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CLINICAL STUDY

Risk of chronic thromboembolic pulmonary hypertension after splenectomy

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ABSTRACT

OBJECTIVES: The purpose of the clinical study was to evaluate the risk of chronic thromboembolic pulmonary hypertension (CTEPH) after splenectomy and to analyze some biochemical and coagulation parameters.

BACKGROUND: CTEPH caused by incomplete resolution of thromboemboli and irreversible remodeling of the pulmonary arteries is a progressive, and without treatment a fatal disease. Although the definite etiopathophysiology is not quite perfectly researched, numerous clinical conditions associated with CTEPH as history of pulmonary embolism, infected ventriculoatrial shunts or permanent intravascular devices, high-dose thyroid hormone replacement, malignancy and chronic inflammatory diseases, including osteomyelitis, inflammatory bowel diseases, are well accepted. These factors also include splenectomy.

METHODS: We performed a prospective follow-up of patients after splenectomy in the period of 5 years (2017-2022). The study population consisted of 62 adult post-splenectomy patients, who were divided into 3 groups based on the cause of the splenectomy – trauma, haematologic diseases, and others. The study population was analyzed in terms of gender, age, cause of splenectomy, blood group, clinical risk factors and thrombophilic conditions. Some basic haemocoagulation parameters and selected coagulation and biochemical parameters were analyzed. All patients underwent screening echocardiography, symptomatic patients repeatedly. In the presence of pulmonary hypertension (PH) unexplained by other diseases, patients underwent ventilation/perfusion lung scan performed to confirm/exclude perfusion defects typical for CTEPH. If PH and perfusion defects persisted despite effective 3-month anticoagulation therapy, patients underwent right heart catheterization to confirm/exclude CTEPH.

RESULTS: The study confirmed a higher incidence of CTEPH after splenectomy compared to published data, the 5-year cumulative incidence was 3.2 %. Other detected clinical risk factors did not affect the incidence of thromboembolism/CTEPH after splenectomy. In our study, the strongest factor in terms of the incidence of thromboembolism/CTEPH after splenectomy was the presence of a thrombophilia detected before the screening echocardiography. Tested haemocoagulation and biochemical parameters in small patient subgroup had no impact on the incidence of thromboembolism/CTEPH – however, the limiting factor was a small patient subgroup.

CONCLUSION: The results of the study suggest that the incidence of thromboembolism after splenectomy was consistent with the present data, but the incidence of CTEPH after splenectomy was significantly higher. This suggests that post-splenectomy condition may be an independent risk factor for CTEPH and may imply different management of these patients in the future *(Tab. 5, Ref. 18)*. Text in PDF *www.elis.sk*

KEY WORDS: chronic thromboembolic pulmonary hypertension, splenectomy.

Introduction

CTEPH is a serious disease significantly reducing quality and length of life. The disease is characterized by the presence of obstructive fibrotic thrombo-embolic material in the pulmonary vasculature and small vessel arteriopathy. Risk factors include several clinical conditions, including splenectomy. The exact prevalence and incidence of CTEPH after splenectomy however are unknown. Large meta-analysis researching the prevalence of splenectomy in CTEPH patients has recently been published. The pooled crude prevalence of splenectomy in CTEPH patients was confirmed to be 4 %, the prevalence ranged from 2 % to 9 % in individual studies (1). The results of the aforementioned meta-analysis and systematic review of previous studies showed a statistically significantly higher incidence of splenectomy in patients with CTEPH compared to patients with pulmonary arterial hypertension (PAH) and thromboembolic disease (1), however, our national data is absolutely missing.

