

HEMOSTASIOLOGICAL DISORDERS IN CERTAIN FORMS OF HEMORRHAGIC DIATHESSES

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Abstract

Objective. Based on assessment of the role of disorders in various links of hemostasis in the pathogenesis of IMTV and ITP and determination of their relation to disease stage, optimize the hemostasiological diagnostic algorithm for the studied pathologies.

Materials and methods. The study included 105 patients with IMTV (51 — in the relapse stage, 54 — in the remission stage); 135 patients with ITP (74 — in the relapse stage, 61 — in the remission stage) and 81 conditionally healthy individuals without pathology of the hemostatic system (all subjects were aged 18 to 70 years). The hemostatic system was examined using a HumaClot Junior coagulometer (HC-4127, Germany) and an ALAT-2 “BIOLA” aggregation analyzer (AAS 748, Russia) with reagents from “NPO RENAM, Russia.”

Results and discussion. A comprehensive study of the links of the hemostatic system indicates pronounced coagulation disorders, which are one of the main mechanisms in the pathogenesis of IMTV and ITP. IMTV is characterized by activation of the vascular–platelet link and moderate hypercoagulation, whereas ITP is characterized by reduced activity of the vascular–platelet link of hemostasis.

Keywords: Immune microthrombovasculitis, immune thrombocytopenia, hemostatic system, vessels, platelets.

Introduction

Hemorrhagic diatheses (HD) are one of the most important problems in clinical hematology. Due to the increasing incidence, more severe clinical courses, and development of serious complications across the larger group of HDs, immune microthrombovasculitis (IMTV) and immune thrombocytopenia (ITP) are of particular current importance and represent a socio-medical problem in modern medicine. Given the protracted course, frequent relapses and chronization of the process, as well as the possibility of a wide range of complications up to fatal outcomes, the ability to diagnose and treat these diseases is necessary both for hematologists and for physicians of many other specialties.

One of the primary mechanisms in the development of IMTV and ITP are complex disturbances of the hemostatic system. [1,2,10,12,18]. Despite the existence of extensive data on the vascular–platelet system, the basis of certain processes observed in these pathologies remains insufficiently



studied to date. [6,7,13,19]. The relatively low informativeness of previously used methods for studying hemostatic parameters significantly reduces timely diagnosis and the effectiveness of therapy for IMTV and ITP. [7,8,14,17].

Objective

On the basis of assessing the role of disorders in various links of hemostasis in the pathogenesis of IMTV and ITP, and of establishing their relationship with disease stage, to optimize the hemostasiological diagnostic algorithm for the studied pathologies.

Materials and Methods

The study included 105 patients with IMTV (51 — in the relapse stage, 54 — in the remission stage) and 135 patients with ITP (74 — in the relapse stage, 61 — in the remission stage). These patients were distributed into two major groups: Group 1 — patients with IMTV; Group 2 — patients with ITP. According to disease stage, they were subdivided into subgroups A — relapse stage and B — remission stage (all subjects were aged 18 to 70 years). All subjects received outpatient or inpatient treatment at the clinic of NIIG and PC of the Ministry of Health of the Republic of Uzbekistan. The control group consisted of individuals from the Uzbek population of comparable age without hemostatic system pathology (n = 81).

In accordance with the study objective, all subjects underwent a comprehensive assessment of hemostatic system parameters.

Hemostasis investigation included:

1. Vascular–platelet link of the hemostatic system (platelet count by hemogram in peripheral blood using phase-contrast microscopy; determination of platelet aggregation induced by ADP (1.0 and 0.5 mmol); von Willebrand factor (vWF); clot retraction in a test tube according to Baluda V.P. et al. (1980));
2. Coagulation link of the hemostatic system (determination of activated partial thromboplastin time of plasma (APTT), prothrombin index (PTI), thrombin time (TT), quantitative ortho-phenanthroline test detecting soluble fibrin-monomer complexes (SFMC) in plasma, fibrinogen concentration);
3. Activity of antithrombin III (AT III);
4. Anticoagulant and fibrinolytic system (XIIa-dependent fibrinolysis according to Eremin G.F. and Arkhipov A.G., 1982).

