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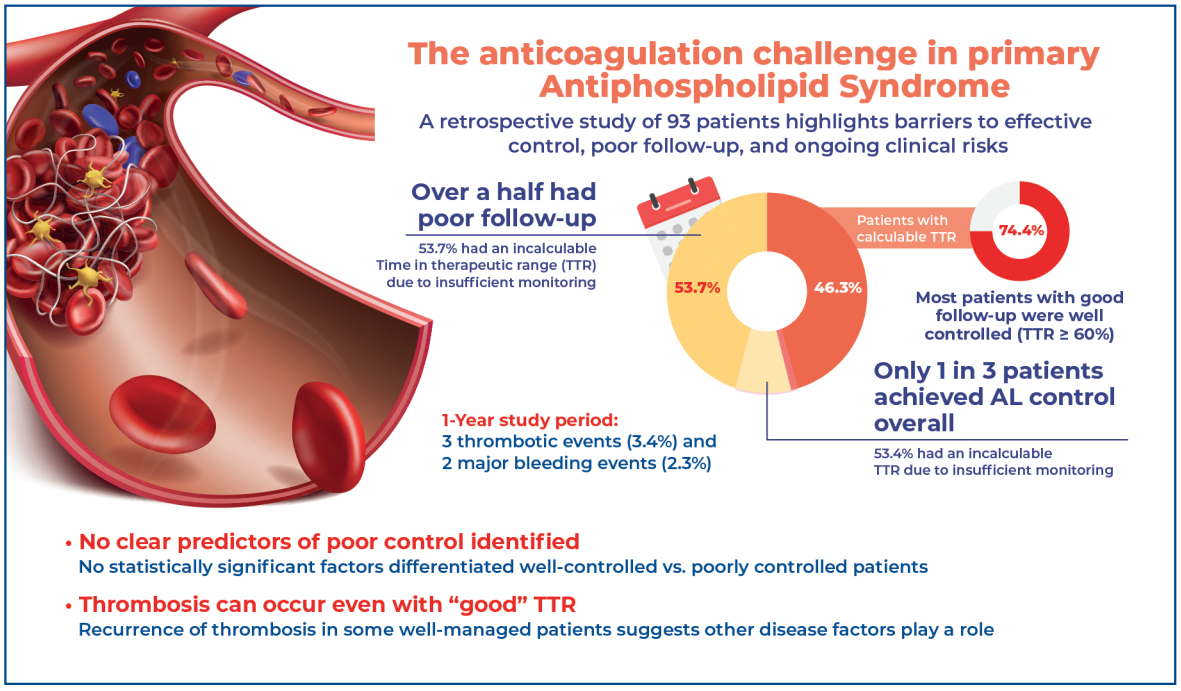
Evaluation of anticoagulation quality in patients with primary antiphospholipid syndrome at a tertiary hospital



Authors

Renata Lys Pinheiro de Mello, Maria Eugênia Teixeira Bicalho, Gustavo Guimarães Moreira Balbi, Flavio Signorelli, Danieli Castro Oliveira de Andrade

Correspondence

E-mail:

DOI

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In Brief

Among 93 patients with primary Antiphospholipid Syndrome receiving warfarin, only 34.4% achieved adequate anticoagulation (time in therapeutic range ≥60%). More than half had insufficient INR monitoring, precluding time in therapeutic range calculation. No clinical variables were associated with poor control, highlighting gaps in follow-up as a key barrier to optimal anticoagulation.

Highlights

- Only 34.4% of patients with primary Antiphospholipid Syndrome achieved adequate anticoagulation (time in therapeutic range ≥60%).
- More than half had insufficient INR monitoring, precluding time in therapeutic range calculation.
- No clinical or demographic factors were associated with poor anticoagulation control.
- Gaps in follow-up and adherence issues appear to be key contributors to suboptimal anticoagulation.

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ORIGINAL ARTICLE

Evaluation of anticoagulation quality in patients with primary antiphospholipid syndrome at a tertiary hospital

Renata Lys Pinheiro de Mello[1], Maria Eugênia Teixeira Bicalho[1], Gustavo Guimarães Moreira Balbi[2], Flavio Signorelli[3], Danieli Castro Oliveira de Andrade[1]

[1] Faculdade de Medicina, Universidade de São Paulo, São Paulo, SP, Brazil.
[2] Universidade Federal de Juiz de Fora, Juiz de Fora, MG, Brazil.
[3] Universidade do Estado do Rio de Janeiro, Rio de Janeiro, RJ, Brazil.