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Patients and methods

Prospective follow-up of post-splenectomy patients was performed for 5 years (2017–2022). Inclusion criteria were age over 18 years and splenectomy. Patients were referred for a screening echocardiography by a haematologist or were in the database of the surgical clinic and were invited from it as part of our study. The next step was to take a medical history and review the available medical documentation, then perform a screening echocardiography according to a uniform protocol. The medical history was focused on subjective difficulties, cause of splenectomy, thromboembolism after splenectomy, other clinical risk factors and thrombophilic diseases/conditions. The splenectomised patients were classified into 3 groups:

1. trauma, in this group were also patients in whom the spleen was iatrogenically damaged during other abdominal surgery,
2. haematological diseases, in our research it was autoimmune thrombotic thrombocytopenic purpura, thrombotic thrombocytopenic purpura, myeloproliferative and lymphoproliferative diseases, hereditary spherocytosis, autoimmune haemolytic anaemia,
3. other – in our research it was splenic cysts, hemangioma, specific inflammatory process, tumors (endocrine, secondary).

Thromboembolism after splenectomy was defined as pulmonary embolism (PE) or deep venous thrombosis (DVT) confirmed by imaging methods (computed tomography pulmonary angiography, ventilation/perfusion lung scan, ultrasonography).

Clinical risk factors were defined as: chronic inflammatory disease such as osteomyelitis and inflammatory bowel disease, thyroid hormone replacement therapy, ventriculo-atrial shunts in hydrocephalus, infected chronic intravenous catheters or pacing leads, malignant disease (treated or actively monitored), myeloproliferative disease. In case medical documentation was available, data were obtained from medical reports.

Before the screening echocardiography the presence of thrombophilic condition was detected (2).

Among other risk factors, blood group was determined. If the patient did not have such knowledge and the medical documentation was not available, the blood group was examined after the patient's consent.

Subsequent echocardiography identified patients with intermediate and high probability of PH. Patients with unexplained intermediate and high probability PH, or symptomatic patients with borderline or indeterminate findings, underwent ventilation/perfusion lung scan to identify lung perfusion defects typical for CTEPH. Patients with PH (based on echocardiography) and perfusion defects (based on lung scintigraphy) were managed depending on previous anticoagulation therapy:

a) patients without anticoagulation therapy without contraindications to anticoagulation were set on anticoagulation with vitamin K antagonists (VKAs) according to current recommendations (INR 2-3) and then reassessed for symptoms, PH and the presence of perfusion defects after 3 months of effective anticoagulation therapy,

b) patients with effective anticoagulation therapy lasting more than 3 months were considered as patients with possible CTEPH. Patients with suspected CTEPH based on previous non-invasive examinations underwent a complete diagnostic algorithm, including right heart catheterization, to confirm/exclude CTEPH at the National CTEPH Expert Centre.

As the first patient examinations started in 2017 and the study was repeatedly interrupted by the COVID-19 pandemic, all patients who had echocardiography performed before 2022 were actively contacted for thromboembolism symptoms, despite recommendation to contact us if difficulties. If symptoms were suspected from thromboembolism, they repeatedly underwent echocardiography to assess PH. Finally, an individual protocol was drawn up for each patient. It included data regarding thromboembolic events, the methods of their diagnosis, the period and circumstances in which they were identified. The protocol included the procedure after screening echocardiography and details of its recurrence.

Baseline haemocoagulation parameters were performed in a subset of enrolled patients – D-dimer level (reference range (rr) up to 0.55 mg/l), platelet count (rr 140–420 x 10^9/l), fibrinogen level (rr 1.80–4.20 g/l), activated partial thromboplastin time ratio – APTR (rr 0.80–1.20) and international normalised ratio – INR (rr 0.80–1.20). Examinations of selected biochemical and coagulation parameters also were performed – antithrombin III activity (rr 75–125 %), lipoprotein (a) level (rr up to 300 mg/l), Factor VIII (rr 70–150 %) and Von Willebrand factor (rr 48–173 %) activity, protein C (rr 70–140 %) and S (rr 60–140 %) activity, lupus anticoagulants screening (rr 31–44 s) or anticardiolipin antibodies (rr up to 10 kIU/l), beta 2 glycoprotein 1 autoantibody (B2GP1**)** level (rr up to 10 IU/ml), plasminogen activator inhibitor 1 (PAI-1) level (rr 0.3–3.5 IU/ml) or genetic testing (homozygote/heterozygote for the mutant allele). Blood was collected in the haematology or cardiology outpatient clinic and examined by standardised methods. Levels of lupus anticoagulants or anticardiolipin antibodies above the reference range were evaluated as a positive/risk sign. PAI-1 levels above the reference range or homozygote/heterozygote for the mutant 4G allele (the 4G allele increases PAI-1 gene expression, leading to increased PAI-1 levels) were evaluated as a positive/risk sign.