The hemostasis investigations were performed using a HumaClot Junior coagulometer (HC-4127, Germany) and an ALAT-2 “BIOLA” aggregation analyzer (AAS 748, Russia) with reagents from “NPO RENAM, Russia.”

Statistical processing of the obtained data was performed by variation statistics using Microsoft Office Excel-2003 with calculation of the standard deviation and the standard error of the mean by the method of moments ($M \pm m$), Student's t-test for significance of differences (t), and significance level (p).

Results and conclusions. Analysis of the comprehensive studies of the hemostatic system carried out with standardized, highly informative methods in patients with IMTV and ITP at different stages demonstrated multidirectional shifts in all studied links of hemostasis.



Comparative analysis in Group 1 made it possible to establish features of hemostatic pathology in IMTV patients that differ between the relapse and remission stages: in subgroup A, relative to the control, there was an increase in platelet aggregation induced by ADP (1 mmol) to $78.9 \pm 1.7\%$ ($p > 0.05$) and (0.5 mmol) to $34.5 \pm 1.28\%$ ($p < 0.001$), and a statistically significant increase in fibrinogen level to 4.61 ± 0.08 g/L ($p < 0.001$) (Fig. 1). The vWF level was found to be significantly higher — 1.33 times relative to control and 1.38 times relative to subgroup B (Fig. 2). All the above parameters in subgroup B were significantly decreased relative to control ($p < 0.001$).

