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Extrahepatic Portal Vein Thrombosis in Childhood: Risk Factors, Clinical Manifestations, and Management

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Highlights of the Study

- Extrahepatic portal vein thrombosis is a common cause of portal hypertension in the pediatric population.
- This study revealed some of the clinical manifestations and the main risk factors for development of extrahepatic portal vein thrombosis in children, highlighting the role of the inherited thrombophilia as a predisposing factor.
- Some of the treatment and prophylactic strategies are also discussed.

Keywords
Extrahepatic portal vein thrombosis · Risk factors · Manifestations

Abstract
Objective: Extrahepatic portal vein thrombosis (EHPVT) is a common cause of portal hypertension in children. The aim of the present study was to identify the clinical manifestations and the risk factors for development of EHPVT in pediatric patients. ***Subjects and Methods:*** This was a single-center retrospective cohort study. A total of 12 children (6 boys and 6 girls) took part in the study. We noted the clinical presentations and the predisposing risk factors for development of EHPVT in all patients. In addition, as all of them had undergone an esophagogastroduodenoscopy for detection and grading of esophageal varices as part of the treatment algorithm, we analyzed the endoscopic findings and the therapeutic approach. ***Results:*** The median age of subjects at diagnosis was 3.5 years (range: 1–17 years). The most frequent initial clinical manifestation was upper gastrointestinal bleeding (6 cases, 50.0%) followed by splenomegaly (3 cases, 25.0%). The most frequent systemic risk factor for EHPVT was presence of inherited prothrombotic disorder (10 cases, 83.3%), and the most common local risk factor for EHPVT was umbilical vein catheterization (5 cases, 41.7%).

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Esophageal varices were revealed in all the study participants, and in the most cases, they were grade ≥2. Propranolol was used as primary or secondary prophylaxis in 7 children (58.3%), and in 5 children (41.7%), a shunt was performed (Meso-Rex bypass in 3 children and splenorenal shunt in 2 children). ***Conclusion:*** Patients with known systemic or local risk factors for EHPVT are indicated for proactive ultrasound screening for early diagnosis and timely management.

Introduction

Portal vein thrombosis (PVT) is a rare condition with an estimated incidence of 1.3/100,000 live births and 36/1,000 neonatal intensive care unit (NICU) admissions [1]. It can occur in the intrahepatic or extrahepatic portal venous tract and can involve the superior mesenteric vein, the splenic vein, or both [2]. Although rare in the pediatric population, extrahepatic PVT (EHPVT) represents an important clinical problem, as it is one of the most common causes of portal hypertension (PH) among children [3–5]. The clinical presentation is quite heterogeneous and can vary from asymptomatic patients incidentally diagnosed to patients with severe complications [2, 6]. As a rule, initial thrombus formation is asymptomatic due to compensatory mechanisms [3]. However, PH persists and with time becomes a symptomatic disease [1]. Based on the literature, upper gastrointestinal bleeding (UGIB) is a common manifestation of PH associated with EHPVT [5]. Other identified clinical presentations are growth retardation, splenomegaly, hypersplenism, cholangiopathy, ascites, hepatopulmonary syndrome, and portopulmonary hypertension [3, 7].

The etiology of EHPVT is multifactorial. Different local events or systemic prothrombotic conditions could be involved, and often more than one predisposing factor is involved [3–5, 8]. The main identified local cause for EHPVT in children is neonatal umbilical vein catheterization (UVC), ranging from 20% in low-income countries to 60% in developing countries [5]. Other important local triggers are transfusion through the UVC, infections (omphalitis or pylephlebitis), abdominal trauma, abdominal surgery, and congenital malformations of the vascular system [1, 3–5, 7]. Among the systemic prothrombotic factors that predispose to venous thrombosis are thrombophilia, sepsis, and dehydration [5]. Some perinatal events such as prematurity, low birth weight, hypoxia, maternal preeclampsia, and gestational diabetes have also been defined as risk factors in terms of the development of thrombosis [9, 10]. The aim of the present study was to identify the clinical manifestations and risk factors for development of EHPVT in pediatric patients in a tertiary university hospital.