In some patients the blood group was determined.

Biochemical and coagulation parameters could not be performed in all patients, as some of them required haematological specialisation (and could not be indicated by the cardiologist).

The research was conducted during the COVID-19 pandemic and was repeatedly interrupted by waves of the pandemic. Regular outpatient follow-ups were failing. Another problem is the fact that many postsplenectomy patients are not regularly followed up by a haematologist. Therefore, biochemical and hematological parameters were evaluated only in a small group of patients. However, the results may be useful for future research.

Statistical methods

Standard descriptive methods were used for the basic statistical analysis. For continuous data (age), the mean and median ± standard deviation were used. Other statistical methods used were the Kolmogorov–Smirnov and Shapiro–Wilk tests of normality. To compare the two groups in the values of continuous random

variables, we used the two-sample t-test or the nonparametric two-sample Mann–Whitney test depending on whether or not we rejected the normal distribution of the values of the continuous random variables being compared. To compare more than two groups in the values of continuous random variables, we used simple analysis of variance or non-parametric Kruskal–Wallis test depending on whether or not we rejected the normal distribution of the values of the compared continuous random variables. We used Chi-square test in contingency tables to detect the relationship between two discrete variables and Fisher's exact test in the case of low expected frequencies. All tests were performed at a significance level of $\alpha = 0.05$. We used IBM SPSS 21 statistical software.

Results

Study population consisted of 62 patients – 39 males (62.9 %) and 23 females (37.1 %). The mean age was 52 (age in years to 2022 or age at death), the minimum was 22, and the maximum 83 years. There were no statistical differences in age between males and females. The mean age at the time of splenectomy was 38 years, the minimum age was 4, and the maximum age was 72 years. There were no statistical differences in age at the time of splenectomy between males and females. Trauma was the cause of splenectomy in 20 patients (32.3 %), heamatologic disease in 34 patients (54.8 %), and other causes of splenectomy were seen in 8 patients (12.9 %). In males, trauma was a statistically more significant cause of splenectomy compared to females ($p = 0.021$). No statistically significant difference in the prevalence of clinical risk factors and thrombophilic conditions was observed before screening echocardiography between patient groups according to the cause of splenectomy.

Thrombophilic conditions detected before the screening echocardiography in our study were: metabolic disorders (hyperhomocysteinemia), deficiency of coagulation factors (factor XII deficiency), autoimmune thrombophilic conditions (antiphospholipid syndrome, lupus anticoagulans).

The clinical risk factors that occurred in our study population were:

- inflammatory bowel disease – 1 patient (1.6 %)
- malignant disease – 4 patients (6.5 %)
- myeloproliferative disease – 1 patient (1.6 %)
- myeloproliferative and malignant disease – 1 patient (1.6 %)

There was no statistically significant difference in the prevalence of clinical risk factors between males and females.

The characteristics of study population are seen in Table 1.

Thromboembolism after splenectomy (HVT/PE) occurred in 9 patients (14.5 %), there was no statistically significant difference between males and females. Thromboembolism after splenectomy occurred on average after 9 years, with the earliest occurrence of thromboembolism immediately after surgery and the latest after 36 years (Tab. 2).

CTEPH after splenectomy occurred in 2 patients (3.23 %) – one male and one female. The cause of the splenectomy in the man was a trauma and, in the woman, a haematological disease. A 56-year-old man underwent balloon angioplasty (BPA) and is being followed up at the Expert Centre. The woman died at the age of 66 due to end-stage right-heart failure and end-stage haematological disease. Both patients with CTEPH had manifestations of thromboembolism prior to CTEPH. As mentioned above, in our study population of post-splenectomy patients, CTEPH occurred in 3.23 % and thromboembolism in 14.52 %. There was no statistically significant difference between male and female in the incidence of CTEPH and manifestations of thromboembolism after splenectomy. Similarly, there was no statistical difference in the incidence of CTEPH and thromboembolism depending on the cause of splenectomy. A statistically significant difference that distinguished post-splenectomy patients with CTEPH or thromboembolism versus others in our study was the presence of a known thrombophilic condition/disease before screening echocardiography ($p = 0.003$).