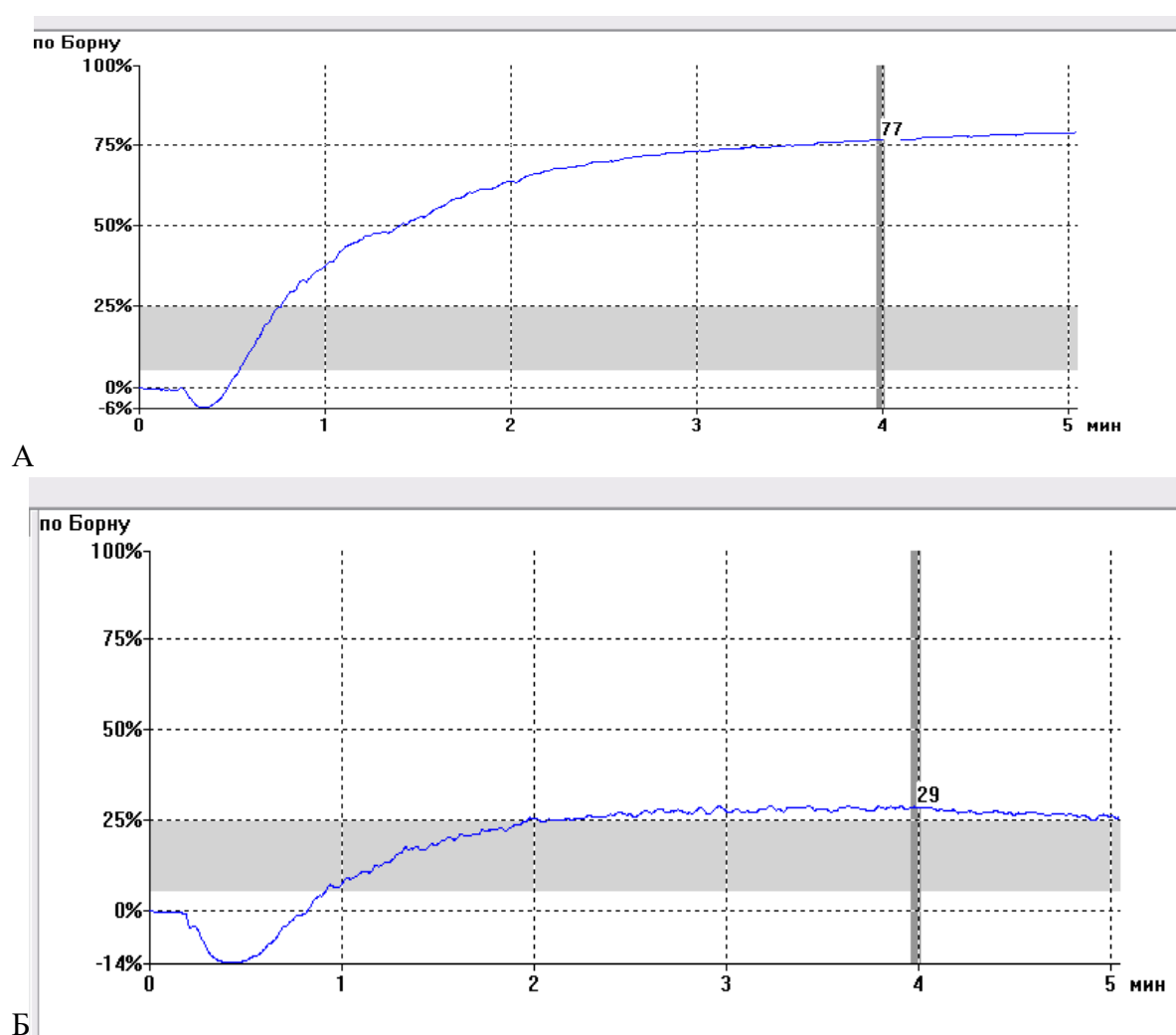


Figure 1. Platelet aggregation induced by ADP at concentrations of 1.0 mmol (A) and 0.5 mmol (B) in a patient with recurrent DVT.

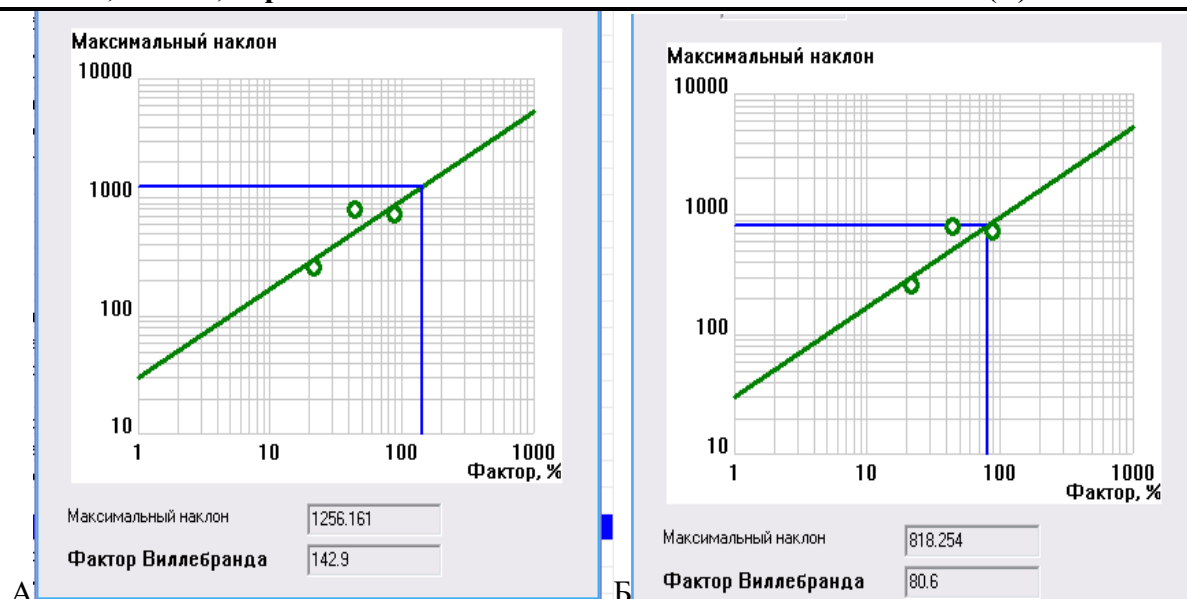


Figure 2. von Willebrand factor levels in a patient with DVT during recurrence (A) and remission (B).

