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ORIGINAL RESEARCH

The Incidence and Characteristics of Thrombosis in Patients with Immune thrombocytopenia: A Retrospective Cohort Study

Ping Zhang, Yanan Cai, Fei Ge, Zunmin Zhu, Kai Sun

Department of Hematology, Henan Provincial People's Hospital, People's Hospital of Zhengzhou University, Zhengzhou, People's Republic of China

Correspondence: Kai Sun, Department of Hematology, Henan Provincial People's Hospital, People's Hospital of Zhengzhou University, #7 Weiwu Road, Zhengzhou, People's Republic of China, Email sunkai900@163.com

Introduction: This study aims to investigate the incidence, clinical characteristics, and prognosis of thrombosis in Chinese patients with immune thrombocytopenia (ITP).

Methods: This was a single-center, retrospective study of adult patients with ITP at the Henan Provincial People's Hospital from January 2018 to June 2023.

Results: A total of 3216 adult patients with primary ITP were included in the study period, with 25 (0.93%) having thrombotic events. The average age of 25 patients with thrombosis is 62.76±12.79 years, including 11 males and 14 females. In addition, among the 25 thrombotic events, 19 cases were arterial thrombosis (AT), and 6 cases were venous thrombosis (VT). The incidence of AT is higher than that of VT (P=0.009). There was no obvious difference in clinical characteristics between the two groups. The median platelet count at the time of thrombosis in 25 patients was 35 (23, 52) $\times 10^9$/L. At the onset of thrombosis, 23 patients (92.0%) had a low PLT ($<100\times10^9$/L). One patient with ischemic stroke died in the hospital due to severe infection.

Conclusion: ITP may be considered a bleeding disorder with a high risk of thrombosis, and AT is more common than VT in the Chinese population.

Keywords: immune thrombocytopenia, arterial thrombosis, venous thrombosis, platelet, hemorrhagic disease

Introduction

Immune thrombocytopenia (ITP) is an autoimmune condition marked by autoantibody-induced platelet destruction and attenuated thrombopoiesis, which results in a decreased platelet count. ($<100 \times 10^9$/L).[1,2] ITP may be primary, which means there is no known underlying cause, or secondary to other diseases, such as autoimmune disease, infection, malignancy, or post-vaccine.[3]

ITP is a common hemorrhagic disease in clinical practice. However, in recent years, it has also been noted that ITP patients have an elevated risk of thromboembolic events.[4–9] Using the Danish National Patient Registry, the incidence rate of venous thrombosis (VT) and arterial thrombosis (AT) in the ITP cohort was 0.53 and 1.14 per 100 person-years, respectively, higher than that in the general population.[4,5] According to the meta-analysis of an observational study, patients with ITP had nearly double the rate of VT and a 50% higher rate of AT than people in the general population.[9] In these cases, AT occurs more frequently than VT. ITP complicated with thrombosis has a complex etiology. The occurrence of thrombosis in ITP patients is an unexpected discovery that poses significant challenges for ITP treatment. Balancing the risk of bleeding and thrombosis has become crucial for these patients.

Nowadays, there is limited clinical data on ITP combined with thromboembolism in the Chinese population. The purpose of this study is to investigate the incidence, clinical characteristics, and prognosis of thrombosis in Chinese ITP patients.

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Methods

Study Population

Adult patients (≥18 years old) with ITP were included in this single-center, retrospective study at the Henan Provincial People's Hospital from January 2018 to June 2023. In our hospital's digital medical records, we looked for individuals who had been given an "immune thrombocytopenia" or "idiopathic thrombocytopenic purpura" diagnosis. Patients with secondary ITP were not included in this study. This research was approved by the Ethics Committee of the Henan Provincial People's Hospital. In addition, written informed consent was obtained from each participant at their enrollment. This study was performed in line with the principles of the Declaration of Helsinki.