Patient subgroup results – blood group

Blood group as a risk factor was examined in 56 patients. The prevalence of each blood groups was as follows: "0" 13/23.2 %, "A" 24/42.9 %, "B" 13/23.2 %, "AB" 6/10.7 % of patients.

In our study of a population of post-splenectomy patients, there was no statistical difference in the incidence of CTEPH and thromboembolism depending on the blood group.

Patient subgroup results – biochemical and coagulation parameters

The subgroup consisted of 24 patients – 13 males and 11 females – who had examined baseline coagulation parameters (Tab. 3) and in addition, 12 patients from this subgroup – 9 males and 3 females – had examined selected biochemical and coagulation parameters (Tab. 4).

Tab. 1. The characteristics of study population.

Parameter		All	Male	Female
Number of patients (n/%)		62/100 %	39/63 %	23/37 %
Mean age (years)		52.3 ± 15.8	52.8	51.4
Mean age at the time of SPLE (years)		37.5 ± 18.7	37.7	37.2
Cause of SPLE (n/%)	Trauma	20/32.3 %	17/27.4 %	3/4.9 %
	Haematological disease	34/54.8 %	19/30.6 %	15/24.2 %
	Other	8/12.9 %	3/4.8 %	5/8.1 %
Clinical risk factors (n/%)		7/11.3 %	4/6.5 %	3/4.8 %
Thrombophilic conditions before echocardiography (n/%)		6/9.7 %	3/4.85 %	3/4.85 %

n – number, SPLE – splenectomy

Tab. 2. Manifestations of thromboembolism after splenectomy.

	TE after SPLE (HVT/PE)		TE after SPLE (HVT/PE) in years (mean)
	YES	NO	
All patients (n/%)	9/14.5 %	53/85.5 %	9.4
Male	5/12.8 %	34/87.2 %	9.2
Female	4/17.4 %	19/82.6 %	9.7

n – number, SPLE – splenectomy, TE – thromboembolism

Tab. 3. Basic coagulation parameters.

Parameter	D-dimer (rr up to 0.55 mg/l)	Platelets (rr 140 – 420 x 10⁹/l)	Fibrinogen (rr 1.80–4.20 g/l)	APTR (rr 0.80–1.20)	INR (rr 0.80– 1.20)
All patients of the subgroup					
mean	**0.84**	396	3.29	1.015	1.019
median±SD	0.59±0.73	368±130	3.25±1.02	1.00±0.107	1.00±0.074
min–max	0.15–2.65	170–679	1.35–6.72	0.88–1.23	0.92–1.2
Male					
mean	1.02	317	2.88	1.0	1.02
median±SD	0.76±0.73	338±99	3.03±0,9	1.0±0.2	1.01±0.01
min–max	0.15–2.65	170–473	1.35–4.17	0.88–1.21	0.92–1.16
Female					
mean	0.63	**490**	**3.77**	1.03	1.01
median±SD	0.58±0.42	512±109	3.49±1.19	1.02±0.11	1.00±0.08
min–max	0.15–0.34	306–679	2.46–6.72	0.89–1.23	0.92–1.2
p	NS	**p <0.001**	**p = 0.03**	NS	NS

rr – reference range, SD – standard deviation, min–max – minimum – maximum, p – statistical significance between genders, NS – nonsignificant

Tab. 4. Selected biochemical and coagulation parameters.

