ORIGINAL ARTICLE

REX SHUNT IN CHILDREN: COULD DYSFUNCTION BE PROGNOSED? A RETROSPECTIVE ANALYSIS

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ABSTRACT

The aim: To analyze retrospectively our experience of Rex shunt in children with symptomatic portal hypertension, its effect on hypersplenism regression and varices eradication, assess shunt survival and investigate risk factors, that could lead to shunt dysfunction and thrombosis.

Materials and methods: 24 children (16 males, 8 females) ,with portal hypertension included into the study. All surgeries were performed within single center in a period from January 2010 to March 2022. Follow up period was 6.75±1.19 years.

Results: Age at diagnosis was 5.39±0.64 years. 5 (20.8%) had umbilical catheter in anamnesis. 16 (66.7%) manifested bleeding episodes as the first sign of portal hypertension. 9 (37.5%) of children manifested severe hypersplenism. Age at Rex shunting was 7.5±0.7 years. In 7 (31.8%) cases Rex shunt thrombosis occurred. 1 successful thrombectomy and 6 splenorenal shunting were performed. Kaplan-Meyer analysis showed Rex shunt survival 0.670 (95%CI 0.420-0.831). Logistic regression model indicated thrombocytes count (p=0.0423) and cytopenia (p=0.0272) as factors that could influence shunt thrombosis. Follow-up group included 18 patients. Spleen volume regression became significant by 1 p/o year p<0,05, thrombocytes significant increasement reached in 1 p/o months (p<0.01), varices involution was achieved by 1 p/o year (p<0,001).

Conclusions: Rex shunt effectiveness in study group was 70.9%., shunt survival assessed 0.670 (95%CI 0.420-0.831). Rex shunt was effective in bleeding prophylaxis in all patients of follow up group. Preoperative thrombocytes count (p=0.0423) and cytopenia (p=0.0272) were detected as factors that could influence shunt thrombosis, that is to be considered in RS preoperative period and require following studies.

KEY WORDS: Children, Portal Hypertension, Rex shunt, Shunt thrombosis, Extrahepatic portal vien obstruction

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INTRODUCTION

Current state methods of extrahepatic portal vein obstruction (EHPVO) surgical treatment in children are focused on two aims: to provide variceal bleedings prophylaxis and to restore the liver perfusion with splanchnic blood [1-4]. Since introduced first in 1992 for a posttransplant patient [5,6], Rex shunt (RS) restoring normal blood flow into the liver resolved at the same time secondary portal hypertension (PH) symptoms, such as recurrent bleedings and hypersplenism. However, it soon became clear that this surgery is feasible only in patients with favorable anatomy [7-9], a relatively small part of EHPVO pediatric patients. Not many authors dedicate their research to study the risk factors that could influence successful RS in pediatric patients [10,11], or factors that could affect shunt patency and therefore RS survival [4,12].

THE AIM

In this study we analyze retrospectively our experience of RS in EHPVO children with symptomatic PH, its effect on hypersplenism regression and varices eradication, assess RS survival and investigate risk factors, that could lead to shunt dysfunction and thrombosis.

MATERIALS AND METHODS

Patients' data was collected from case-records retrospectively. Out of 475 children, who underwent surgical treatment for symptomatic portal hypertension, in 24 RS was considered feasible. All surgeries were performed within single center in a period from January 2010 to March 2022. The follow up period was assessed by September 2022, median 6.75±1.19 years.

For all patients, the following criteria were analyzed: gender, age of disease debut, age at operation, basic symptoms and signs (bleeding episodes, thrombocytes count, spleen volume), complications, endoscopic examinations and procedures, the result of treatment, complications of treatment – shunt thrombosis occurrence.