Data Collection

Clinical information was obtained from the Henan Provincial People's Hospital's Medical Information Recording System. The information gathered included: demographic data (age and gender), medical history (diabetes mellitus, hypertension, coronary artery disease, stroke), laboratory data, ITP treatment strategies (glucocorticoids, recombinant human thrombopoietin (rhTPO), intravenous immunoglobulin (IVIG), and platelet transfusion), and clinical characteristics.

Definitions

Primary ITP was diagnosed according to the universal definition.[1,10] Primary ITP is an autoimmune disorder characterized by isolated thrombocytopenia (peripheral blood platelet count $<100 \times 10^9$/L) in the absence of other causes or disorders that may be associated with thrombocytopenia. Secondary ITP was defined as immune thrombopenia associated with another immune-mediated thrombocytopenia (ie systemic vasculitis, systemic lupus erythematosus, hepatitis C virus, chronic lymphocytic leukemia, autoimmune endocrinopathy, common variable immunodeficiency). Thrombotic events were divided into arterial thrombosis and venous thrombosis. AT included ischemic stroke (IS), acute myocardial infarction (AMI), peripheral artery thrombosis (PAT), etc. VT included deep vein thrombosis (DVT), pulmonary embolism (PE), portal vein thrombosis (PVT), cerebral venous sinus thrombosis (CVST), etc.

Statistical Analysis

Continuous data were reported as the mean ± standard deviations (SD), while categorical variables were displayed as frequencies and percentages. The Chi-square or Fisher's exact test was used to compare categorical variables, while the Mann–Whitney *U*-test was used to compare continuous variables. The statistical analysis was done with SPSS 23.0 software. Statistical significance was defined as a two-sided P-value < 0.05.

Results

During the study period, 3216 adult patients with primary ITP were included, of which 25 (0.78%) experienced thrombotic events (Figure 1).

Tables 1 and 2 show the clinical characteristics of ITP patients complicated with thrombosis. The average age of 25 patients with thrombosis is 62.76±12.79 years, including 11 males and 14 females. 84.0% of patients are over 50 years old. Most patients (80.0%) had one or more conventional thrombosis risk factors, such as coronary artery disease (32.0%), hypertension (52.0%), diabetes mellitus (28.0%), and stroke (20.0%). Glucocorticoids (64.0%) were used to treat the majority of ITP patients. Some received platelet transfusion, rhTPO, or IVIG.

Among the 25 thrombotic events, 19 cases (76.0%) were AT, and 6 cases (24.0%) were VT. The incidence of AT is higher than that of VT (P=0.009). There was no obvious difference in clinical characteristics between the two groups (Table 1).

The number of various thrombotic events is shown in Figure 2. The distribution of subtypes was as follows: 4 cases of AMI, 15 cases of IS, 2 cases of DVT, 2 cases of DVT combined with PE, one case of PVT, and one case of CVST.

The median platelet count at the time of thrombosis in 25 patients was 35 (23, 52) $\times 10^9$/L. At the onset of thrombosis, 23 individuals (92.0%) had a low level of PLT ($<100\times10^9$/L). Among them, five patients had platelet levels below