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ABSTRACT

Objective: This study aimed to evaluate the quality of anticoagulation control in patients with primary antiphospholipid syndrome, using time in therapeutic range. Secondary objectives included identifying factors associated with poor anticoagulation control. **Methods:** Anticoagulation quality was assessed in a retrospective study including patients with primary Antiphospholipid Syndrome. Time in therapeutic range was calculated using the Rosendaal method for patients with at least four international normalized ratio measurements in 2019. Statistical comparisons were performed between patients with time in therapeutic range ≥60% and those with lower or incalculable time in therapeutic range. **Results**: A total of 93 patients were included, of whom 43 (46.2%) had a calculable time in therapeutic range. Among these, 32 patients (74.4 achieved time in therapeutic range ≥60%, with a median time in therapeutic range of 89.3%. However, 61 patients (65.6%) had insufficient follow-up, resulting in an incalculable time in therapeutic range. No significant differences were observed between patients with good and poor anticoagulation control regarding demographic or clinical variables. During the follow-up period, three thrombotic events (3.4%) and two major bleeding events (2.3%) were recorded. **Conclusion:** Our findings indicates that only 34.4% of patients with primary antiphospholipid syndrome achieved adequate anticoagulation control and inadequate follow-up remains a major barrier. Further studies are needed to identify factors contributing to suboptimal time in therapeutic range and to improve anticoagulation management in this high-risk population.

Keywords: Antiphospholipid syndrome; Acarboxiprotrombin; Warfarin

INTRODUCTION

Antiphospholipid Syndrome (APS) is a multisystem autoimmune disorder characterized by recurrent venous and arterial thrombotic events, as well as microthrombotic and non-thrombotic manifestations and/or pregnancy morbidity, associated with the persistent presence of antiphospholipid antibodies (aPL).[1] Antiphospholipid Syndrome is classified as primary when it occurs in the absence of other autoimmune disorders, and secondary when it is associated with other autoimmune diseases, particularly systemic lupus erythematosus (SLE).[2] The management of thrombotic APS primarily focuses on thrombosis prevention, mainly achieved through anticoagulation therapy, either alone or in combination with antiplatelet agents.[3] For patients with persistent aPL positivity and unprovoked thrombotic events, long-term anticoagulation with vitamin K antagonists (VKAs), such as warfarin, is the

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Associate Editor:
Kenneth Gollob
Hospital Israelita Albert Einstein, São Paulo, SP, Brazil
https://orcid.org/0000-0003-4184-3867

Corresponding Author:
Maria Eugênia Teixeira Bicalho
Rua Francisco Cruz, 100
Zip code: 04117-090 - São Paulo, SP, Brazil
Phone: (55 31) 99701-7069
E-mail: metb1993@icloud.com

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standard recommendation.[4] This approach requires regular monitoring of the international normalized ratio (INR), target range of 2-3 or 2.5-3.5, to ensure both efficacy and safety.[5,6] However, maintaining effective anticoagulation with VKA is challenging in clinical practice.[7] Achieving a stable INR over time can be difficult due to several factors, including dietary influences, drug interactions, changes in gut microbiota, and individual variability in warfarin metabolism through the CYP2C9 and VKORC1 enzyme pathways.[8-11]