The indicators of the coagulation link of hemostasis also differed from those in the control: APTT in subgroup A was significantly shorter by a factor of 1.06 ($p < 0.001$); PTI and TT were $104 \pm 1.33\%$ ($p < 0.001$) and 12.3 ± 0.16 s ($p < 0.001$) in subgroup A, and $95.6 \pm 0.81\%$ ($p < 0.001$) and 13.3 ± 0.17 s ($p < 0.001$) in subgroup B, respectively (in the control group: $91.0 \pm 1.01\%$ and 8.86 ± 0.10 s). At the same time, AT III values decreased in both subgroups by factors of 1.12 and 1.09, while SFMC (soluble fibrin-monomer complexes) increased by factors of 2.16 and 1.4 ($p < 0.001$) relative to control.

In addition, study of the fibrinolytic system revealed a significant decrease in XIIa-dependent fibrinolysis in the examined subgroups (Table 1).

Table 1. Hemostasis parameters in patients with DVT and in the control group

($M \pm m$).

Hemostasis parameter	Unit of measurement	Control (n = 81)	DVT (n=105)	
			Acute phase (n=51)	Remission (n=54)
Platelet aggregation with ADP (1.0 mmol)	%	$56,8 \pm 0,90$	$78,9 \pm 1,7$	$43,5 \pm 1,17^{***}$
Platelet aggregation with ADP (0.5 mmol)	%	$28,9 \pm 0,44$	$34,5 \pm 1,24^{***}$	$23,9 \pm 0,74^{***}$
APTT	sec	$30,7 \pm 0,24$	$28,8 \pm 0,47^{***}$	$33,5 \pm 0,44^{***}$
PTI	%	$91,0 \pm 1,01$	$104 \pm 1,33^{***}$	$95,6 \pm 0,81^{***}$
Trombin time	sec	$8,86 \pm 0,10$	$12,3 \pm 0,16^{***}$	$13,3 \pm 0,17^{***}$
Fibrinogen	g/l	$3,20 \pm 0,05$	$4,61 \pm 0,08^{***}$	$3,5 \pm 0,07^{***}$
Factor XIIa-dependent fibrinolysis	min	$6,42 \pm 0,13$	$11,0 \pm 0,30^{***}$	$7,0 \pm 0,12^{***}$
AT III	%	$106 \pm 0,97$	$94,2 \pm 0,99^{***}$	$97,1 \pm 1,0^{***}$
RFMK	mg/ml	$3,85 \pm 0,05$	$8,32 \pm 0,32^{***}$	$5,34 \pm 0,22^{***}$
vWF	%	$100,4 \pm 1,4$	$134 \pm 4,37^{***}$	$97,3 \pm 0,85$

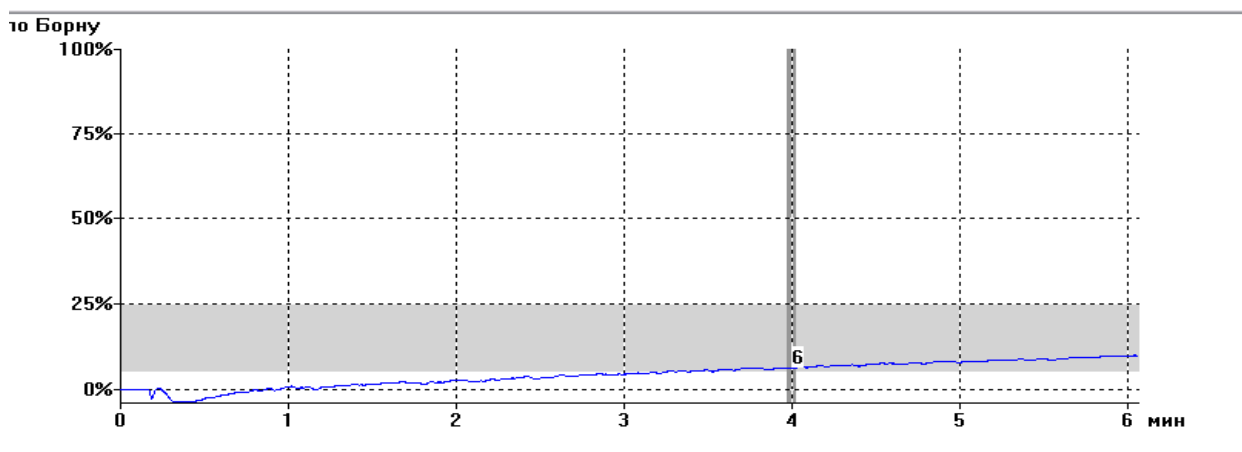
Note: *** – $p < 0.001$, statistically significant compared with the control group.