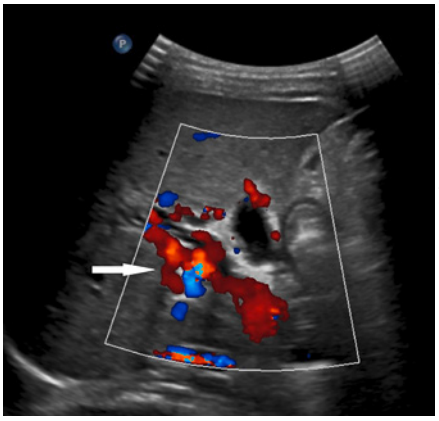


Fig. 1. Color Doppler ultrasound showing multiple serpiginous vessels in the periportal region, indicative of cavernous transformation.

Subjects and Methods

Study Design and Study Population

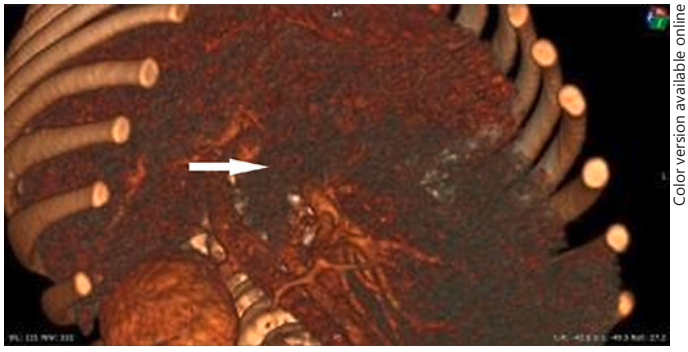
This is a single-center retrospective observational cohort study. We reviewed the medical records of all patients with EHPVT treated at the Department of Pediatrics of University Hospital "Saint George," Plovdiv, during January 2015–March 2020. Diagnosis in all patients had been established by Doppler ultrasound and confirmed by computed tomography angiography (Fig. 1, 2). Children with other causes of PH, incomplete data, or those lost to follow-up were excluded from the study. We noted the clinical presentations and analyzed the presence of predisposing factors for development of EHPVT. We evaluated the historical data considering the following risk factors: prematurity, low birth weight, admission at NICU, neonatal UVC, blood transfusion through UVC, omphalitis, pylephlebitis, sepsis, gastroenteritis, dehydration, family history of thrombophilia, and presence of inherited prothrombotic disorders.

In addition, as all of the study participants had undergone an esophagogastroduodenoscopy for detection and grading of esophageal varices as part of the treatment algorithm, we analyzed the endoscopic findings and the therapeutic approach. Esophageal varices had been classified according to the Dagradi classification [11] in five grades: grade I – linear varices <2 mm, reddish/blue, not raised on moderate insufflation, can be revealed by applying pressure with the endoscope; grade II – blue, 2–3 mm, slightly tortuous, raised above the surface of the esophagus on moderate insufflation, sometimes also visible in the form of an "anterior sentinel vein"; grade III – prominently elevated bluish veins, 3–4 mm, straight or tortuous, isolated distribution in the esophageal wall,

Table 1. Demographic, clinical, and laboratory characteristics of the study participants at diagnosis

	All ($N = 12$)	Boys ($N = 6$)	Girls ($N = 6$)
Age at diagnosis, mean±SD, years	5.6±5.1	5.3±6.3	6.0±4.4
History of admission at NICU, *n* (%)			
No	5 (41.67)	3 (50.0)	2 (33.33)
Yes	7 (58.33)	3 (50.0)	4 (66.67)
Abnormal findings in physical examination, *n* (%)	12 (100)	6 (50.0)	6 (50.0)
Splenomegaly	12 (100)	6 (50)	6 (50.0)
Skin pallor	4 (33.3)	1 (8.3)	3 (25.0)
Visible collateral circulation	1 (8.3)	1 (8.3)	0
Growth failure	1 (8.3)	1 (8.3)	0
Underweight	1 (8.3)	1 (8.3)	0
ALT, mean±SD, U/L	32.7±11.7	29.0±12.3	36.0±11.9
AST, mean±SD, U/L	20.6±8.7	14.1±4.2	26.6±6.8
GGT, mean±SD, U/L	20.8±15.2	27.6±15.8	14.0±12.6
ALP, mean±SD, U/L	207.3±29.9	196.0±94.8	218.6±57.6
Bilirubin total, mean±SD, mmol/L	16.1±10.1	16.3±3.0	16.1±6.5
Bilirubin direct, mean±SD, mmol/L	4.7±2.1	6.1±5.4	4.6±3.4
Albumin, mean±SD, g/L	42.2±2.3	45.1±22.8	43.0±11.4
INR	1.45±0.5	1.25±0.5	1.73±0.6
White blood cells, mean±SD, /mm^3	3.6±1.8	2.8±0.5	4.3±1.2
Hb, mean±SD, g/L	83.6±22.2	82.6±37.4	84.6±30.2
Platelets, mean±SD, /mm^3	100.3±54.2	89.2±21.2	111.6±31.4

