PEDIATRIC SCIENCES JOURNAL
The Official Journal of the Pediatric Department, Faculty of Medicine, Cairo University, Egypt

Original Article

Shear Wave Elastography in Children with Portal Vein Thrombosis is not a Sensitive Predictor of Upper Gastrointestinal Bleeding: a Pilot Study

Magd Ahmed Kotb[1], Marwa Mohamed Onsy[2], Bothainah M. Abdulwahab Abduljalil[3], Mona Ahmed Kamel[1*], Rania Hamdy Hashem[1]

[1] Department of Pediatrics, Faculty of Medicine, Cairo University, Egypt
[2] Department of Radiology, Faculty of Medicine, Cairo University, Egypt
[3] Department of Radiology, Faculty of Medicine, Dhamar University, Yemen
***** Correspondence: mona.a.kamel@kasralainy.edu.eg
Received: 28/8/2023; Accepted: 27/10/2023; Published online: 20/11/2023.

Abstract:
Background: Extrahepatic portal vein thrombosis (EHPVT) is a cause of portal hypertension in children. It is complicated by upper gastrointestinal variceal bleeding.
Aim of the work: to study shear wave elastography (SWE) assessed liver and spleen stiffness among children with EHPVT as a predictor of esophageal varices, its grade and/or upper gastrointestinal (GIT) bleeding.
Methods: This case-control study included 18 children with EHPVT who were not secondary to liver disease and 18 healthy children as a control group who underwent ultrasonography and SWE of the liver and spleen. The patient group underwent upper GIT endoscopy as well.
Results: The mean ± SD age of the children with EPVT was 9.11 ± 5.26 years, and 5 (27.7%) were females. Three (16.7%) had thrombophilia, 11 (61.1%) had undergone neonatal placement of umbilical catheter, both neonatal intensive care unit admission and thrombophilia in 2 (11.1%) and omphalitis in one (5.5%). All had clinically evident splenomegaly and sonographic evidence of portal vein cavernoma, 2 had recanalized portal vein. SWE stiffness of the right lobe was 7.39 ± 0.86 kPa, the left lobe was 7.64± 0.99 kPa and splenic stiffness was (mean± SD was 68.1 ± 22.8 kPa and range 28-121 kPa) among those with EHPVT, compared to the control group which was 6.83 ± 0.37 kPa, 7.39 ± 0.85 kPa, and (mean± SD was 19.61 ± 2.7 kPa and range 17.2-24.2 kPa), (p = 0.018), (p=0.036) and (p=0.00001) respectively. Esophageal varices bleeding and grade did not correlate with the modified caudate to right lobe diameter ratio (p=0.621), and (p= 0.53), stiffness of the right lobe (p=0.64) and (p= 0.684), left lobe (p=0.297) and (p= 0.223), or spleen stiffness (p=0.499) and (p= 0.196) respectively. Eleven (61.1%) had patent lienorenal collaterals, they were older (mean age 10± 5.3years) compared to those who did not develop (6.7 ± 3.6 years) lienorenal collaterals (p=0.06). The development of spontaneous lienorenal shunts was associated with a decreased risk of variceal bleeding (p= 0.013).
Conclusion: EHPVT in children was associated with hepatic and splenic stiffness compared to the control group. The stiffness did not correlate with the upper GIT variceal grade or bleeding. The development of spontaneous lienorenal shunts seems to deflate portosystemic shunt pressure and reduce the risk of variceal bleeding.

Level of Evidence of Study: IV (*1*).
Keywords: Shear wave elastography; upper gastrointestinal bleeding; portal vein thrombosis.
Abbreviation: ALT: alanine aminotransferase; AST: aspartate aminotransferase; C:RL: caudate to right lobe diameter ratio; Cm3: cubic centimetres; CRI: circular region of interest; D: dimensional; EHPVT: Extrahepatic portal vein thrombosis; F: fibrosis; GIT: gastrointestinal bleeding; GGT: gamma-glutamyl transpeptidase; IQR: interquartile range; METAVIR: meta-analysis of histological data in viral hepatitis; NICU: neonatal intensive care unit; PLT: platelet; RPV: right portal vein; SD: standard deviation; SMV: superior mesenteric vein; SWE: Shear wave elastography; UGIB: upper gastrointestinal bleeding.