Examination was as follows: CBC with thrombocytes count, thrombophilia panel, including protein C, protein

S, and antithrombin. Ultrasonography (US) in gray scale with spleen volume measurement (using the standard prolate ellipsoid formula: length × width × depth × 0.523), color Doppler, and spectral Doppler tracings, which were performed as initial screening to each patient and at later stages of treatment and follow-up. US was also used for initial IJV assessment (patency and diameter). Endoscopy was performed in all patients (n=24) to assess the grade of esophageal varices and gastric mucosa, and to perform variceal band ligation when necessary. Contrast-enhanced CT was performed to all patients before surgery with additional 3D-modeling in recent cases, and on the first postoperative day. Initial neurologist consult was performed at admission to all patients of the study group.

Surgical procedure was performed according to the technique for RS described by authors [6]: laparotomy, Rex-recessus revision. If left portal vein branch and its outflow were considered patent and satisfactory, intraoperation portography was performed to visualize its intrahepatic branches. After superior mesenteric vein (SMV) was accessed. When SMV was identified as patent, venous autograft was harvested. Previously detected as better graft, left or right internal jugular vein (IJV) is anastomosed with left portal vein branch. And then, being passed through mesocolon "window", to SMV. In four cases gastric vein (GV) was appropriate for its length and patency, and therefore used as a "graft", preserving the natural IJVs: GV was dissected, ligated and after interposition anastomosed with left portal vein branch. Portal system pressure was measured intraoperatively before and after performing RS, to assess its decreasement.

All patients received loading heparin dose of 5 units/kg in the moment of shunt forming and had continuous heparin infusion in maintenance dose of 10 units/kg/hour, to support the target ATTP level at 30 seconds and higher.

Data distributions were compared (for different surgical methods) using the paired Student's t-test or Wilcoxon criteria. The logistic regression model was built to identify factors that could influence the risk of shunt thrombosis. Kaplan-Meier estimator was used to assess shunt survival. Scheffe's method, Cruscal-Wallis multiple comparison and Dunn test were used to compare the follow-up results. Chi-square test was used to assess nonparametric data analysis for varices regression assessment. Statistical analysis was preformed using IBM SPSS for Windows version 24.0 (IBM Corp., Armonk, NY) and EZR (R-statistics). A *P*-value <0.05 was considered statistically significant.

The Committee on Clinical Investigation of Bogomolets National Medical University approved this study (Protocol №141 27.01.2021). All the studies were conducted according to implemented guidelines in consideration of GCP-ICH and Declaration of Helsinki [13]. The written informed consent of all participants' parents/guardians was achieved.

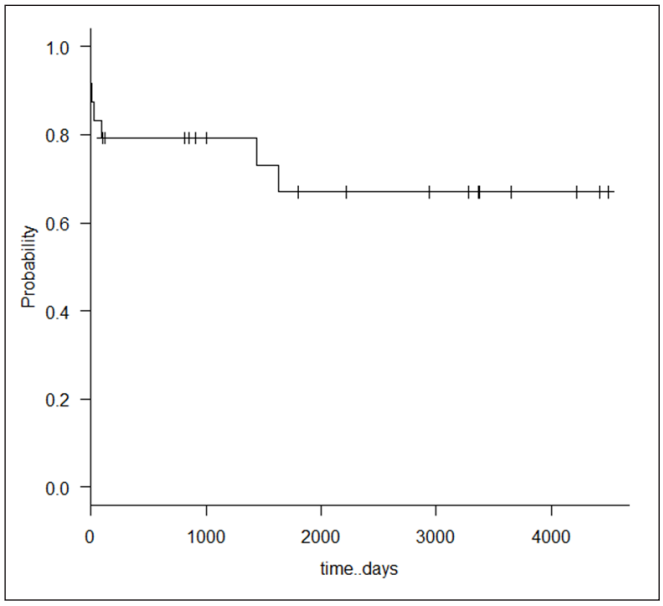

Fig. 1. Shunt survival (Kaplan-Meier curve) for RS (uniform line). RS survival 0.670 95%CI(0.420-0.831).