The identified features of disturbances in the hemostatic system in the relapse stage of IMTV are caused by the influence of an immune-complex process, which leads to persistent hypercoagulation and microthrombus formation, decreased activity of AT III, and increased SFMC.

In Group 2, subgroup A, patients showed a decrease in platelet count to $25.4 \pm 1.34 \times 10^9/L$ and platelet aggregation induced by ADP (1 mmol) to $4.8 \pm 0.52\%$ ($p > 0.05$) and (0.5 mmol) to $1.97 \pm 0.26\%$ ($p < 0.001$) (Fig. 3), and clot retraction to 0.06 ± 0.01 (Table 2).

The TT and APTT indicators in ITP patients, compared to the control group, showed little difference from those of the control group (Table 2).

A



Б

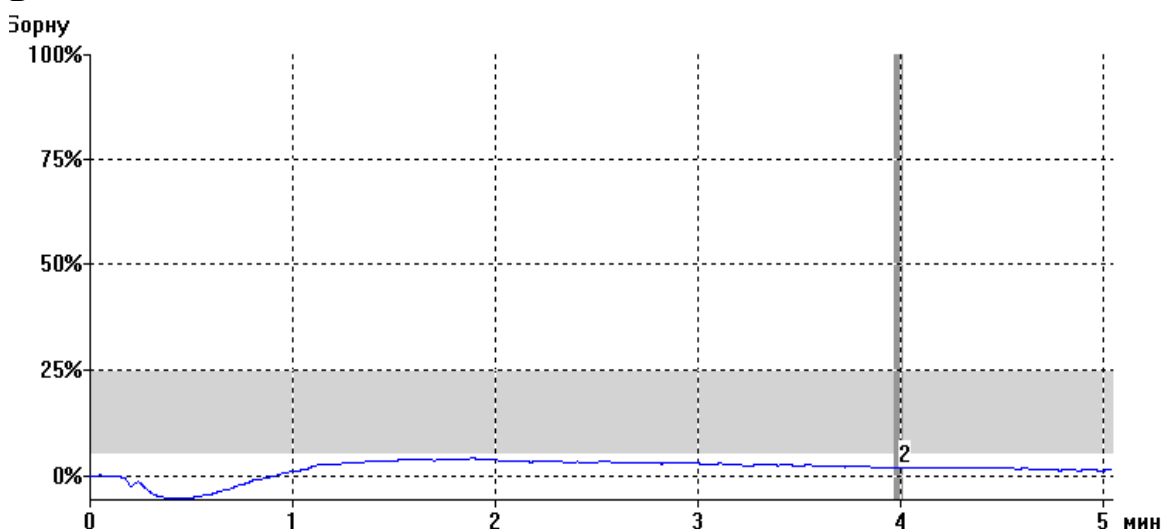


Figure 3. Platelet aggregation induced by ADP at concentrations of 1.0 mmol (A) and 0.5 mmol (B) in a patient with recurrent ITP.

The TT and APTT values in patients with ITP differed little from those in the control group (Table 2).

Table 2. Hemostasis parameters in patients with ITP and in the control group (M ± m).