SD, standard deviation; NICU, neonatal intensive care unit; ALT, alanine transaminase; AST, aspartate transaminase; GGT, gamma-glutamyl transferase; ALP, alkaline phosphatase; INR, international normalized ratio; Hb, hemoglobin.



Color version available online

Fig. 2. Computed tomography angiography demonstrating multiple vascular structures in the periportal region, which enhance during the venous phase and not during the arterial phase.

"good mucosal coverage"; grade IV – >4 mm, circular extension around the esophageal wall; varices almost meet in the middle of the lumen, with or without "good mucosal coverage"; grade V – racemose varices occluding the lumen, particularly marked with cherry red spots or varices on varices ("cherry red varices"). Gastric varices had been classified according to the sarin's classification [12] in gastro-esophageal varices type 1: esophageal varices spreading into the lesser curvature of the stomach; gastro-esophageal varices type 2: esophageal varices spreading into the greater curvature of the stomach; isolated gastric varices type 1: varices in the gastric fundus and cardia without esophageal varices; isolated gastric varices type 2: varices outside of cardio-fundal region or first part of duodenum.

Statistical Analysis

Statistical analyses used in this study were of a descriptive type. Categorical variables were described using numbers (*n*) and proportions (%). Continuous variables were described using means and standard deviation (SD) if they were normal in type or using medians and ranges if normality was not respected.

Results

A total of 12 children (6 boys and 6 girls) with EHPVT took part in the study. The median age at diagnosis was 3.5 years (range: 1–17 years). All baseline characteristics of the study participants are presented in Table 1. The most frequent initial presenting symptom of the disease was UGIB followed by splenomegaly. Table 2 presents the reasons for which our patients were referred to our center. All clinical manifestations of EHPVT observed in the study cohort are summarized in Table 3.

Table 2. Reasons for which our patients sought medical help or were referred to our center for further investigations

Clinical manifestation	Patients, *n* (%)
UGIB	6 (50.0)
Splenomegaly	3 (25.0)
Occasional finding	2 (16.7)
Thrombocytopenia	1 (8.3)

EHPVT, extrahepatic portal vein thrombosis; UGIB, upper gastrointestinal bleeding.

Table 3. Clinical manifestations of EHPVT in the study cohort

Clinical manifestation	Patients, *n* (%)
UGIB	6 (50.0)
One episode	4 (33.3)
More than one episode	2 (16.7)
Splenomegaly	12 (100.0)
Hypersplenism	7 (58.3)
Anemia	4 (33.3)
Thrombocytopenia	3 (25.0)
Growth failure	1 (8.3)
Underweight	1 (8.3)
Caput medusae	1 (8.3)

EHPVT, extrahepatic portal vein thrombosis; UGIB, upper gastrointestinal bleeding.

Table 4. Prevalence of risk factors for EHPVT in the study cohort

Risk factor	Patients, *n* (%)
Prematurity	6 (50.0)
Low birth weight	4 (33.3)
UVC	5 (41.7)
Omphalitis	1 (8.3)
Abdominal surgery	2 (16.7)
Sepsis	1 (8.3)
Inherited thrombophilia	10 (83.3)

EHPVT, extrahepatic portal vein thrombosis; UVC, umbilical vein catheterization.

Table 5. Distribution of type and prevalence of mutations in the study cohort

Mutation	Patients, *n* (%)
MTHFR C677T polymorphism	5 (41.7)
PAI-1 4 G/5 G polymorphism	3 (25.0)
PAI-1 4 G/4 G polymorphism	2 (16.7)
Factor V Leiden mutation (R506Q)	3 (25.0)
Antithrombin III deficiency	1 (8.3)
Protein C deficiency	1 (8.3)

MTHFR, methylenetetrahydrofolate reductase; PAI-1, plasminogen activator inhibitor type 1.

