociaux.

Je respecterai toutes les personnes, leur autonomie et leur volonté, sans aucune discrimination selon leur état ou leurs convictions. J'interviendrai pour les protéger si elles sont affaiblies, vulnérables ou menacées dans leur intégrité ou leur dignité. Même sous la contrainte, je ne ferai pas usage de mes connaissances contre les lois de l'humanité.

J'informerai les patients des décisions envisagées, de leurs raisons et de leurs conséquences.
Je ne tromperai jamais leur confiance et n'exploiterai pas le pouvoir hérité des circonstances pour forcer les consciences.

Je donnerai mes soins à l'indigent et à quiconque me les demandera. Je ne me laisserai pas influencer par la soif du gain ou la recherche de la gloire.

Admis(e) dans l'intimité des personnes, je tairai les secrets qui me seront confiés. Reçu(e) à l'intérieur des maisons, je respecterai les secrets des foyers et ma conduite ne servira pas à corrompre les mœurs.
Je ferai tout pour soulager les souffrances. Je ne prolongerai pas abusivement les agonies. Je ne provoquerai jamais la mort délibérément.

Je préserverai l'indépendance nécessaire à l'accomplissement de ma mission. Je n'entreprendrai rien qui dépasse mes compétences. Je les entretiendrai et les perfectionnerai pour assurer au mieux les services qui me seront demandés.

J'apporterai mon aide à mes confrères ainsi qu'à leurs familles dans l'adversité.

Que les hommes et mes confrères m'accordent leur estime si je suis fidèle à mes promesses ; que je sois déshonoré(e) et méprisé(e) si j'y manque.

Nom, Prénom Signature

SERMENT D'HIPPOCRATE

En présence des Maîtres de cette FACULTE et de mes chers CONDISCIPLES, je promets et je jure d'être fidèle aux lois de l'Honneur et de la Probité dans l'exercice de la Médecine.

Je donnerai mes soins gratuits à l'indigent et je n'exigerai jamais un salaire au-dessus de mon travail. Admis dans l'intérieur des maisons, mes yeux ne verront pas ce qui s'y passe, ma langue taira les secrets qui me seront confiés et mon état ne servira pas à corrompre les mœurs ni à favoriser le crime.

Respectueux et reconnaissant envers mes MAÎTRES, je rendrai à leurs enfants l'instruction que j'ai reçue de leurs pères.

Que les HOMMES m'accordent leur estime si je suis fidèle à mes promesses. Que je sois couvert d'OPPROBRE et méprisé de mes confrères si j'y manque.

Nom, Prénom Signature

Risk of thrombosis associated with antiphospholipid antibodies in immune thrombocytopenia: a retrospective study of 152 patients.

Abstract:

CONTEXT Immune thrombocytopenia (ITP) is associated with both bleeding and thrombotic events. Antiphospholipid antibodies (APL) are frequently found during ITP, but their involvement in this increased thrombotic risk is still debated.

OBJECTIVES We conducted an observational retrospective monocentric study to evaluate the bleeding and thrombotic risks associated with APL positivity in ITP.

METHODS One hundred and fifty-two patients diagnosed with ITP were retrospectively included in our study, with a mean follow-up of 105 months. ITP associated with connective tissue diseases such as systemic lupus were not excluded. ITP related to neoplasia, myelodysplastic syndrome of chronic viral infection were excluded. Conventional risk factors for venous and arterial events were collected.

RESULTS Twenty-five patients (16.4%) were positive for at least 1 APL. The frequency and severity of bleeding events were not influenced by APL status. Eighteen patients (11.8%) developed 20 thromboembolic events, with a Hazard ratio of APL-positive to APL-negative patients for thrombosis was 7.15 (95% confidence interval 2.52-20.24), after adjusting for confounding factors. The arterial risk was superior to the venous risk.

CONCLUSION APL positivity in ITP is frequent and associated with a higher risk of venous and arterial thrombotic events. Systematic screening of APL status in ITP seems useful to identify patients at high-risk to experience thrombosis.

Keywords :

- Immune thrombocytopenia
- Thrombosis
- Antiphospholipid antibodies
- Venous thrombosis
- Arterial thrombosis
- Thrombopoietin receptor agonist