Introduction

Extrahepatic portal vein occlusion caused by extrahepatic portal vein thrombosis (EHPVT) is one of the most common causes of portal hypertension in children (*2–4*). Occlusion of the portal

vein increases the resistance to blood flow within its lumen causing portal hypertension with subsequent development of oesophageal varices (*3*, *5*). Within 6 to 20 days after the onset of EHPVT, numerous periportal venous collaterals called cavernomas are formed (*6*). At least 50% of those with EHPVT will suffer from hematemesis (*4*), which might be fatal (*7*). Upper endoscopy is the gold standard to diagnose oesophageal varices (*8*). The sensitivity and specificity of alternative less invasive imaging techniques are being investigated as trans-abdominal ultrasound (*9*), multi-detector computed tomography imaging (*8*), transient elastography, magnetic resonance elastography, and shear wave elastography (SWE) (*10*). SWE is operator-dependent, uses a conventional ultrasound scanner, and is not a specific fibroscan. Given that long-standing liver disease causes liver scaring -whether fibrosis or cirrhosis- and decreased elasticity of the liver. SWE was reported to be a valuable screening tool for varices bleeding treatments among adults with advanced liver disease (*11*). We aimed to study SWE-assessed liver and spleen stiffness among children with EHPVT as a predictor of esophageal varices, its grade and/or upper gastrointestinal (GIT) bleeding.

Subjects and Methods

This prospective descriptive study was carried out at Children Hospital, Faculty of Medicine, Cairo University, Egypt, between March 2022 and January 2023. The study was approved by the Ethical Committee of Faculty of Medicine, Cairo University, Egypt (MS- 278-2022) consistent with the Helsinki Declaration of studies (*12*). A verbal consent was obtained from parents /caregivers of the child in both groups before enrolment in the study.

Participants

The study included a group of 18 children with EHPVT aged 2 - 17 years, attending Pediatric Hepatology and Gastroenterology Clinics Children Hospital, Faculty of Medicine, Cairo University, Cairo, Egypt. To avoid confounding causes of liver pathology causing probable change of liver or spleen elasticity, the enrolled cohort was selected free from underlying primary liver disease, was free of ascites, none had storage disease, or Budd Chiari syndrome, or cardiac disease. None were on betablockers, anticoagulants or other medications. The study included another control group of 18 age and gender matched children who had no history or current gastrointestinal, hepatic, pancreatic, biliary, splenic or cardiovascular diseases, and were attending the hospital for an irrelevant condition. Children in the control group were included only if they had normal grey scale and doppler examination of the liver and spleen, and no family history of liver disease.

Methods

Both groups underwent clinical examination, complete blood count, liver function tests (alanine aminotransferase (ALT), aspartate amino transferase (AST), gamma glutamyl transpeptidase (GGT), total and direct bilirubin), prothrombin time and concentration and thrombophilia panel (Protein C, protein S, methyltetrahydrofolate reductase (MTHFR), lupus anticoagulants, and factor V Leiden).

All children in both groups underwent liver and spleen stiffness measurements were performed by the same investigator using Canon (TOSHIBA, Japan) Aplio-500 ultrasound system that was equipped by 1-6 MHz convex transducer, with 4-6 hours of child fasting.

Abdominal ultrasound and Doppler:

- Ultrasound examination of the liver was performed in supine and right anterior oblique positions with abduction of the right arm; it included study of the main portal vein, its intrahepatic branches, splenic and superior mesenteric vein. It included spleen volume estimation.
- The longitudinal dimension of the right liver lobe was measured on a parasagittal scan from the posterior diaphragm to the lower edge of the right liver lobe on the midclavicular line (*13*, *14*).
- The transverse dimension of both right hepatic and caudate lobes were obtained from right subcostal approach in axial plane and the modified caudate to right lobe diameter ratio (C: RL) was calculated (transverse diameter of the caudate lobe was measured from its medial border to the point of right portal vein (RPV) bifurcation and was divided by the transverse diameter of the right hepatic lobe)(*15*). The C: RL of the study group was compared to known norms ratios 0.22- 0.33 (*16*).

Shear Wave Elastography (SWE)

- Liver elastography examination was performed at mid-inspiration or during quiet breathing in uncooperative children. Readings from the right hepatic lobe were recorded through the 6th- 9th intercostal space at segment VI and VIII. The left lobe measurements were taken through the subxiphoid or para-midline intercostal approach. Five valid shear wave measurements were obtained from each site about 1 cm deep to the liver capsule (not more than 6 cm deep), away from vessels, bile ducts and gallbladder. Readings were taken after a stable SWE image with a homogeneous colour filling on the elastogram images and parallel wave propagation on the wave propagation image using 1-cm circular region of interest (ROI) (*17*).
- Spleen examination was performed in supine and left anterior oblique positions with abduction of the ipsilateral arm. Spleen volume was measured (in cm^3). After that 2 dimensional (D)-SWE was performed through subcostal approach at mid- region or lower pole of the spleen during inspiration or quiet breathing in uncooperative children. Between five to ten valid measurements were obtained about 1-2 cm deep to the spleen capsule.