The time in therapeutic range (TTR) is widely used in clinical trials to assess the quality of warfarin anticoagulation, particularly in patients with atrial fibrillation (AF).[12-14] The Rosendaal method[15] is a commonly used approach for calculating TTR, estimating the percentage of time patient's INR remains within the target range. The time in therapeutic range values range from 0% to 100%, with TTR <60% being associated with higher rates of mortality, major bleeding, myocardial infarction, and stroke.[16,17] Two large cohorts studies highlight the importance of achieving a high TTR in patients with AF and other conditions. Liu et al. in the U.S. found that only 35% of 127,385 AF patients with AF achieved a TTR> 65%, with lower TTR being associated with increased risks of stroke, bleeding, and mortality.[18] McAlister et al. in Canada reported similar findings, with 41% of 57,669 patients with AF achieving a TTR >65%, and lower TTR being associated with comorbidities such as heart failure, cirrhosis, and dementia.[19] In Brazil, Silva et al. conducted a retrospective, single-center cohort study (2014 - 2016), involving 1,220 patients with non-valvular AF. Only 31% of patients achieved a TTR >65%. The study found that suboptimal TTR (<65%) was associated with an higher incidence of major bleeding events (5.3% *versus* 1.6%; p<0.01) and 40% higher healthcare costs in the public system (R$35,384 *versus* R$25,352; p<0.01) compared with patients who achieved better anticoagulation control.[20] Although numerous studies have assessed anticoagulation control in patients with AF, data on TTR in the patients with primary APS are limited, and the clinical consequences of poor INR control in this population remains unclear. These findings highlight the need for tailored management strategies to improve patient outcomes. This study aims to evaluate the quality of anticoagulation in patients with primary APS, using TTR as a key metric. Additionally, it sought to identify factors associated with poor anticoagulation control, with the goal of informing strategies to optimizing the clinical management of this high-risk population.

OBJECTIVE

To evaluate the quality of anticoagulation in patients with primary Antiphospholipid Syndrome followed at the Rheumatology Department of a tertiary hospital and to assess factors associated with lower anticoagulation quality, including disease-related factors (severity profile, demographic characteristics, and presence of non-criteria manifestations) and patient-related factors (comorbidities and lifestyle habits).

METHODS

Study design

This was a retrospective, single-center study based on a review of medical records of patients with APS followed at the Rheumatology Department of HC-FMUSP. The evaluation period was restricted to 2019, as this was the recent year with complete data available prior to the onset of the COVID-19 pandemic, which affected outpatient care. Clinical and laboratory data were obtained from medical records.

Inclusion criteria

Patients aged ≥18 years who initiated follow-up at the hospital service before 2019, maintained continuous warfarin therapy between January 2019 and January 2020, and met the criteria for thrombotic primary APS according to the 2023 ACR/EULAR classification criteria.[1]

Exclusion criteria

Patients not receiving warfarin therapy, those with secondary APS or obstetric APS without thrombosis, and individuals who died before or during 2019 were excluded.

Baseline data

Demographic characteristics, including age, sex, ethnicity, and age at disease onset, were recorded. Patient residence was categorized as within Sao Paulo city or outside São Paulo city and educational level was classified as illiterate or as having some level of formal education. The APS profile at baseline was recorded, including thrombotic and obstetric events, as well as non-thrombotic manifestations (valvopathy, nephropathy, digital ulcers, thrombocytopenia, livedo *reticularis*, Raynaud's phenomenon, and migraine). Antiphospholipid antibodies were considered positive when at least two tests, performed at least 12 weeks

apart, yielded positive results. The following assays were included: lupus anticoagulant (LA), determined according to the International Society on Thrombosis and Haemostasias (ISTH) guidelines; [21] anticardiolipin antibodies (aCL) and anti-β2 glycoprotein I antibodies (aβ2GPI), both assessed using standardized ELISA tests. IgG and IgM aCL were measured using Phadia EliA® fluorescence enzyme immunoassays (Thermo Fisher) while IgG and IgM aβ2GPI were measured, using QUANTA Lite® aβ2GPI ELISA kits (INOVA Diagnostics).[22,23]

Atherosclerosis risk factors (hypertension, *diabetes mellitus*, dyslipidemia, obesity, and smoking), the Adjusted Global Antiphospholipid Syndrome Score (a GAPSS), which indirectly predicts future thrombotic risk,[24] and the use of hydroxychloroquine were also assessed.

Thrombosis and major bleeding

Thrombotic outcomes were defined as confirmed arterial or venous thrombosis identified through imaging.[25] Major bleeding was defined as symptomatic bleeding meeting at least one of the following criteria: fatal bleeding; bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, pericardial, or intramuscular with compartment syndrome; or a drop in hemoglobin levels of ≥2g/dL or requiring transfusion of two or more units of whole blood or red blood cells.[26]

Time in therapeutic range calculation

The TTR was calculated using the Rosendaal method,[15] which incorporates the frequency of INR measurements and their actual values, assuming that changes between measurements occur linearly over time. As previously described, a higher TTR reflects a greater proportion of time during which the patient's INR remains within the target range over the assessment period (Figure 1).

$$TTR(\%) = \frac{\sum_{i=2}^{n} \left(\frac{TSwR}{TS}\right) \text{ x D}}{\sum_{i=2}^{n} \text{D}} \text{ X } 100 \quad \text{for } i = 2, \ldots n$$

TS: amount of the total shift between INR measurements; TSwR: amount of the total shift between INR measurements that is within the therapeutic range (i.e., 2.0 - 3.0); D: number of days since last visit; i: visit number.