A history of risk factors was found in all of the study participants, and the majority of them had more than one predisposing factor. Two children (16.7%) had 2 risk factors, and 5 children (41.7%) had 3 risk factors. The most frequent risk factor, identified in 83.3% of the cases, was presence of an inherited prothrombotic disorder. The rest of the observed risk factors associated with development of EHPVT are presented in Table 4. Types and prevalence of the genetic mutations for thrombophilia are summarized in Table 5.

At the initial esophagogastroduodenoscopy, esophageal varices were detected in all of our patients. Two of them had grade I, 2 patients had grade II, 7 patients had grade III, and 1 patient had grade IV. Gastric varices were established in four of the study participants (gastro-esophageal varices type 1 in 2 children and gastro-esophageal varices type 2 in 2 children). Most episodes of acute UGIB were successfully treated with octreotide infusion (3 initial episodes and 9 rebleeding episodes). A Sengstaken-Blakemore tube was used in 3 cases. Propranolol was used as primary or secondary prophylaxis in 7 children (58.3%). PH improved in most of them; 2 children had an insufficient response; thus, surgical treatment was necessary. 5 patients (41.7%) received a shunting procedure (3 children received a Meso-Rex bypass, and 2 children received a splenorenal shunt). In 2 patients, the surgical treatment was due to refractory variceal bleeding and in three of them due to hypersplenism. Intraoperative splenectomy was performed in 2 patients. At follow-up, 1 patient developed a total stenosis of the shunt and needed a re-operation. The remaining 4 cases were without complications. Anticoagulation therapy was administered to none of the study participants. The median follow-up of our patients was 43.5 months (range: 7–76 months). Their clinical and the laboratory characteristics at last follow-up visit prior to the study enrolment are summarized in Table 6.

Table 6. Clinical and laboratory characteristics of the study participants at last follow-up visit prior to study enrolment

	All patients (n = 12)	Patients without therapy (n = 2)	Patients on propranolol prophylaxis (n = 5)	Patients after shunting procedure (n = 5)
Follow-up, mean ± SD, months	39.9±18.6	45.0±43.8	34.8±17.8	43.0±9.9
Abnormal findings in physical examination, n (%)	5 (41.6)	2 (100.0)	3 (60.0)	0
Splenomegaly	5 (41.6)	2 (100.0)	3 (60.0)	0
Skin pallor	0	0	0	0
Visible collateral circulation	0	0	0	0
Growth failure	0	0	0	0
Underweight	0	0	0	0
ALT, mean ± SD, U/L	27.2±5.3	32.5±0.7	28.2±4.7	24.2±5.2
AST, mean ± SD, U/L	35.7±8.6	40.8±1.5	38.8±5.6	30.6±10.6
GGT, mean ± SD, U/L	31.7±10.6	32.0±5.6	28.6±10.9	34.8±12.6
ALP, mean ± SD, U/L	165.0±59.5	166.5±38.9	151.6±73.5	178.0±59.3
Bili total, mean ± SD, mmol/L	15.3±2.3	17.1±3.3	14.5±3.2	15.6±2.6
Bili direct, mean ± SD, mmol/L	3.8±1.8	5.1±1.9	3.6±1.4	3.6±2.2
Alb, mean ± SD, g/L	40.6±4.0	39.0±4.2	41.2±4.6	40.6±4.2
INR	1.1±0.2	1.0±0.1	1.1±0.2	1.2±0.3
WBC, mean ± SD, /mm^3	6.1±2.2	6.2±0.1	5.1±2.2	6.9±2.6
Hb, mean ± SD, g/L	124.7±22.4	151.5±31.8	112.0±9.5	126.6±21.6
Platelets, mean ± SD, /mm^3	203.7±93.9	181.0±11.3	122.8±15.8	293.6±73.9

SD, standard deviation; ALT, alanine transaminase; AST, aspartate transaminase; GGT, gamma-glutamyl transferase; ALP, alkaline phosphatase; Bili, bilirubin; Alb, albumin; INR, international normalized ratio; WBC, white blood cell; Hb, hemoglobin.