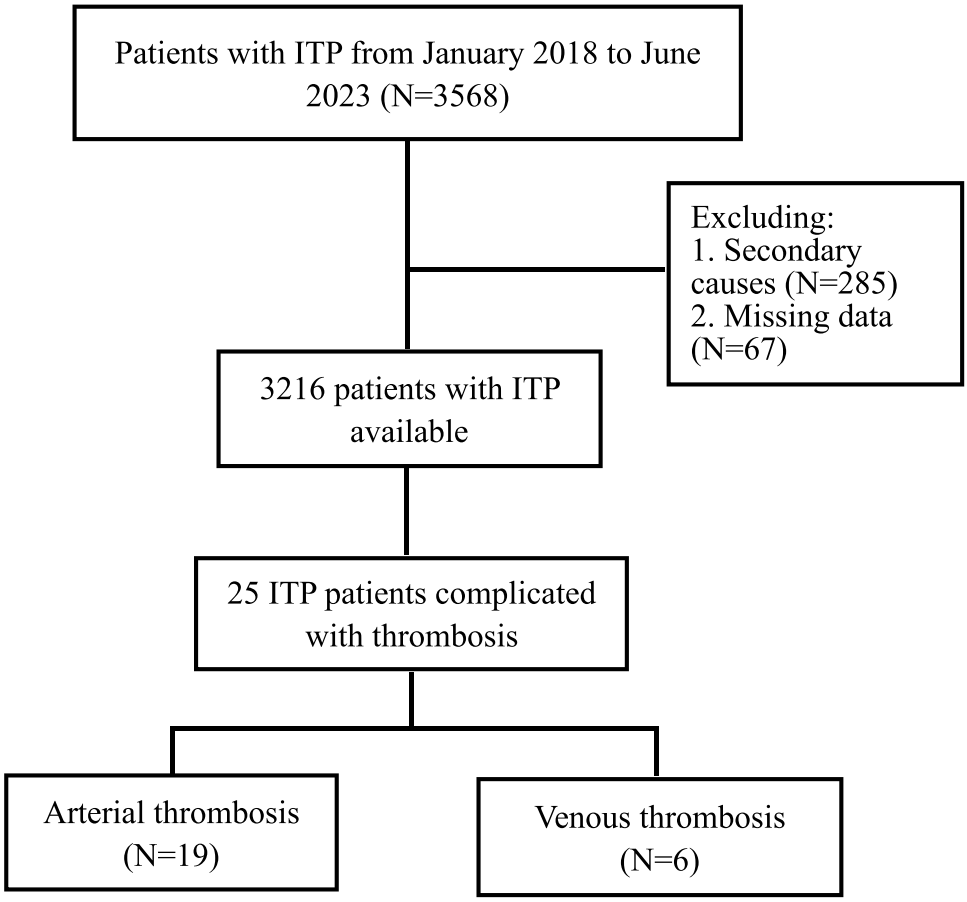

Figure 1 Flow chart for selection of study population.

20×10^9/L, six patients had platelet levels between 21 and 30×10^9/L, eight patients had platelet levels between 31 and 50×10^9/L, and four patients had platelet levels between 51 and 99×10^9/L (Table 3).

Among 25 patients with ITP complicated with thrombosis, one patient with IS died in the hospital due to severe infection. All other patients improved after treatment.

Table 1 Characteristics of ITP Patients with Thrombosis Stratified by Thrombus Type

Demographic Variables	Total N=25	Arterial Thrombosis N=19	Venous Thrombosis N=6	*P-value**
Age, years	62.76±12.79	65.89±9.47	52.83±17.52	0.069
≥50 years, n (%)	21 (84.00)	17 (89.47)	4 (66.67)	0.234
Male, n (%)	11 (44.00)	9 (47.37)	2 (33.33)	0.661
Medical history, n (%)				
Coronary artery disease	8 (32.00)	8 (42.11)	0 (0.00)	0.129
Hypertension	13 (52.00)	10 (52.63)	3 (50.00)	1.000
Diabetes mellitus	7 (28.00)	5 (26.32)	2 (33.33)	1.000
Stroke	5 (20.00)	3 (15.79)	2 (33.33)	0.562

(*Continued*)

Table 1 (Continued).