Figure 1. Time therapeutic range by the Roosendaal method

Quality of anticoagulation and follow-up definition

Time in therapeutic range was calculated for patients with adequate follow-up, defined as having anticoagulation, where measurements with TTR with a maximum interval of 3 months between measurements Among these, patients with TTR ≥60% were classified as having adequate anticoagulation, whereas those with TTR <60% were considered to have poor anticoagulation control.

Patients who did not meet the criteria for adequate follow-up did not have TTR calculated and were classified as having incalculable TTR due to insufficient follow-up data.

Statistical analysis

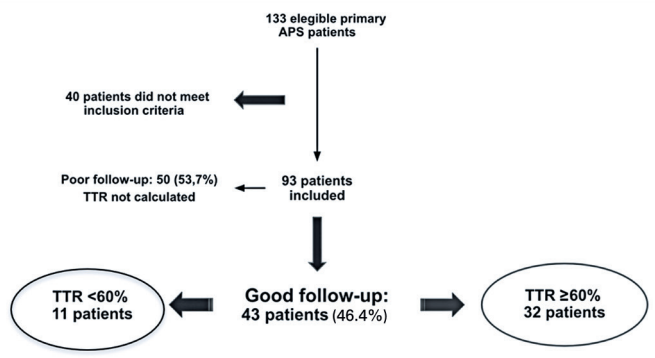
Statistical analyses were performed using SPSS version 23.0 (Chicago, Illinois). Bivariate comparisons between patient subgroups (well-anticoagulated and poorly anticoagulated) were conducted using the chi-square or Fisher's exact test for categorical variables. For continuous variables, the Student's *t*-test or Mann-Whitney test was applied. Normality was assessed using the Kolmogorov-Smirnov test and graphical methods. Continuous variables were expressed as means±standard deviation for normally distributed data and as median (interquartile range) for non-normally distributed data. A $p<0.05$ was considered statistically significant.

RESULTS

A total of 133 patients were screened, and 93 were included. Of these, 50 (53.7%) had an incalculable TTR due to inadequate follow-up, while 43 (46.4%) had adequate follow-up and calculable TTR Among patients with adequate follow-up, 32 (74.4%) had TTR ≥60% and 11 (25.6%) had a TTR <60%. The median TTR among those with a calculable TTR was 93% (87.1%-99.6%). Overall, of the 93 included patients, only 32 (34.4%) achieved adequate anticoagulation (Figure 2).

Demographic and clinical characteristics

The median age at disease onset and median disease duration were 30 (24.0-37.5) and 15 (9.5-22.0) years, respectively. Most patients were female (83.9%), of Caucasian ethnicity (77.4%), had some level of formal education (95.7%), and lived within the city of São Paulo (71%) (Table 1).



APS: antiphospholipid syndrome; TTR: time in therapeutic range.

Figure 2. General flowchart of the study

Table 1. Clinical and demographic characteristics of the patients included in the study

Variable	Categories
Demographic data	
Age, median (IQR)	46 (37-58.5)
Age at onset, median (IQR)	30 (24-37.5)
Disease duration, median (IQR)	15 (9.5-22)
Female sex, n (%)	78 (83.9)
Caucasian, n (%)	72 (77.4)
Education, n (%)	89 (95.7)
Residence in São Paulo, n (%)	66 (71.0)
Non-thrombotic manifestations – n (%)	
Livedo reticularis	41 (44.1)
Raynaud's phenomenon	30 (32.3)
Valvopathy	18 (19.4)
Thrombocytopenia	16 (17.2)
Nephropathy	6 (6.5)
Digital ulcers	4 (4.3)
Cardiovascular risk factors – n (%)	
Dyslipidemia	51 (54.8)
Obesity	43 (46.2)
Systemic arterial hypertension	42 (45.2)
Smoking	34 (36.6)
Diabetes mellitus	8 (8.6)
Disease severity profile – n (%)	
Triple positive	37 (39.8)
Double positive	24 (25.8)
Single positive	32 (34.4)
Venous thrombosis	65 (69.9)
Recurrent venous thrombosis	29 (31.2)
Arterial thrombosis	44 (47.3)
Recurrent arterial thrombosis	19 (20.4)
Hydroxychloroquine (HCQ)	31 (37.8)
aGAPSS, median (IQR)	11 (8-13)