RESULTS

Patients' characteristics are summarized in Table I. Male predominance (16 males and 8 females) can be seen. Mean age at diagnosis was 5.39±0.64 years. 5 patients (20.8%) had umbilical catheter in anamnesis, in others EHPVO was considered as idiopathic. 3 children had surgeries in anamnesis: 1 - Sugiura procedure (complete portoazygos disconnection) for acute bleeding at the age of 1 y.o., 1 – Kasai procedure for biliary atresia at the age of 3 m.o., the same patient later underwent liver transplantation, 1- diagnostic laparotomy at the rural hospital. 16 (66.7%) patients manifested bleeding episodes as the first sign of PH, 5 of them were admitted with signs of acute bleeding. Others (n=8) were directed to examination for accidentally detected splenomegaly either anemia. According to Endoscopy data, only 1 of 24 patients had initial grade I esophageal varices. Other 23 had grade II – grade III varices (Figure 5-a). In 5 cases surgery was urgent. By the time of surgery all patients had splenomegaly with median spleen volume of 453 cm^3 (95%CI 353-503) and thrombocytopenia with mean thrombocytes count of 62.6±6.2. 9 (37.5%) of children developed severe hypersplenism, with cytopenia: leucocytes count less than $1.5 \cdot 10^9$/l, erythrocytes count less than $1.8 \cdot 10^{12}$/l,

Table I. Characteristics of study group patients

Characteristic	Total	Percent
Gender		
Male	16	66.7%
Female	8	33.3%
Aethiology		
Umbilical catheter	5	20.8%
Idiopathic	19	79.2%
Anamnesis at admission		
Previous surgeries	3	12.5%
Bleeding episodes	16	66.7%
Clinical presentation		
Splenomegaly	24	100%
Severe hypersplenism with cytopenia*	9	37.5%
….Isolated thrombocytopenia	2	8.3%
Isolated anemia without bleeding in anamnesis	3	12.5%
Ascites	2	8.3%
Esophageal varices at admission		
Grade I	1	4.1%
Grade II	6	25%
….Grade III	17	70.9%

* Leucocytes less than $1.5 \cdot 10^9$/l, erythrocytes less than $1.8 \cdot 10^{12}$/l regardless of acute or anamnestic bleeding episodes

Table II. Risk factors that were included into the logistic regression model of RS thrombosis risk

Risk factors	OR (95% CI)	p-value
Preoperative acute bleeding episode	0.107 (0.000342000 -33.50)	0.446
Bleeding episodes in anamnesis	3.4300 (0.14200000 - 82.50)	0.448
Learning curve	0.908 (0.69800000 - 1.18)	0.476
Umbilical catheter in anamnesis	2.550 (0.04430000 - 147.0)	0.65
Thrombocytes count	1.030000 (1.00000000 - 1.060)	0.0349
Preoperative portal system pressure	0.9840 (0.94800000 - 1.02)	0.387
Cytopenia[a]	141.000000 (1.63000000 - 12200.0)	0.0297

[a] Leucocytes less than $1.5 \cdot 10^9$/l, erythrocytes less than $1.8 \cdot 10^{12}$/l regardless of acute or anamnestic bleeding episodes