Discussion

EHPVT is one of the most common causes of nonliver disease-related PH in childhood [3, 5]. In this study, we described some of the clinical manifestations and the main risk factors for development of EHPVT in a small cohort of Bulgarian pediatric patients. Similar to Ferri et al. [4] and Grama et al. [5], we identified UGIB and splenomegaly as the most frequent initial clinical manifestations of PH due to EHPVT. In contrast, Abd El-Hamid et al. [13] and Weiss et al. [14] reported a greater proportion of patients with splenomegaly as an initial finding. In two of our patients, the disorder was occasionally diagnosed during routine exam, which is also in line with the literature [4].

Most cases of pediatric EHPVT occur in the neonatal period and are initially asymptomatic [1, 10, 15]. In part of the cases, the thrombosis is spontaneously completely reversible [1, 15, 16]. In the rest of them, it persists and despite the formation of a collateral network some of the patients develop a PH of varying grades within the time [1, 3, 7]. Most of the cases of PH associated with EHPVT in childhood are diagnosed several years after the initial thrombotic event, when the PH becomes symptomatic [1]. The age at diagnosis varies in different studies. The median age at diagnosis of our participants was 3.5 years (range: 1–17 years). In contrast, Ferri et al. [4] reported a lower median age at diagnosis (2.6 years, IR 1–5.5), and according to Khodayar-Pardo et al. [7], the age at diagnosis of the pediatric cases of PH due to EHPVT is significantly higher (10–14 years).

The etiology of EHPVT in children is considered multifactorial [4, 10]. Different factors that comprise the so-called Virchow's triad (hypercoagulability, endothelial dysfunction, and stasis) predispose to its development [2, 6]. However, according to the literature the etiology is not identifiable in about 50% of cases of childhood EHPVT [1, 4, 10]. Contrary to these data, we detected a risk factor for development of EHPVT in all our patients. Furthermore, in most cases we found a combination of systemic prothrombotic factor and a local prothrombotic trigger, which is in line with previous observations [3–5, 17]. We identified the presence of an inherited prothrombotic disorder as the most frequent systemic risk factor for development of EHPVT in our cohort. These data are in agreement with reports by Grama et al. [5] who identified mutations for thrombophilia in 91.67% of tested children with EHPVT. Most of the existing studies of EHPVT in the pediatric population did not screen their participants for thrombophilia, which is a potential explanation of the

reported lower rate of identified potential etiological factors. Furthermore, Pietrobattista et al. [18] suggested that children with PVT should be screened for inherited prothrombotic disorders regardless of a history of an obvious local risk factor. Other systemic predisposing factors established in our cohort were prematurity, low birth weight, and neonatal sepsis.

Previous studies revealed UVC as the most common local risk factor for development of EHPVT in children with a frequency varying from 36.4% to 73.02%, depending on sample size and study design [1, 4, 5]. Our data are in agreement with these findings, as we found a history of UVC in 41.7% of our patients. Generally, UVC predisposes the development of EHPVT due to the local vein injury. However, there are many additional catheter-related (size of the catheter, duration of catheterization, blood transfusion through the catheter, etc.) and patient-related (dehydration, presence of prothrombotic disorder, gestational diabetes, etc.) variables that affect the process [10]. In our cohort, all children with EHPVT and a history of UVC had at least one more additional risk factor for thrombosis.

According to the literature, approximately 79% of children diagnosed with PVT will have at least one episode of UGIB in their lifetime [19]. In this study, the initial esophagogastroduodenoscopy revealed esophageal varices in all study participants, which is in line with previous observations [4]. As the development of PH and varices is a time-dependent phenomenon, timely disease diagnosis and appropriate management are crucial for the favorable outcome [3]. However, considering the controversial data regarding the use of anticoagulation in PVT and the lack of evidence-based guidelines the main treatment goal is to avoid long-term complications such as PH and UGIB [15]. Unfortunately, there is no universal approach how to achieve this goal. A consensus or position paper about the management of PH and prevention of UGIB in children is also not available. The current recommendations are based on expert opinions, case series, or are extrapolations of treatment in adults [3–5, 7]. There are medical, endoscopic, and surgical therapeutic measures. Generally, the treatment approach depends on the patient's age, as some endoscopic procedures are not feasible in infants, and on the capabilities of each center [5, 7]. We did not perform sclerotherapy or endoscopic band ligation due to technical reasons. More than half of our patients (58.3%) received propranolol as primary or secondary prophylaxis, and a shunt operation was performed in 41.7% of the patients, which is not in conflict with the available treatment recommendations in the pediatric population [1, 3–5, 7, 8]. Although the use of beta-blockers for primary prophylaxis in children is controversial and the evidence regarding its administration for secondary prophylaxis is sparce, it is the first-choice medical treatment for EHPVT in the everyday practice [3, 5, 7, 17]. We use it in a significant number of patients, and the response is favorable in most of the cases. PH improved in five of the 7 patients on propranolol therapy; they had no episodes of bleeding and variceal progression and spleen sizes decreased. There was not a significant response in 2 patients, and after several episodes of bleeding episodes (1 patient had 6 episodes and 1 patient had 3 episodes) they received surgical treatment.