Severity profile and quality of anticoagulation

Regarding the severity profile, 37 patients (39.8%) were triple-positive, 24 (25.8%) were double-positive, and 32 (34.4%) had single positivity, of whom 27 were positive for LA. A history of venous thrombosis at baseline was observed in 65 patients (69.9%), with 29 (31.2%) experiencing recurrent events. Arterial events were observed in 47.3% of patients, with 19 (20.4%) experiencing recurrent events before the study. Additionally, 31 patients (37.8%) were receiving combined therapy with hydroxychloroquine and warfarin, and the median adjusted aGAPSS was 11 (8-13).

When comparing the clinical profiles of patients with TTR ≥60% to those with TTR <60% or incalculable TTR, no variables reached statistical significance (Table 2), however a trend toward significance was observed for dyslipidemia. When TTR was further categorized as ≥70%, 29 patients (31.2%) met this criterion. No significant differences were observed between the two groups (data not shown).

Table 2. Comparison of patients with primary antiphospholipid syndrome according to time in therapeutic range ≥60% *versus* time in therapeutic range <60% or incalculable time in therapeutic range

Categories	TTR ≥60% (n=32)	TTR <60% or incalculable (n=61)*	p value
Age, median (IQR)	48.0 (41.3-56.8)	47.1(35.5-61.0)	0.315
Female, n (%)	26 (81.3)	52 (85.2)	0.619
Caucasian, n (%)	26 (81.3)	46 (75.4)	0.522
Education, n (%)	29 (90.6)	60 (98.4)	0.116
Residence in São Paulo city, n (%)	23 (71.9)	43 (70.5)	0.889
Systemic arterial hypertension, n (%)	12 (37.5)	30 (49.2)	0.282
Diabetes mellitus, n (%)	4 (12.5)	4 (6.6)	0.440
Dyslipidemia, n (%)	22 (68.8)	29 (47.5)	0.051
Obesity, n (%)	14 (43.8)	29 (47.5)	0.728
Smoking, n (%)	14 (43.8)	20 (32.8)	0.297
Triple positive, n (%)	14 (43.8)	23 (37.7)	0.572
Low intensity INR target, n (%)	23 (71.9)	46 (75.4)	0.711
HCQ, n (%)	14 (43.8)	22 (36.1)	0.470
Thrombotic antihemorrhagic events*, n (%)	2 (6.6)	3 (4.76)	0.650
Venous thrombosis, n (%)	24 (75.0)	41 (67.2)	0.437
Recurrent venous thrombosis, n (%)	10 (31.3)	19 (31.1)	0.650
Arterial thrombosis, n (%)	16 (50.0)	28 (45.9)	0.707
Recurrent arterial thrombosis, n (%)	8 (25.0)	11 (18.0)	0.490

* Hemorrhagic events occurred in one patient in each group; whereas, thrombotic events occurred in onepatient in the TTR ≥60% and in two patients in the TTR <60% or incalculable TTR group.
SP: Sao Paulo city; INR: international normalized ratio; HCQ: hydroxychloroquine; TTR: time in therapeutic range.

Thrombotic and hemorrhagic events

In 2019, three thrombotic events (3.4%) were recorded, including two pulmonary embolisms and one stroke. Additionally, two major bleeding events (2.3%) were observed, comprising one inner ear hemorrhage and one retropharyngeal hematoma (Table 3).

Table 3. Description of thrombotic and major hemorrhagic events in patients with primary antiphospholipid syndrome

Patient	Type of event	TTR (%)	INR Target	Using HCQ	Triple positive	aGAPSS
1	Pulmonary embolism	Incalculable	2 - 3	Yes	Yes	14
2	Ischemic event	72.9	2.5 - 3.5	No	Yes	17
3	Pulmonary embolism	Incalculable	2.5 - 3.5	Yes	Yes	13
4	Inner ear bleeding	41.8	2 - 3	Yes	Yes	16
5	Retropharyngeal hematoma	89.3	2.5 - 3.5	No	No	12

TTR: time in therapeutic range; INR: international normalized ratio; HCQ: hydroxychloroquine; aGAPSS: Adjusted Global Antiphospholipid Syndrome Score.