Demographic Variables	Total N=25	Arterial Thrombosis N=19	Venous Thrombosis N=6	*P-value**
Examinations				
Hemoglobin, g/L	120.8±16.06	121±17.78	120.17±9.95	0.828
Red blood cell, 10^{12}/L	3.87±0.66	3.84±0.59	3.95±0.92	0.642
Platelet, 10^9/L	47±48.54	43.74±41.23	57.33±70.86	1.000
White blood cell, 10^9/L	6.53±2.59	6.17±2.66	7.67±2.17	0.092
D-dimer, mg/L	1.84±3.48	2.04±3.97	1.24±0.88	0.246
PT, s	11.85±1.74	11.86±1.83	11.83±1.6	0.926
APTT, s	32.99±9.35	30.98±4.5	39.35±16.82	0.246
TT, s	16.25±1.99	16.11±2.22	16.7±0.98	0.274
FIB, g/L	3.39±1.24	3.43±1.38	3.26±0.74	0.877
INR	0.95±0.15	0.95±0.17	0.95±0.06	0.877
CRP, mg/L	42.4±36.85	61.93±69.38	43.82±58.66	0.687
ITP treatment				
GC, n (%)	16 (64.00)	11 (57.89)	5 (83.33)	0.364
rhTPO, n (%)	9 (36.00)	7 (36.84)	2 (33.33)	1.000
IVIG, n (%)	3 (12.00)	2 (10.53)	1 (16.67)	1.000
Platelet transfusion, n (%)	4 (16.00)	3 (15.79)	1 (16.67)	1.000
In-hospital mortality, n (%)	1 (4.00)	1 (5.26)	0 (0.00)	1.000

Notes: Data are presented as means±SD or n(%). *P-value, arterial thrombosis versus venous thrombosis.
Abbreviations: ITP, immune thrombocytopenia; PT, prothrombin time; APTT, activated partial thromboplastin time; TT, thrombin time; FIB, fibrinogen; INR, international normalized ratio; CRP, C-reactive protein; GC, glucocorticoids; rhTPO, recombinant human thrombopoietin; IVIG, intravenous immunoglobulin G.

Table 2 Characteristics of Patients with ITP Complicated with Thrombosis

Patient Number	Sex	Age	Thrombotic Event	PLT Count at the Time of Thrombosis (10^9/L)	Duration of ITP	ITP Treatment	In-Hospital Mortality
1	F	56	AMI	197	3 years	GC\PLT transfusion	-
2	F	80	AMI	30	3 years	GC	-
3	F	69	AMI	1	3 years	GC\IVIG\PLT transfusion	-
4	F	49	AMI	25	20 years	GC\rhTPO	-
5	F	60	IS	13	1 month	GC\rhTPO	-
6	F	50	IS	73	2 years	GC	-
7	M	71	IS	47	New	GC	-
8	M	74	IS	35	New	TPO	-
9	F	67	IS	37	10 months	IVIG\rhTPO	-
10	F	75	IS	29	New	GC\rhTPO	-
11	M	74	IS	21	New	rhTPO	Yes
12	M	70	IS	45	New	None	-
13	M	61	IS	66	New	None	-
14	M	69	IS	27	2 months	GC\PLT transfusion	-
15	M	61	IS	48	4 years	None	-
16	M	71	IS	13	New	GC\rhTPO	-
17	M	49	IS	33	New	None	-
18	F	71	IS	35	New	None	-
19	F	75	IS	56	5 years	GC	-
20	F	52	DVT	64	6 months	None	-
21	M	73	DVT	3	1 month	GC\rhTPO	-

(*Continued*)

Table 2 (Continued).

Patient Number	Sex	Age	Thrombotic Event	PLT Count at the Time of Thrombosis (10^9/L)	Duration of ITP	ITP Treatment	In-Hospital Mortality
22	F	46	PE/DVT	32	1 years	GC\rhTPO	-
23	F	66	PE/DVT	45	2 months	GC	-
24	M	57	PVT	6	9 months	GC\IVIG\PLT transfusion	-
25	F	23	CVST	194	1 months	GC	-

Abbreviations: ITP, immune thrombocytopenia; PLT, platelet; AMI, acute myocardial infarction; IS, ischemic stroke; DVT, deep vein thrombosis; CVST, cerebral venous sinus thrombosis; PE, pulmonary embolism; PVT, portal vein thrombosis; GC, glucocorticoids; rhTPO, recombinant human thrombopoietin; IVIG, intravenous immunoglobulin G.