Readings from both liver and spleen were taken after a stable SWE image with a homogeneous color filling on the elastogram images and parallel wave propagation on the wave propagation image using 1-cm circular region of interest (ROI). The stiffness of both the liver and spleen were measured in kilopascals by the ultrasound machine at the time of the study. Median, IQR and IQR/median are calculated thereafter using Microsoft Excel 2016, (Microsoft Corporation, USA). Reliability criterion used refers to IQR/M of < 30% of the measurements (2D SWE) for kilopascals. Liver stiffness results were interpreted using the manufacturer's reference values and their equivalent METAVIR scores (*18*). Cut-offs to classify liver fibrosis stages relied upon the classification for transient elastography (*19*), where METAVIR score F0 coincided with liver stiffness threshold value of < 7kPa, > F1 of 7-9 kPa, score > F2 coincided with 9-11.5 kPa, score > F3 coincided with 11.5-14.5 kPa, and F4 > 14.5. SWE was performed by the same operator to alienate into-operator variability.

Upper Gastrointestinal Endoscopy

The studied cohort with EHPVT underwent Upper GI endoscopic results were obtained using (FUJINON CC-500 machine, Germany). The variceal grading was as follows: Grade I: varices collapse on inflation of esophagus with air; Grade II: these are varices between grades 1 and 3 (< 1/3 of lumen); Grade III: these are large enough to occlude the lumen (> 1/3 of lumen). Supplementary descriptive terms e.g., with stigmata, red spots, red wheals, vessels on vessels etc. (*20*).

Statistical Analysis

Statistical analyses were performed in modules of SciPy 1.7 package (Texas,USA) (*21*). Descriptive statistics was used to summarize patient characteristics. According to Shapiro-Wilk test, all quantitative variables showed normal distribution pattern except spleen volume measurement. Normality of data distribution was assessed by Shapiro-Wilk test and the differences between normally distributed data were evaluated by independent t-test. For non-normally distributed variables, Mann-Whitney U test was used to assess the difference between patient and control groups. ANOVA test was used to evaluate the differences between groups. Correlation of the elastography measurements with clinical and radiological parameters was done using Pearson correlation coefficient. Correlation strength of 0–0.19 was considered very weak; 0.20–0.39 weak; 0.40–0.59 moderate, 0.60–0.79 strong and 0.80–1 very strong (*22*). Prediction of elastography from other clinical or radiological findings was done by regression analysis. A p-value of less than 0.05 was considered significant. The wide range of age of the included children could not allow correct correlation of splenic size, as it different according to age, hence spleen volume was estimated as folds of upper limit for age.

Results

Age and sex of the 36 enrolled children in the study are presented in Table 1. Clinically all had normal liver span, while all those with EHPVT had splenomegaly. The cases had a mean ± standard deviation (SD) age of 9.11 ± 5.26 years, of them 13 (72.2%) were males, that matched the age and sex of the control group. The control group had a mean ± SD age of 9.33 ± 5.06 years, of them males were 13 (72.2%) (p=0.401) and (p=0.258) respectively.

Clinically all those with EHPVT had varying degrees of splenomegaly, no purpuric eruptions or wet purpura. Otherwise by examination there was no clinical abnormality. Platelet count

reduction among 16 (88.8%) with EHPVT (mean± SD was 88,500 ± 23,627/ml and range 56,000-135,000/ml) was significant (p= 0.001), compared to that of control group (mean± SD was 305,000 ± 86,554, range 160,000-456,000/ml). Apart from the encountered thrombocytopenia, all had normal levels of hemoglobin, white blood count, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, albumin, bilirubin levels, prothrombin time and concentration.

The risk factors encountered among the children with EHPVT were neonatal intensive care unit (NICU) admission in 11(61.1%) children, thrombophilia in 3 (16.7%), both NICU admission and thrombophilia in 2 (11.1%) and omphalitis in one (5.5%). The thrombophilia was due to protein C deficiency in one and the others had heterozygous and homozygous MTHFR deficiency respectively. History of previous upper gastrointestinal bleeding was present among 14 (77.8%), of them 4 (22.2%) bled within the past 6 months prior to enrollment in the study. Four (22.2%) never bled before. None of the children was on beta blockers, or bile acids (usrodeoxycholic acid or others.).