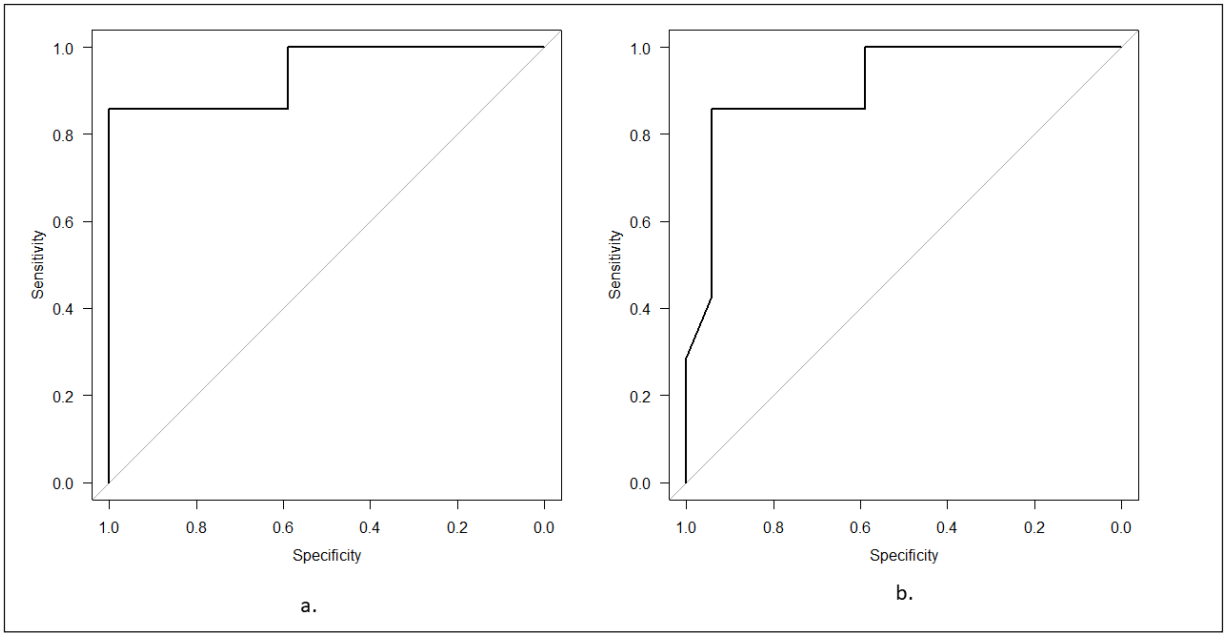

Fig. 2. a. ROC-curve of 7-factor logistic regression model of RS thrombosis occurrence risks. AUC= 0.941 (95% CI 0.821 – 1). b. Final 2-factors logistic regression model of RS thrombosis occurrence risks AUC= 0.912 (95% CI 0.78 – 1).