Parameter	Antithrombin III activity (rr 75– 125%)	Lipoprotein (a) (rr up to 300 mg/l)	Factor VIII activity (rr 70 – 150%)	B2GP1 autoantibodies (rr up to 10 IU/ml)
All patients of the subgroup				
mean	97.09	108.63	142.95	2.40
median±SD	94.50 ± 13.62	107.70 ± 13.63	138.90±53.44	2.45 ± 0.73
min–max	70.70–118.80	12.44–196.50	71.10–266.90	1.20–3.50
Male				
mean	95.6	92.94	144.71	2.41
median±SD	92.6±28.42	81.67±112.61	133.5±110.33	2.5±1.59
min–max	70.7–118.8	12.44–196.50	71.10–266.9	1.20–3.50
Female				
mean	101.5	155.7	137.67	2.38
median±SD	100.8±9.07	173.3±42.25	163.6±45.96	2.4±0.35
min–max	92.8–110.9	107.5–186.3	84.6–164.8	2.0–2.7
p	NS	NS	NS	NS

rr – reference range, SD – standard deviation, min–max – minimum – maximum, p – statistical significance between genders, NS – nonsignificant

In our study, lipoprotein (a) values were significantly higher in patients with haematological disease compared to patients with trauma (p = 0.032) (Tab. 5). There was no statistical difference between males and females in selected biochemical and coagulation parameters.

- LA/anticardiolipin antibodies – positive/increased in 4 patients (33.3 %). There was no statistically significant difference between males and females in this parameter.
- PAI-1 or genetic testing – increased/positive in 7 patients (58.33 %). There was no statistically significant difference between males and females in this parameter.
- The activity of vWF, protein C and S could not be evaluated by exact statistical methods because values with sign > (more than) were represented. It can only be noted that elevated vWF activity (rr 48–173 %) – as a laboratory risk parameter for CTEPH – was present in 6 patients (50 %). Decreased activity of protein C (rr 70–140 %) and protein S (rr 60–140 %) – as a parameter for thrombophilia – was present in 1 (8.33 %) and none of the patients (0 %), respectively.

Discussion

CTEPH is considered a rare generally underdiagnosed disease. Currently, the number of patients diagnosed with CTEPH increases due to more active screening for this disease in patients after PE. Registry data indicate CTEPH incidence and prevalence of 2–6 and 26–38 cases/million adults, respectively (3, 4). Research in Slovakia published in 2016 confirmed CTEPH prevalence of 18 cases/million adults, splenectomy occurred in 2.5 % of CTEPH patients (5). Based on the systematic review and meta-analysis, the pooled crude prevalence of splenectomy in CTEPH patients

Tab. 5. Lipoprotein (a) in patients with haematological disease and trauma.

	Lipoprotein (a) (rr up to 300 mg/l) – mean	p
Trauma	72.65	
Haematological disease	**144.94**	**0.032**

rr – reference range, p – statistical significance

was confirmed to be 4 %, the prevalence ranged from 2 % to 9 % (1). The association between splenectomy and development of CTEPH was confirmed by a recent analysis of epidemiological studies, which demonstrated up to an 18-fold higher risk for the development of CTEPH in post-splenectomy patients compared to the control group (6).

Splenectomized patients are at increased risk of cardiovascular events, but it remains unclear whether this is due to lack of the spleen or due to the underlying disease leading to splenectomy/cause of splenectomy. Danish study following post-splenectomy patients between 1996 and 2012 showed differences in the incidence of vascular complications – stroke, myocardial infarction, PH – depending on the cause of the splenectomy, both by comparison with the general population and by comparison with a population that had approximately the same risk profile as the post-splenectomy patients. The study suggested that splenectomy was associated with a higher risk of stroke regardless of the cause of the splenectomy (trauma, haematological disease, malignancy, etc.). In contrast, a higher incidence of myocardial infarction and PH was more related to the cause of the splenectomy than the splenectomy itself. The 5-year cumulative incidence of all types of PH was 0.4 %, indicating that the incidence of CTEPH was even lower (7).