Ultrasonographic Findings:

Portal vein cavernoma was seen in all the studied cases, only two patients had partially occluded/recanalized main portal vein and two other patients had superior mesenteric vein (SMV) thrombosis, and all had splenomegaly.

The mean ± SD of C:RL was found to be 0.95 ± 0.21 (range 0.7- 1.4) among those with EHPVT, which was significantly higher than that of the accepted norms ($p < 0.001$) (*16*).

Eleven (61.1%) had patent lienorenal collaterals, they were older (mean age 10± 5.3years) compared to those who did not develop (6.7 ± 3.6 years) lienorenal collaterals (p=0.06).

Shear Wave Elastography Findings:

Astonishingly 11 and 13 exhibited right and left hepatic lobes fibrosis. (Figure 1). Liver stiffness measurements showed that only 7 (38%) of those with EHPVT had normal right lobe stiffness and 5 (27.7%) had left lobe stiffness showed association with C:RL ratio (p= 0.025), but not to the oesophageal varices bleed (p= 0.62), not to the grade of the varices (0.684) and no association with other clinical findings. (Table 1). All those with EHPVT had splenomegaly with increased splenic volume (mean± SD was 689.4 ± 576/cm^3 and range 220-1588 cm^3) compared to the control group (mean± SD was 125.6 ± 63.2/cm^3 and range 40-248cm^3) (p=0.00013). The mean spleen volume folds of upper normal value for age of those with EHPVT was (mean± SD was 5.44 folds of normal for age) compared to control group (mean± SD was 0.69 folds of normal for age) (p= 0.019). All had increased splenic stiffness (mean± SD was 68.1 ± 22.8 kPa and range 28-121 kPa) compared to the control group (mean± SD was 19.61 ± 2.7 kPa and range 17.2-24.2 kPa) (p<0.00001). (Figure 2). Liver stiffness of patients with different grades of oesophageal varices. a) Stiffness of both hepatic lobes showed poor association with the grades of oesophageal varices (R^2 = 0.151 and R^2=0.24). Nonetheless, right lobe stiffness measurements in patients with no oesophageal varices were higher than left lobe readings (8.90 vs 7.85 kPa).

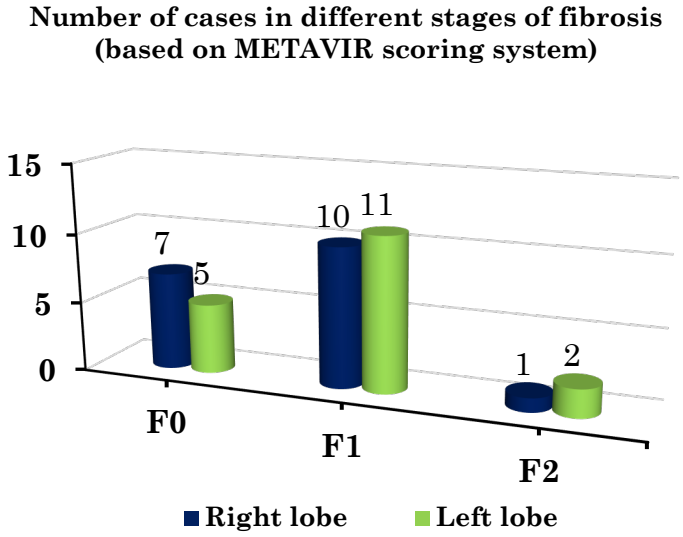

Figure 1. Shear wave elastography of children with EHPVT according to stages of fibrosis based on METAVIR scoring system.

Table 1. Correlations of liver stiffness with other parameters (Pearson correlation).

Right lobe	r^2	P value	Left lobe	r^2	P value
Age	0.33	0.175	Age	0.21	0.401
Gender	0.08	0.238	Gender	0.08	0.258
Risk factors	0.03	0.50	Risk factors	0.16	0.100
Resent UGIB	0.02	0.571	Resent UGIB	0.07	0.287
PLT (103/ml)	0.01	0.955	PLT (103/ml)	0.02	0.935
C:RL ratio	0.39	0.109	C: RL	0.47	0.051
Esophageal varices grade	-0.10	0. 684	Esophageal varices grade	-0.21	0.40

C: RL: caudate to right lobe ration; PLT: platelet; UGIB: upper gastrointestinal bleeding. P value is significant at < 0.05.