Hemostasis parameter	Unit of measurement	Control (n = 81)	ITP (n=135)	
			Acute phase (n=74)	Remission (n=61)
Platelet count	$\times 10^3/\mu\text{L}$	220,3 $\pm$ 2,84	25,4 $\pm$ 1,34***	190,6 $\pm$ 3,7***
Platelet aggregation with ADP (1.0 mmol)	%	57,1 $\pm$ 0,97	4,8 $\pm$ 0,52***	53,1 $\pm$ 0,86***
Platelet aggregation with ADP (0.5 mmol)	%	29,1 $\pm$ 0,52	1,97 $\pm$ 0,26***	26,3 $\pm$ 0,47***
APTT	sec	30,5 $\pm$ 0,28	30,7 $\pm$ 0,41	30,5 $\pm$ 0,35
PTI	%	90,8 $\pm$ 1,10	94,5 $\pm$ 1,05***	91,5 $\pm$ 1,26
Thrombin time	sec	8,9 $\pm$ 0,12	10,2 $\pm$ 0,20***	9,9 $\pm$ 0,23***
Fibrinogen	g/l	4,1 $\pm$ 0,53	3,34 $\pm$ 0,057	4,3 $\pm$ 0,70
Factor XIIa-dependent fibrinolysis	Min	6,4 $\pm$ 0,15	9,4 $\pm$ 0,028***	6,5 $\pm$ 0,20
Retraction	-	0,30 $\pm$ 0,009	0,06 $\pm$ 0,01***	0,29 $\pm$ 0,0024

Note: *** – $p < 0.001$, statistically significant compared with the acute phase of the disease.

A comprehensive study of hemostatic system parameters in ITP patients revealed their significance according to the disease stage. Thus, in the relapse stage of ITP, statistically significant findings were a decrease in platelet count, platelet aggregation induced by ADP, and clot retraction; whereas in the remission stage, the only significant parameter was a decrease in platelet aggregation induced by ADP (Fig. 4). This, in turn, indicates that in patients in remission, studying the remaining hemostatic parameters is not informative.