Discussion

Thrombosis in patients with ITP is a clinical dilemma that requires balancing the risk of bleeding and thrombosis during treatment. Thrombosis occurred in 0.78% of ITP patients in our center, and AT was more common than VT in patients with ITP. Besides, a low platelet count in ITP patients does not protect against thrombosis, as 92.0% of patients in this study had low PLT counts when thrombotic events occurred.

ITP is a blood condition that manifests as bleeding and a low PLT count. Nonetheless, recent studies have shown that ITP patients have a higher tendency for thrombosis.[4–9] The precise rate of thrombosis in individuals with ITP is unclear, however most researchers believe that individuals with ITP have a higher risk of thrombosis than the general population. Aledort et al initially revealed a 5% rate of thrombotic events in chronic ITP.[11] Another meta-analysis also discovered that individuals with ITP had a greater risk of thromboembolism (mostly AT).[12] Huang et al found that the prevalence of thrombosis in Chinese patients with ITP was 1.43%, slightly higher than our results.[13]

ITP patients have a life-threatening risk of bleeding, nevertheless it is equally important to recognize that they also have a risk of thromboembolism. It can be assumed that owing to the crucial role of platelets in the process of thrombosis, thrombocytopenic patients with ITP might be protected against thromboembolism. On the contrary, ITP patients had higher risks of both venous and arterial thromboembolic events. Thrombosis events may occur at all stages

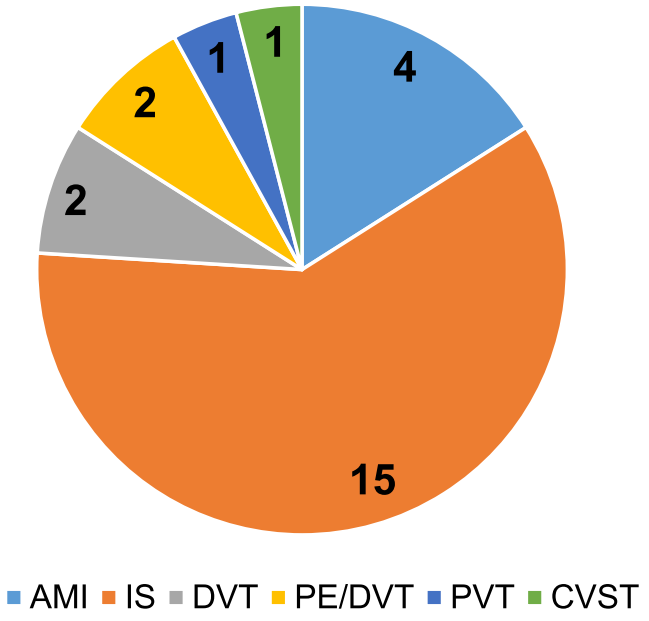

Figure 2 Distribution of thrombotic events.
Abbreviations: AMI, acute myocardial infarction; IS, ischemic stroke; DVT, deep vein thrombosis; CVST, cerebral venous sinus thrombosis; PE, pulmonary embolism; PVT, portal vein thrombosis.

Table 3 Number of Thrombotic Events in ITP Patients with Different Platelet Levels

Platelet Count (10^9/L)	Thrombotic Events (n/%)	Thrombotic Events in Females (n/%)	Thrombotic Events in Males (n/%)
≤20	5 (20.00)	2 (14.29)	3 (27.27)
21–30	6 (24.00)	4 (28.57)	2 (18.18)
31–50	8 (32.00)	3 (21.43)	5 (45.46)
51–99	4 (16.00)	3 (21.43)	1 (9.09)
≥100	2 (8.00)	2 (14.29)	0 (0.00)

of ITP, including individuals receiving active therapy, patients not taking medication, and patients with different levels of PLT.[14,15] In our study, 92.0% of patients had lower PLT counts when thrombotic events occurred. Among them, 11 patients (44.0%) had platelet levels below 30×10^9/L. Therefore, a low level of platelet in ITP patients cannot protect against thromboembolic events.