DISCUSSION

Although the quality of anticoagulation has been widely studied in cardiology trials, data in primary APS remain scarce. A prospective study by Pengo et al. comparing anticoagulation control between 30 patients with APS and 30 with AF, showed a significantly lower median TTR in the APS group (53.5% *versus* 68%, p=0.001), APS was identified as an independent predictor of poorer anticoagulation control, requiring higher doses of VKAs than those indicated for patients with AF.[27]

In a tertiary center in Rio de Janeiro (2015-2017), a retrospective study including 68 patients with primary APS reported a mean TTR of 36.7% ±25.0%. Only 31.7%±22.7 of INR values were within the target therapeutic range (2-3). Pastori et al. found an association between TTR <60% and systemic arterial hypertension (p=0.018) and dyslipidemia (p=0.024), while multivariate analysis identified a history of recurrent venous thromboembolism as being associated with poor anticoagulation quality.[28] In our study, a substantial proportion of patients exhibited suboptimal anticoagulation control, and less than half (46.2%) had adequate follow-up. Among those with adequate follow-up, the median TTR was 93.0%, with the majority (74.4%) achieving TTR≥60%, suggesting good anticoagulation control. However, when considering the entire cohort, only 34.4% achieved adequate anticoagulation as measured by TTR. The presence of 50 patients with incalculable TTR highlights that maintaining adequate follow-up and adherence to anticoagulation therapy remains a challenge in this population. More recently, a study by Meir et al. evaluated anticoagulation control in 67 patients with APS receiving VKA therapy between 2012 and 2023. The study found that only 29.9% of patients achieved a TTR ≥70%, with the lowest rate observed in those with three or more comorbidities (9.1%), compared with patients who had fewer comorbidities (40%). Suboptimal TTR was strongly associated with an increased risk of recurrent thrombotic events, particularly arterial thrombosis. However, the sample was not limited to primary APS, as 18% of the patients included had SLE.[29] Our proportion of well anticoagulated patients was similar to that reported in Rio de Janeiro (34.4% *versus* 36.7% with TTR ≥60%, respectively)[28] and in Israel (31.2% *versus* 29.9% with TTR ≥70%, respectively).[29] Furthermore, it is important to understand why some patients had adequate follow-up but still present <60%. Several modifiable barriers to anticoagulation therapy may contribute to this, including dietary and drug interactions. In this context, we analyzed potential demographic, clinical and laboratory factors that could influence anticoagulation quality, however no variables showed statistically significant differences between patients with adequate and poor anticoagulation control. This findings contrasts with previous studies that identified three or more comorbidities[29] and hypertension and dyslipidemia[28] as factors associated with poorer anticoagulation quality. These associations may be explained by pharmacokinetic interaction between warfarin and statins, involvingcytochrome P450 isoenzymes wichcan affect the effectiveness of VKA therapy.[30,31] We observed nearly 40% of triple positivity in our cohort, along with a high frequency of recurrent thromboembolic events and a median aGAPSS of 11 (8-13). These findings indicate a population with a severe disease profile.[24] Notably, despite a substantial proportion of patients with severe disease, no statistically significant differences in clinical or demographic characteristics were observed when comparing patients with TTR ≥60% to those with TTR <60% or incalculable TTR.

Moreover, nearly half of the patients had at least one cardiovascular risk factor. These factors may influence anticoagulation quality, as polypharmacy for the treatment of comorbidities and greater disease severity may contribute to reduce adherence, increased drug interactions, and variability anticoagulant effect of warfarin.

During the one-year follow-up, three thrombotic events (3.4 cases/100 patients-year) and two major bleedings events (2.3 cases/100 patients-year) were recorded. Sevim et al.[32] reported approximately two thrombotic events per 100 patients-year in the most recent analysis of the APS ACTION data. Similarly, Balbi et al. reported a thrombotic recurrence rate of 3.82 cases per 100 patients-year in a Brazilian cohort from Rio de Janeiro (APS-Rio), 5.5 years after its inception. Therefore, we observed a slightly higher rate of thrombotic recurrence than that reported in APS ACTION, but a similar rate to that reported in the APS-Rio cohort. These differences may be influenced by factors such as study population characteristics, follow-up duration, and treatment strategies. It is important to note that the APS ACTION cohort includes a more heterogeneous APS population compared with the Brazilian cohort.