Until not long ago, only patients with refractory variceal bleeding, frequent rebleeding episodes, or those with severe hypersplenism were managed surgically [3, 4]. Recent advances in vascular surgery have challenged this conservative approach. The available shunting procedures directly decompress the portal venous system, reducing the risk of bleeding and other complications. Distal splenorenal shunt and the Meso-Rex bypass are generally preferred [3–5, 8]. They are widely recommended in some international referral services, and Rex shunts are the treatment of choice for both primary and secondary prophylaxes of variceal bleeding in children with PH [3, 8]. Five of our patients received shunting procedures, and all of them demonstrated an excellent response concerning their PH. The varices were completely eradicated in all the cases, and 3 patients showed a marked regression in their spleen size (2 patients had undergone splenectomy during the shunting procedure).

Doppler ultrasound is the method of choice for detection of EHPVT and for the surveillance, as it is a noninvasive, informative, and relatively cheap imaging modality [3, 5, 15]. Based on our experience and the literature data that 97.2–100% of neonatal PVT resolved spontaneously at 1 year [20, 21], we recommend Doppler ultrasound for active follow-up and screening approximately 1 year after each potential triggering event for all children with known risk factors for development of PVT, especially for those with more than one predisposing factor. We believe that this proactive approach is patient-friendly and could prevent further complications.

The present study was designed to evaluate the characteristics of EHPVT in Bulgarian pediatric patients. It has strengths but also limitations. The main limitations are the single-center retrospective design and the small sample size. EHPVT is a rare condition, and most cases of neonatal EHPVT are asymptomatic and resolve spontaneous within the time. Only a small proportion of pa-

tients with neonatal EHPVT have residual thrombosis at follow-up and may develop complications. We assessed only the symptomatic cases and were not able to analyze all potential risk factors for the development of EHPVT. However, the results of the present study could be an important starting point for future multicenter prospective investigations.

Conclusion

Most clinical manifestations of pediatric EHPVT are long-term complications due to PH and are time-dependent. Therefore, early diagnosis and management are essential for favorable outcome. This study confirms the multifactorial etiology of EHPVT in the pediatric population and the role of the inherited thrombophilia as a predisposing factor; it also demonstrates that most patients had a combination of local and systemic risk factors for the disease. In addition, it suggests a proactive screening approach among the children with known predisposing factors. Investigation with Doppler ultrasound 1 year after a potential triggering event could exclude or confirm the diagnosis and prevent further complications.

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Statement of Ethics

This study was approved by the Institutional Review Board in the Department of Pediatrics of the Medical University of Plovdiv (Protocol No 6/May 11, 2021). Formal individual informed consent for participation in the study was not sought due to its retrospective design, as all analyzed data had been collected as part of routine diagnosis and treatment, consistent with the current standard of care.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Conception and design: Ivan Yankov and Rayna Shentova-Eneva. Acquisition of data: Ivan Yankov, Hristo Mumdzhiev, Penka Petleshkova, Maya Krasteva, Dimitar Chatalbashev, Penka Stefanova, Evgeniy Moshekov, and Teodora Gogova. Analysis and interpretation of data: Ivan Yankov, Maya Krasteva, Penka Stefanovae, and Evgeniy Moshekov. Drafting: Ivan Yankov, Rayna Shentova-Eneva, Hristo Mumdzhiev, and Teodora Gogova. Critical revision and final approval: all the authors.

Data Availability Statement

The data that support the findings of this study are available on request from Ivan Yankov: Ivan.Yankov@mu-plovdiv.bg.

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