Previous research has revealed that age is a risk factor for thrombosis in ITP patients.[16] In our study, the average age of individuals with thrombosis is 62.76±12.79 years, and 84.0% of patients are over 50 years old, which is consistent with prior research. Besides, other risk variables such as history of VT, cardiovascular disease, and atrial fibrillation may contribute to the occurrence of thrombosis.[16,17] In our study, most patients (80.0%) with thrombosis have conventional thrombosis risk variables, such as coronary artery disease, diabetes, hypertension, and stroke.

In clinical practice, once ITP patients develop thrombosis, treatment becomes challenging. The risk of bleeding and thrombosis needs to be dynamically assessed throughout the course of treatment. When the PLT is less than 50×10^9/L, most guidelines advise against taking anticoagulant or antiplatelet medications in patients with ITP.[18–20] The major obstacle is the lack of anticoagulants that could be used to treat thromboembolism without raising the risk of bleeding. As a result, managing ITP patients complicated with thromboembolism is challenging, and there is no standard treatment guideline for this condition. In clinical practice, platelet transfusion or other treatments are used to increase the count of PLT to a safe level, after which antiplatelet or anticoagulant therapy is administered.

Our study has certain limitations. First, this was a retrospective study, with the common shortcomings of analysis of the prerecorded data. Second, our hospital does not have a database of all patients, and we are unable to provide a complete detailed comparison between ITP patients who experience thrombosis and those who do not. Moreover, due to the retrospective design of the study, we do not have follow-up data for patients with thrombosis, and then we are not sure about the long-term prognosis of ITP patients with thrombosis.

Conclusions

ITP may be considered a bleeding disorder with a high risk of thromboembolism, and AT is more common than VT in the Chinese population. Besides, a low level of platelet in ITP patients does not protect against thromboembolism. Balancing the risk of bleeding and thromboembolism in patients with ITP is challenging. Future multicenter, large-scale studies are warranted to investigate the optimal treatment strategy for thrombosis in ITP.

Data Sharing Statement

Upon reasonable request, the corresponding author will provide the original data.

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Disclosure

The authors declare no conflicts of interest.