Our results confirmed a significantly higher 5-year cumulative incidence of CTEPH in post-splenectomy patients, reaching 3.2 %. In addition, during the research, a patient in the diagnostic phase of CTEPH died (due to severe PH) and was not listed as a patient with confirmed CTEPH in the final dataset. This patient – 61-year-old man with confirmed thromboembolism (PE and DVT) was inadequately treated also due to his non-compliance. Thanks to our proactive approach, the patient was contacted and because of symptoms suspicious of CTEPH after PE, invited for a screening echocardiography. Echocardiography confirmed severe PH and ventilation/perfusion lung scan confirmed perfusion defects. Subsequently, anticoagulation therapy with VKA was initiated. The next step was planned according to our research design: after 3 months of effective anticoagulation reassessment of PH and complete examination including right heart catheterization in the National CTEPH Expert Centre. However, the patient died within this 3-month period. Our results, which confirm a higher incidence of CTEPH after splenectomy, were achieved thanks to active contacting of patients and performing echocardiography if signs of thromboembolism were present. This means that some patients had echocardiography performed repeatedly (10 patients, 16 %). The limitation of these results may be the smaller number of patients coming from one region (western Slovakia).

According to the results of the aforementioned Danish study, splenectomy was associated with a higher risk of stroke regardless of the cause of the splenectomy, but higher incidence of myocardial infarction and PH was more related to the cause of the splenectomy than the splenectomy itself (7). In our study, there was no statistically significant difference between men and women in the incidence of thromboembolism/CTEPH after splenectomy. We observed a statistically significant difference in the cause of splenectomy. Trauma was predominant in males and haematological and other causes of splenectomy in females. However, in our study, the cause of splenectomy did not affect the incidence of thromboembolism and CTEPH. This finding was supported by the fact that there was no statistically significant difference between genders in clinical risk factors, thrombophilic conditions and blood groups.

According to available data, the interval between splenectomy and the diagnosis of CTEPH ranges from 2 to 34 years (8). This was confirmed in our study. The interval between splenectomy and CTEPH in a female patient with haematologic disease was 8 years and in a male patient after trauma 3 years. Another data in the literature is that the incidence of thromboembolism after splenectomy (including DVT and PE) ranged of 12–29 % (9, 10). In our study, thromboembolism occurred in 14.5 % of patients, i.e. at the lower limit of the interval reported in the literature (14.5 % is a cumulative incidence during the 5-year follow-up). Our results, such as the relatively lower incidence of thromboembolism according to the available data on the one hand and the relatively higher incidence of CTEPH on the other hand, evoke the question whether splenectomy might be an independent risk factor for CTEPH. This reasoning is supported by the recently published Dodson study (2022), which suggests that it is the post-splenectomy condition that could be considered the strongest risk factor for CTEPH after PE (11). This is indirectly supported by other studies documenting how splenectomy changes the clinical presentation of CTEPH, one of which is a study comparing the incidence of splenectomy in patients with inoperable and operable CTEPH. The results suggest that splenectomy is associated with an increased risk of distal – inoperable form of CTEPH, which is associated with microangiopathy (12, 13). That is, splenectomy may be a risk factor for thromboembolism and also an independent risk factor for CTEPH. In our study, thromboembolism occurred in 9 patients (14.5 %) and 2 of them (22.22 %) developed CTEPH. Was it the post-splenectomy condition that caused such a high incidence of CTEPH in patients with thromboembolism? Further research is needed to confirm this hypothesis.

The epidemiological impact of splenectomy as a risk factor for CTEPH is given by the number of splenectomies per year. According to some data, the incidence of splenectomy is 64–71/million inhabitants/year (14). Another source reports a prevalence of splenectomy in a population with a mean age of 50 years of approximately 0.4 % (7). And according to other data, approximately 22 000 splenectomies are performed annually in the United States (15), which corresponds to an incidence of 71/million inhabitants/year (converted to the 2009 U.S. population). Using this data, there are approximately 355 splenectomies per million population over a 5-year period. Based on our results, the 5-year cumulative incidence of CTEPH after splenectomy was 3.2 %. This means that up to 11 new cases of CTEPH per million adults – more than 2 cases/million adults/year – can occur over a 5-year period related to splenectomy. Registry data indicate a CTEPH incidence of 2–6 cases/million adults (3, 4). Based on the above, the incidence of CTEPH after splenectomy may be more than 2 cases/million adults.