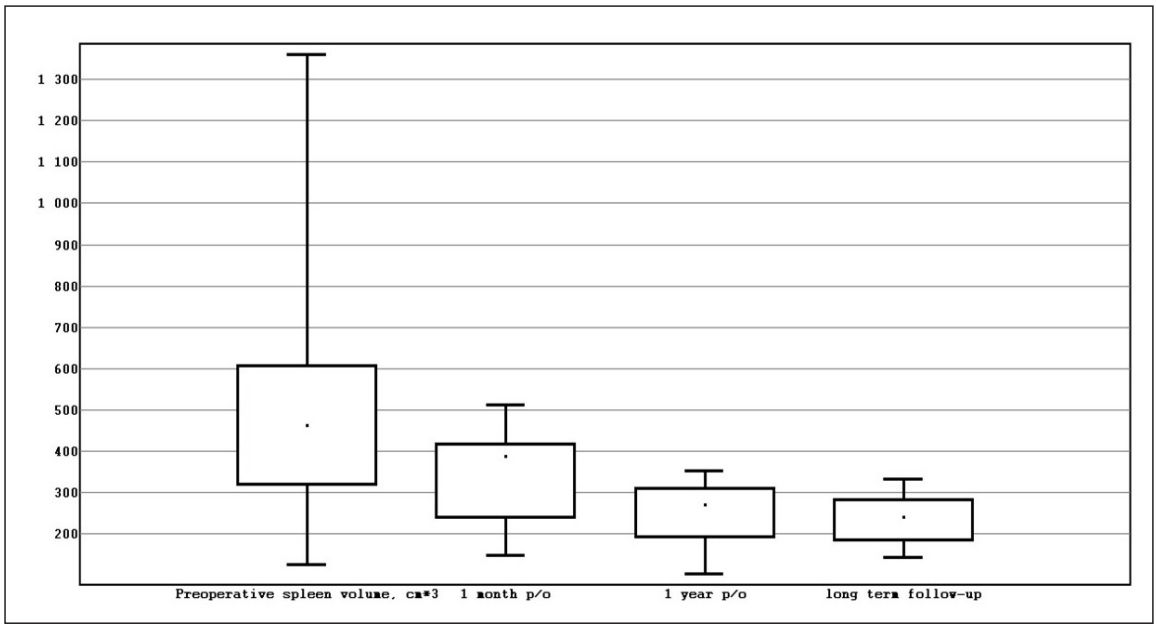

Fig. 3. Spleen volume regression graphic. Preoperative median volume was 453 cm^3 (95%CI 353-503), 1 month after MPS 388,5 cm^3 (95%CI 239,5-418,5), 1 year p/o 271,5 cm^3 (95%CI 191,5-310), and 242 cm^3 (95%CI 183-283,5) in long term follow-up.

regardless of current or previous acute bleeding in anamnesis. In 3 isolated anemia (hemoglobin level lower than 70 g/l) without registered bleeding episodes in anamnesis, and 2 had isolated thrombocytopenia with low but normal leucocytes and erythrocytes counts. In 5 (22.8%) patients acute variceal bleeding short-term conservative treatment by means of octreotide 2mg/kg/hour in continuous intravenous infusion and RBC transfusion at the rate of 5 ml/kg. 3 (12.5%) required urgent band ligation procedure.

Mean age at RS was 7.5±0.7 years. Median operation time for RS was 320 (95%CI 280-357) minutes, shorter in cases when GV interposition was used to redirect blood into the liver. No perioperative complications occurred. Median initial pressure in portal blood system was 347.5 mmHg (95%CI 320-360). After RS in both modifications portal blood system pressure was 212.5 mmHg, (95%CI 200-230)mmHg. T-Wilcoxon criteria showed significant decreasing ($p<0.001$).

In 7 (31.8%) cases shunt thrombosis occurred. Early thrombosis occurred in 3 cases. On the 1 p/o day in a patient in which later thrombophilia was confirmed: enhanced CT chowed the absence of the blood flow in the shunt. Relaparotomy was performed, the graft was found filled with thrombotic masses for all its length, graft patency was impaired, and therefore blockage of vessel anastomosis was recognized, and venous graft war removed. Splenorenal shunting was performed. On the p/o day 2, confirmed by repeated Doppler US and CT. In this patient thrombectomy was successfully performed with following uneventful postoperative course. The absence of blood flow in the shunt was revealed on p/o day 6 by repeated Doppler US and following CT in the third patient with early RS thrombosis. 1 patient manifested ascites on p/o day 27. The rest 3 patients in which shunt thrombosis occurred in p/o months 3, 48, and 68 correspondingly, manifested bleeding episodes. All had developed portal hypertension symptoms, such as high-grade varices, splenomegaly, and thrombocytopenia recurrence. Splenorenal shunting was performed in latter four described cases.

Kaplan-Meyer survival analysis was performed to estimate RS survival. Median overall shunt survival was not reached by the patients of the study group (Fig 1).

For multifactorial analysis logistic regression model was constructed (Figure 2a) to identify factors that could prognose the risk of RS thrombosis. Factors investigated are represented in Table II.

Stepwise method revealed two factors were revealed that are connected to RS thrombosis risks: "Thrombocytes count" and "cytopenia". Based on these two factors logistic prognosing model was constructed (Figure 2b).