References

1. Rodeghiero F, Stasi R, Gernsheimer T, et al. Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group. *Blood*. 2009;113(11):2386–2393. doi:10.1182/blood-2008-07-162503
2. Cines DB, Blanchette VS. Immune thrombocytopenic purpura. *New Engl J Med*. 2002;346(13):995–1008. doi:10.1056/NEJMra010501
3. Cines DB, Liebman HA. The immune thrombocytopenia syndrome: a disorder of diverse pathogenesis and clinical presentation. *Hematol Oncol Clin North Am*. 2009;23(6):1155–1161. doi:10.1016/j.hoc.2009.09.003
4. Severinsen MT, Engebjerg MC, Farkas DK, et al. Risk of venous thromboembolism in patients with primary chronic immune thrombocytopenia: a Danish population-based cohort study. *Br J Haematol*. 2011;152(3):360–362. doi:10.1111/j.1365-2141.2010.08418.x
5. Nørgaard M, Severinsen MT, Lund Mægbæk M, et al. Risk of arterial thrombosis in patients with primary chronic immune thrombocytopenia: a Danish population-based cohort study. *Br J Haematol*. 2012;159(1):109–111. doi:10.1111/j.1365-2141.2012.09231.x
6. Sarpatwari A, Bennett D, Logie JW, et al. Thromboembolic events among adult patients with primary immune thrombocytopenia in the United Kingdom General Practice Research Database. *Haematologica*. 2010;95(7):1167–1175. doi:10.3324/haematol.2009.018390
7. Rodeghiero F. Is ITP a thrombophilic disorder? *Am J Hematol*. 2016;91(1):39–45. doi:10.1002/ajh.24234
8. Ruggeri M, Tosetto A, Palandri F, et al. Thrombotic risk in patients with primary immune thrombocytopenia is only mildly increased and explained by personal and treatment-related risk factors. *J Thromb Haemost*. 2014;12(8):1266–1273. doi:10.1111/jth.12636
9. Langeberg WJ, Schoonen WM, Eisen M, et al. Thromboembolism in patients with immune thrombocytopenia (ITP): a meta-analysis of observational studies. *Int j Hematol*. 2016;103(6):655–664. doi:10.1007/s12185-016-1974-6
10. Mititelu A, Onisâi M-C, Roşca A, et al. Current understanding of immune thrombocytopenia: a review of pathogenesis and treatment options. *Int J Mol Sci*. 2024;25(4):2163. doi:10.3390/ijms25042163
11. Aledort LM, Hayward CPM, Chen M-G, et al. Prospective screening of 205 patients with ITP, including diagnosis, serological markers, and the relationship between platelet counts, endogenous thrombopoietin, and circulating antithrombopoietin antibodies. *Am J Hematol*. 2004;76(3):205–213. doi:10.1002/ajh.20104
12. Doobaree IU, Nandigam R, Bennett D, et al. Thromboembolism in adults with primary immune thrombocytopenia: a systematic literature review and meta-analysis. *Eur J Haematol*. 2016;97(4):321–330. doi:10.1111/ejh.12777
13. Huang YT, Liu XF, Chen YF, et al. 原发免疫性血小板减少症患者血栓发生情况 及相关危险因素分析 [The incidence and risk factors for thrombosis in primary immune thrombocytopenia]. *Zhonghua Xue Ye Xue Za Zhi*. 2018;39(11):942–946. Chinese. doi:10.3760/cma.j.issn.0253-2727.2018.11.014
14. Tărniceriu CC, Hurjui LL, Florea ID, et al. Immune thrombocytopenic purpura as a hemorrhagic versus thrombotic disease: an updated insight into pathophysiological mechanisms. *Medicina*. 2022;58(2):211. doi:10.3390/medicina58020211
15. Swan D, Newland A, Rodeghiero F, et al. Thrombosis in immune thrombocytopenia - current status and future perspectives. *Br J Haematol*. 2021;194(5):822–834. doi:10.1111/bjh.17390
16. Lafaurie M, Maquet J, Baricault B, et al. Risk factors of hospitalisation for thrombosis in adults with primary immune thrombocytopenia, including disease-specific treatments: a French nationwide cohort study. *Br J Haematol*. 2021;195(3):456–465. doi:10.1111/bjh.17709
17. Ito S, Fujiwara S-I, Ikeda T, et al. Evaluation of thrombotic events in patients with immune thrombocytopenia. *Ann Hematol*. 2020;99(1):49–55. doi:10.1007/s00277-019-03886-6
18. Song F, Al-Samkari H. Management of Adult Patients with Immune Thrombocytopenia (ITP): a review on current guidance and experience from clinical practice. *J Blood Med*. 2021;12:653–664. doi:10.2147/JBM.S259101
19. Napolitano M, Saccullo G, Marietta M, et al. Platelet cut-off for anticoagulant therapy in thrombocytopenic patients with blood cancer and venous thromboembolism: an expert consensus. *Blood Transfusion*. 2019;17(3):171–180. doi:10.2450/2018.0143-18
20. Pishko AM, Misgav M, Cuker A, et al. Management of antithrombotic therapy in adults with immune thrombocytopenia (ITP): a survey of ITP specialists and general hematologist-oncologists. *J Thromb Thrombol*. 2018;46(1):24–30. doi:10.1007/s11239-018-1649-7