Analyzing these events individually, we found that four patients were triple-positive, and two had TTR≥60%. This finding highlights the role of additional disease-related factors in thrombotic recurrence, which may occur even in patients with adequate anticoagulation control.

One noteworthy finding is that 53.7% of patients had an incalculable TTR, likely due to inadequate follow-up. This group may include patients with poor adherence, as well as those facing barriers in accessing healthcare services and difficulties in maintaining regular INR monitoring.

Our patient population has low socioeconomic status and education level, which makes the anticoagulation follow-up even worse. These factors are already known to be associated with worse outcomes. Therefore, anticoagulation control in our setting may be less favorable than previously reported, limiting the generalizability of our findings to other populations. Identifying the causes of inadequate follow-up is essential, extending the analysis beyond anticoagulation management to include aspects related to healthcare system organization, socioeconomic disparities, and patient education. Overall anticoagulation control with vitamin K antagonists remains challenging worldwide.

Our study has several limitations. First, its retrospective design relies on medical records and patient-reported information, which may introduce information and recall bias. Additionally, survivorship bias may be present, potentially affecting the generalizability of the results. Furthermore, the study was conducted at a single tertiary center, which may limit the generalizability of the findings to other clinical settings and regions. Additionally, it is a cross-sectional analysis, which limits its ability to establish causality or assess changes over time. Lastly, the follow-up period for assessing outcomes is confined to 2019, which may not capture long-term trends or fluctuations in disease severity and treatment effectiveness. On the other hand, there is limited literature on anticoagulation monitoring in APS, particularly in PAPS patients, who were exclusively evaluated in our study.

CONCLUSION

In conclusion, our study provides valuable insights into anticoagulation control in patients with primary antiphospholipid syndrome. While we did not identify specific factors associated with poor anticoagulation control in our cohort, comorbidities and polypharmacy may contribute to suboptimal management. An intriguing finding was the recurrence of thrombosis in triple-positive patients despite well-maintained time in the therapeutic range. Further research is needed to better understand how physicians can improve anticoagulation adherence and impact clinical outcomes in this population.

The implementation of an active follow-up program, including regular telemedicine consultations, may represent an effective strategy to improve anticoagulation quality in public healthcare settings, particularly considering that 30% of patients in our study reside outside São Paulo city, which may hinder adequate follow-up. Additionally, the development of educational initiatives, such as lectures or informational videos on anticoagulation, could help reinforce the importance of treatment adherence and its impact on patient outcomes. These strategies may enhance patients' understanding of their condition and promote active engagement in treatment, ultimately leading to improved clinical outcomes.

Further studies are needed to evaluate the factors underlying the high proportion of patients with time in therapeutic range. This assessment should include barriers within the healthcare system, patient-reported adherence challenges, and the impact of polypharmacy. Future studies designed to test interventions such as educational programs or digital monitoring tools may help address these issues. Moreover, studies aiming at identifying biomarkers or genetic predictors that influence anticoagulation control would be valuable to improve outcomes in this population.

DATA AVAILABILITY

Data are available to reviewers upon request. After publication, de-identified data will be available from the authors upon reasonable request, as justified in the manuscript. The dataset contains clinical and sensitive patient information; therefore, due to ethical and confidentiality constraints, it cannot be made publicly available. However, de-identified data may be shared with reviewers and, after publication, with qualified researchers upon request to the corresponding author.

AUTHORS' CONTRIBUTION

Renata Lys Pinheiro de Mello and Maria Eugênia Teixeira Bicalho: investigation, data curation, writing - original draft, data analysis and interpretation, critical review. Gustavo Guimarães Moreira Balbi and Flavio Signorelli: methodology, formal analysis, data validation, critical review. Danieli Castro Oliveira de Andrade: conceptualization, project administration, overall supervision, and approval of the submitted version.

AUTHORS' INFORMATION

Mello RL: http://orcid.org/0009-0000-0120-2251
Bicalho ME: http://orcid.org/0009-0001-0713-6790
Balbi GG: http://orcid.org/0000-0003-0235-8834
Signorelli F: http://orcid.org/0000-0002-5565-1017
Andrade DC: http://orcid.org/0000-0002-0381-1808

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