Follow-up group included 18 patients, 17, whose postoperative course and follow-up were not complicated and 1, who successfully underwent thrombectomy and reshunting. No recurrent bleeding episodes were registered. All patients were seen first one month after surgery to undergo a Doppler US and CBC with Thrombocytes count. Later laboratory tests and Doppler US took place once in two months, and from half a year after surgery – once in 6 months, from a second year after surgery – once a year. First Endoscopy was performed in 6 months after surgery, later – in every annual follow-up visit. 6 (33.3%) patients of the follow

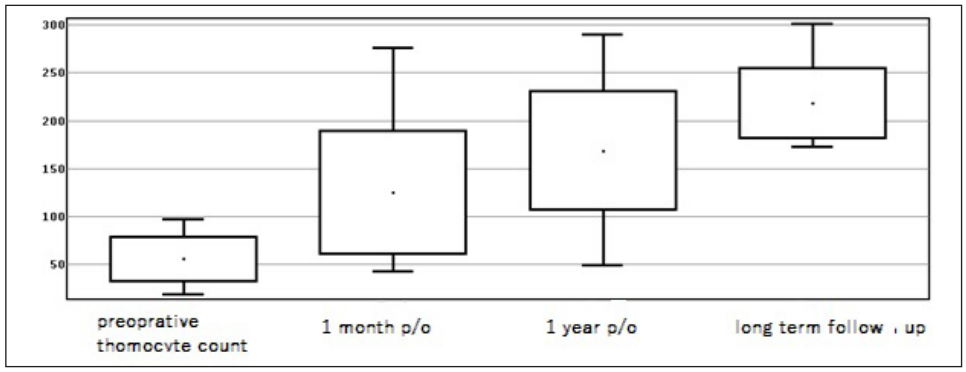

Fig. 4. Evolution of thrombocytes. Initial preoperative mean thrombocytes count was 55.4±5.8, 1 month after MPS 125.1±16.11, 1 year p/o 168.6±15.63, and 218±9.24 in long term follow-up.

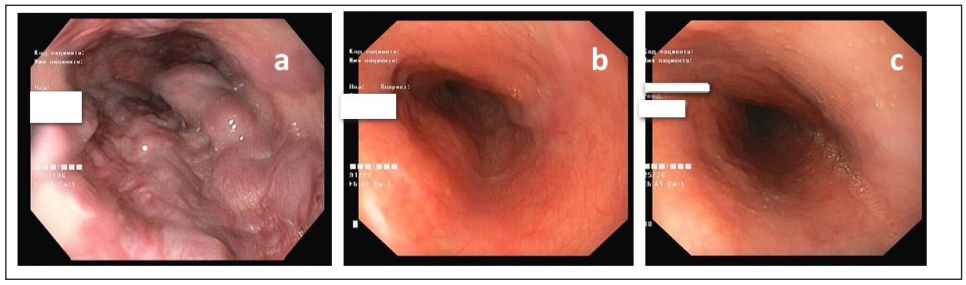

Fig. 5. Endoscopic appearance of the same patient within the course of treatment and follow up.
a. Preoperative endoscopic appearance - varices grade 3.
b. 1 year p/o – varices grade 1.
c. long term follow-up - varices grade 0.

up group reached age over 18 years by the end of assessed follow-up period. One of adult patients was at 18 weeks pregnant by the moment of study completion, the course of pregnancy was uneventful.

Dunn's teat was used for multiple-comparison procedure of spleen volume regression assessment. Spleen volume regression was not significant by the first p/o month $p>0,05$, became significant by 1 p/o year $p<0,05$, and in long term follow-up $p<0,001$ (Fig 3).

Preoperatively all patients manifested thrombocytopenia. Thrombocytes count was analyzed by means of Sheffe's multiple analysis test, that showed thrombocytes significant increasement in 1 months, 1 year and in long term follow-up after RS ($p<0.01$ in all cases). In long term follow up Thrombocytes count normalized in all patients. Results are represented on Fig 4.

Before RS 17(70.9%) patients had grade 3 varices, and 6(25%) – grade 2 varices. Two of them underwent preoperative varices band ligation procedure preoperatively. Endoscopy was repeated 1 year after RS and revealed grade 1 varices in 8 (50%) patients, and grade 2 in all other children of the group. In long term follow-up 6(37.5%) patients had grade 0, 9(56.3%) patients had grade 1, and 1(6.2%) patient had longstanding varices grade 2, that required 2 procedures of endoscopic ligation. Two patients of the follow up group have not reached the long-term period yet. Chi-square test was used to analyze varices involution and revealed the difference $p<0,001$. Endoscopic appearance is represented on Figure 5. It represents initial preoperative endoscopic appearance (Figure 5a), varices eradication to safe grade 1 (Figure 5b) which followed in one year after RS, and total eradication in long-term follow-up, which was 2.5 years for this specific patient on the represented image (Figure 5c).