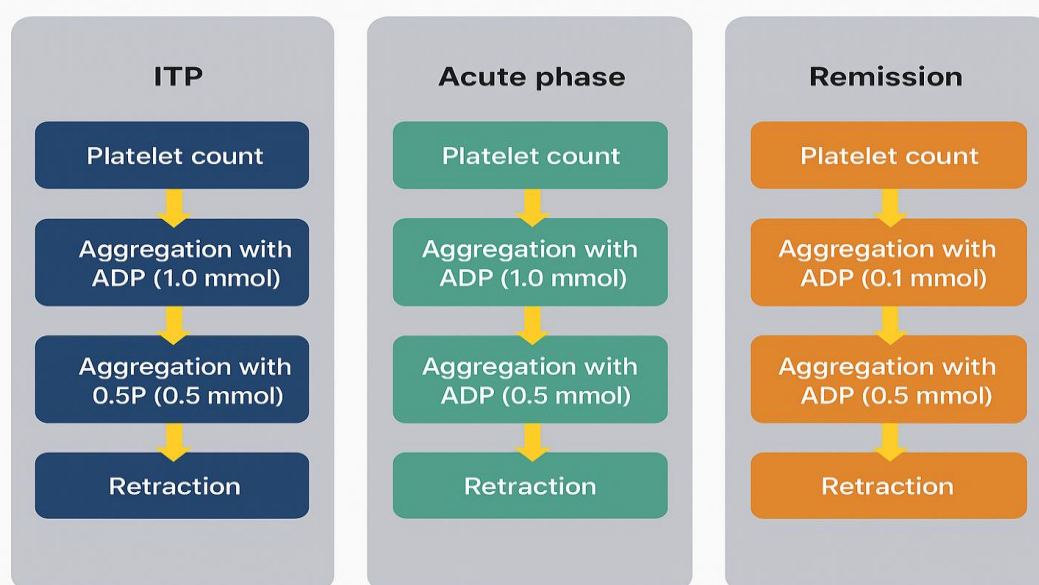
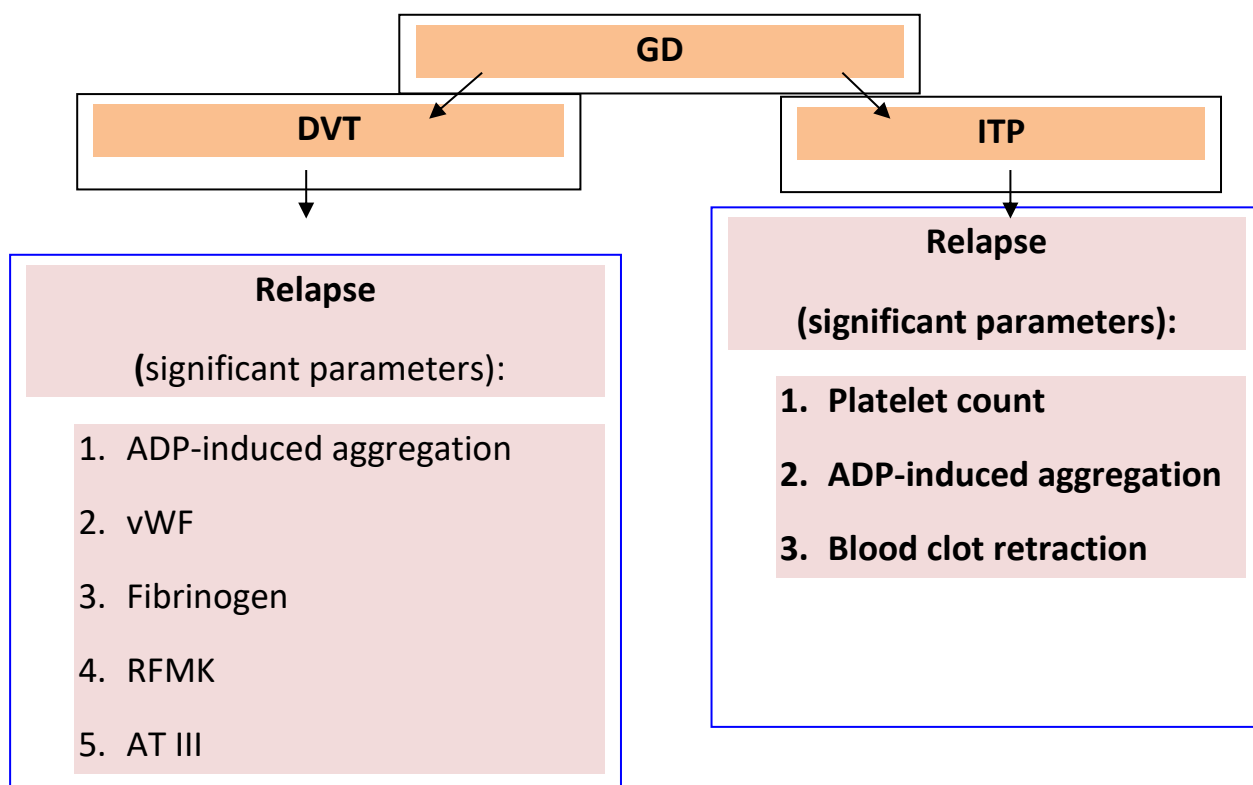


Figure 4. Statistically significant decrease in hemostasis parameters in patients with ITP at different stages of the disease (Student's t-test).



Thus, a comprehensive study of hemostatic system parameters in IMTV and ITP patients indicates the presence of multidirectional disorders. Pronounced changes in the hemostatic system in IMTV were characterized by hypercoagulation, thrombinemia, and vascular–platelet disturbances, which were further aggravated by decreased antithrombin III activity and elevated SFMC levels. A comparative analysis of hemostatic system results in ITP patients revealed significant impairments of the blood’s hemostatic potential, with reduced platelet hemostasis activity manifested by decreased platelet counts, impaired aggregation, and diminished clot retraction.



Scheme 1. Algorithm of hemostasiological assessment in patients with DVT and ITP.

The conducted research made it possible not only to determine the role of disturbances in various links of the hemostatic system in the pathogenesis of IMTV and ITP, but also, on this basis, to optimize the algorithm of hemostasiological investigation for patients (Scheme 1).

Conclusions:

1. A comprehensive study of the links of the hemostatic system indicates the presence of pronounced coagulation disorders, which are one of the main mechanisms in the pathogenesis of IMTV and ITP.
2. Hemostasiological disorders in IMTV and ITP determine a characteristic disease profile that defines their specific features: IMTV is characterized by activation of the vascular–platelet link and moderate hypercoagulation, while ITP is characterized by reduced activity of the vascular–platelet link of hemostasis.

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