The results of baseline coagulation parameters in a subgroup of 24 patients provided data that may be an inspiration for haema-

tologists and a topic for discussion. D-dimer is a fibrin degradation product that is found in low concentrations in the peripheral blood under physiological conditions. Its presence is not specific for thromboembolism (it may be increased after surgery, in pregnant women, in malignancy and elderly patients, etc.). Despite the above, it is the recommended and most used laboratory test in thromboembolism (16, 17). In our study population, the mean value of D-dimer was 0.84 mg/l, demonstrating an increase in this parameter in post-splenectomy patients. The mean values of the other basic coagulation parameters were within the reference range. However, women had higher mean fibrinogen and platelet values, which may be related to the difference in the cause of splenectomy between the genders. However, in our study, the cause of splenectomy did not affect the incidence of thromboembolism and CTEPH. A surprising result was the higher mean INR values in patients with thromboembolism/CTEPH ($p = 0.039$). This outcome was not affected by anticoagulants for the following reason. We expected to find post-splenectomy patients who would be treated with VKAs because of previous thromboembolism. However, patients enrolled in the study had completed anticoagulation therapy (thromboembolism was considered as cured). If VKAs were indicated during the study, this did not affect the results because laboratory parameters were taken before anticoagulation was started. All INR values were within the reference range. That is, although the mean value was significantly higher in patients with thromboembolism/CTEPH, all individual values were within the reference range and did not differentiate the risk group in real clinical practice. Will there be a new cut-off value that reveals this risk group? This could be the key to elucidate the pathophysiology of haemocoagulation in post-splenectomy patients. Another finding in our follow-up was statistically higher lipoprotein (a) values in haematologic patients compared with patients after trauma. Although elevated lipoprotein (a) levels are considered a laboratory risk factor for CTEPH, its association with thromboembolism is still controversial (18). This controversy was confirmed by our study. Despite statistically significantly higher values in haematological patients, the cause of splenectomy did not affect the incidence of thromboembolism or CTEPH. And other data from our study, all patients with thromboembolism/CTEPH had a blood group other than "0". However, evaluation of all patients with an identified blood group (56 patients) did not confirm a statistically significant difference of blood group other than "0" in relation to thromboembolism/CTEPH. The above is contrary to the current findings (12). The limitation of our results may be the smaller number of patients. Except the mean INR value, no laboratory parameter differentiated patients with thromboembolism/CTEPH from others. However, the small number of patients in the subgroups is a major limitation of this claim.

Conclusion

The results of our study suppose a higher incidence of CTEPH after splenectomy compared with published data, the 5-year cumulative incidence was 3.2 %, more than 2 cases/million adults/year. The strongest factor influencing the incidence of thromboembolism and CTEPH in post-splenectomy patients was the presence of a thrombophilic condition detected before screening echocardiography. In terms of laboratory parameters, post-splenectomy patients had higher mean D-dimer values, but this parameter did not differentiate patients with thromboembolism/CTEPH from others. In our study the cause of splenectomy did not affect the incidence of thromboembolism/CTEPH. The only coagulation parameter that differentiated patients with thromboembolism/CTEPH from others was higher mean INR values.

Is splenectomy an independent risk factor for CTEPH?

Performing screening echocardiography after PE or in symptomatic patients is in the diagnostic algorithm of CTEPH. However, based on our research experience, patients with CTEPH and also their general practitioners did not attribute symptoms to this serious disease. And, in contrast, most patients in whom we did not confirm this disease reported dyspnea after exertion. Performing regular screening echocardiography at specified intervals regardless of symptoms may be a solution. In our study, abnormal screening echocardiography statistically significantly differentiated ($p = 0.001$) patients with thromboembolism/CTEPH from others. Elucidation of changes in the coagulation cascade in patients after splenectomy could provide new insights into the pathophysiology of CTEPH. In our opinion, collaboration between haematologist and cardiologist is essential, because thrombophilic condition detected before screening echocardiography had a statistically significant impact on the incidence of thromboembolism/CTEPH after splenectomy.

The results were achieved by prospective 5-year follow-up of patients after splenectomy and active search for patients with thromboembolism. Limitations of the research were the smaller number of patients, especially in the subgroups. Organisational aspects have also been affected by the waves of the pandemic COVID-19.

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