DISCUSSION

Despite endoscopic bend ligation success in variceal bleeding primary prophylaxis [14-16], all portal hypertension symptoms, such as hypersplenism, cytopenia, encephalopathy, and growth impairment, only surgical treatment, and RS particularly, can resolve [2,3,17,18]

Some authors name RS and "ideal", the only physiological shunt, which provides the liver perfusion restoration, contemporaneously eliminating all portal hypertension signs [2, 3, 12, 16, 19]. Since the very first publication in virtue of further research RS was considered a "golden standard" for treatment of children with EHPVO [20], however noting patients should have favoravle anatomy. Some authors emphasize RS is to be performed in asymptomatic patients who were already diagnosed EHPVO and in which visualization showed intrahepatic portal vein branches patency [1, 2, 7, 21, 22]. Other authors [4, 23] advice to perform RS in patients with high grade varices and bleeding risks, considering this surgical procedure the best bleeding prophylaxis method. Planned RS would provide the physiological development in a child with restored portal blood flow against the background of pathologic portal hypertension symptoms. Moreover, some authors mention encephalopathy resolution [4, 22, 24], growth acceleration [19], hepatopulmonary syndrome recovery, and vanishing of adenomas and focal nodular hyperplasia of the liver tissue [4,7] in patients who underwent RS. In a study where children with EHPVO

who were treated by means of RS it is mentioned that RS is effective in physical development improvement and optimizing of liver metabolic function [19, 24].

All patients from the study group were initially consulted by the neurologist. Encephalopathy was registered in none, therefore was not followed further. Growth impairment was not significant among children of the study group, and was not the purpose of our study, therefore, not assessed within it.

5 (20,8%) children of our group were admitted with acute bleeding as the first sign of PH. All were considered healthy before this initial hospitalization. We consider unique compensatory reserve of child's organism, absence of regular physical examination culture, and low awareness of primary care pediatricians to be the key causes of late EHPVO with symptomatic PH identification. Surgical treatment postponement since the settled diagnosis, that was 1.5 years (3 months – 15 years) in the children of our study group was determined by young age and initial visualization results, that were considered as not appropriate for any type of shunting (n=3).

We consider variceal band ligation to be effective as a primary bleeding prophylaxis, as it is already mentioned in our earlier publications [14,15]. Band ligation is widely used in our clinic since 2017, therefore all patients treated before 2017, which were included into the study group, were prescribed either conservative therapy, or urgent surgery when admitted with acute bleeding.

It was already shown in early studies that US shows signs of patency of Rex-zone only in 63% patients [25]. In the last two decades CT improved intrahepatic portal branches visualization significantly, however authors mention that in patients with large cavernoma CT or MRI results are not reliable sometimes, as hypodynamic circulation of intrahepatic portal branches and Rex-zone is visualized [9,20]. Bambini D.A. et al [8] in his study mentioned, that in a part of patients of his group, whose visualization results showed no patency in Rex-zone, RS was eventually feasible. Other authors consider direct intraoperative visualization to be the best way to detect left portal branch patency [8, 9]. We used all the mentioned techniques in patients of our study group.

RS with IJV allograft surgical technique corresponded to one published by De Ville De Goyet et al. in the beginning of 1990th [1, 6] and further detailed descriptions [21,23]. Except this technique, it was also proposed to reconnect left intrahepatic portal branch with splanchnic blood communicants by means of large saphenous graft [12, 26], or by means of gastric, spleen, inferior mesenteric vein grafts, or large cavernoma branch interposition [1, 27].

In our study group it was possible to perform RS with GV interposition in four cases, which allowed to preserve patients natural IJVs. 1 out of 7 thrombosis occurred among these patients.

The initial idea of multifactorial analysis logistic regression model construction was to prove umbilical catheter in anamnesis is not the factor that could influence the risk of mesoportal shunt thrombosis in children of our study group. Some authors mention umbilical catheter as unfavorable factor for following RS success [23], or even state it as a contradiction [4]. We had 5(20.8%) patients with umbilical catheter in anamnesis in our group, only one of them developed shunt thrombosis, the only child in which thrombophilia was confirmed. Other study revealed anticoagulation therapy regimen and blood transfusion as factors that could influence the risk of mesoportal shunt thrombosis [10]. As all the patients from study group received the same anticoagulation therapy, this factor was not included into the model. In other study [12] authors detected low body mass study and preoperative thrombocytes count as factors which could influence mesoportal shunt thrombosis occurrence. Bleeding episodes in anamnesis (p=0.448) either acute bleeding within a week in preoperative period (p=0.446) showed no significance as RS thrombosis risk factors. It is well known RS is a procedure for a surgeon of expertise, considering the fact all surgeries were performed by one team, it was suggested the learning curve could matter, but it didn't either (p=0.476). According to multivariant analysis in our study preoperative thrombocytes count (p=0.0349) and cytopenia (p=0.0297) were identified as risk factors for RS thrombosis development, which should be, to our thought, considered in the preoperative period. We have not assessed growth impairment; therefore, the body mass was not included into factors investigated.

Chin A.C. showed previous portal hypertension surgeries have deleterious effects on RS results [11]. Three of patients from our group had previous surgeries, and all three had uneventful postoperative RS course.

According to literature, shunt occlusion occurs in 1.6-16.4% cases [3] and was not observed in patients of our group. In his study Zhang Z. showed that according to currently published studies shunt thrombosis occurs in 8-40% of described groups [3]. There were 7 episodes of RS thrombosis registered in our group, which is 29.1%. Therefore, RS effectiveness in our group is, 70.9%, with RS survival assessed as 0.670.

The main role in RS thrombosis detection belongs to CT [20]. Enhance CT was performed in all children with RS thrombosis to confirm the diagnosis.

Discussing the surgical tactics in cases of RS thrombosis, Zhang, J.-S. Et al. in their study showed splenorenal shunting was a better treatment after bypass failure,

with faster recovery and symptoms relief than those who underwent re-shunting [27]. At the same time, it must be mentioned that children of their group developed RS thrombosis in long-term follow-up period with bleeding episodes in most cases. In our group successful RS reshunting was performed on the second postoperative day, and this patient was included into follow-up group according to his following uneventful postoperative period. All the other children with RS failure underwent splenorenal shunting, that corresponds to the results presented in the mentioned study.

Most authors show in their studies thrombocytes count restoration and significant decreasement or normalization of spleen volume within 6-12 months after RS. [1,8,10,12]. In our study thrombocytes count significantly increased by the first postoperative year, together with spleen size and volume significant decrease, that correlates with data provided in literature sources.

CONCLUSIONS

RS is a golden standard surgical treatment of children with symptomatic PH caused by EHPVO, that restores the splanchnic blood flow into the liver and resolves portal hypertension symptoms, such as, esophageal varices with bleeding episodes, splenomegaly, and hypersplenism. Different surgical techniques that are used to perform RS provide wider arsenal of possibilities to restore the splanchnic blood flow into the liver in children with PH. RS effectiveness in the study group was 70.9%. RS gave excellent result in thrombocytes count increase, varices eradication, and normalization of spleen volume, therefore was effective in bleeding prophylaxis. RS thrombosis occurred in 7 (29.1%) cases. Preoperative thrombocytes count (p=0.0423) and cytopenia (p=0.0272) were detected as factors that could influence shunt thrombosis, that is to be considered in RS preoperative period and require following studies .

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