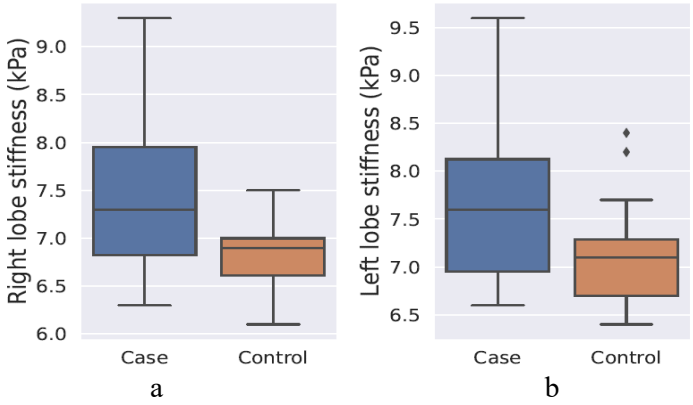

Figure 2. Shear wave elastography among children with extrahepatic portal vein thrombosis and control group. a) right lobe stiffness (7.39 ± 0.86 kPa vs 6.83 ± 0.37 kPa, respectively) (p = 0.018); b) left lobe stiffness (7.64± 0.99 kPa vs 7.39 ± 0.85 kPa, respectively) (p=0.036).

Upper Gastrointestinal Endoscopy:

All the children with EHPVT had varices, 2 had only fundal, 16 had oesophageal varices and 9 had both. Among the studied children with EHPVT 15 had grade 2 oesophageal varices (83.3%), and 3 (17.7%) had grade 3. C: RL did not correlate with history of bleeding (p=0.621) or grade of varices (p= 0.53). Right lobe stiffness and left lobe stiffness did not correlate with history of bleeding (p=0.64) and (p=0.297) or grade of varices (p= 0.684) and (p= 0.223) respectively. Splenic stiffness and size did not correlate with history of bleeding (p=0.499) and (p=0.55) or grade of varices (p=0.196) and (p= 0.552) respectively. The recanalization of portal vein did not correlate with the bleeding (p=0.84) or grade of varices (p=0.55). Eight of the 11 children with lienorenal collaterals did not bleed within the past 2 years (p= 0.013). Lienorenal shunt did not correlate to grade of varices (p= 0.843). (Figures 3 and 4).

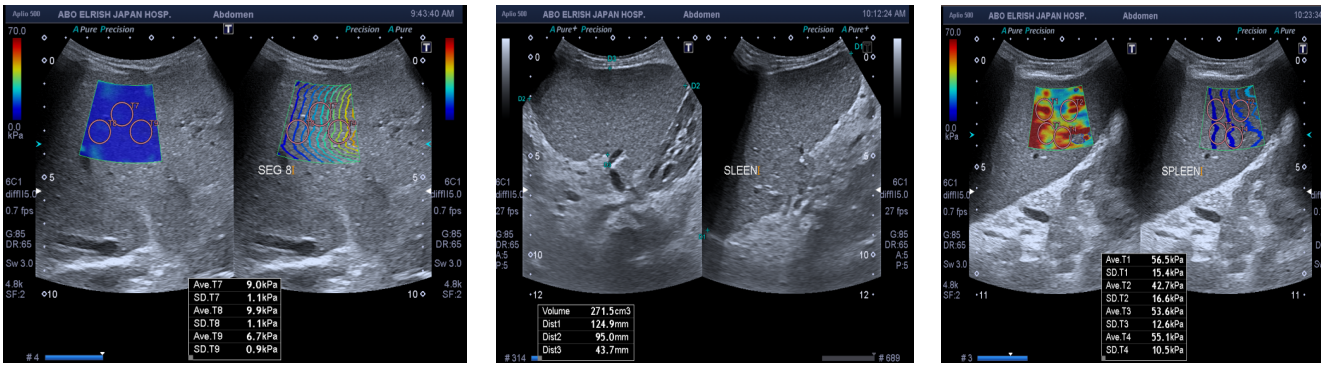

Figure 3. Liver elastography and spleen volume and elastography in 3 years old patient with EHPV. She had chronically occluded portal and superior mesenteric veins with multiple collateral venous channels as well as splenomegaly by ultrasonography. Right lobe METAVIR score 7-9 kPa (mild fibrosis). Left lobe METAVIR score 9–11.5 kPa (moderate fibrosis). There was no history of upper GIT bleeding. No history of NICU admission, or other risk factors. Her platelet count =135,000/mlL. Upper endoscopy revealed grade I oesophageal varices.

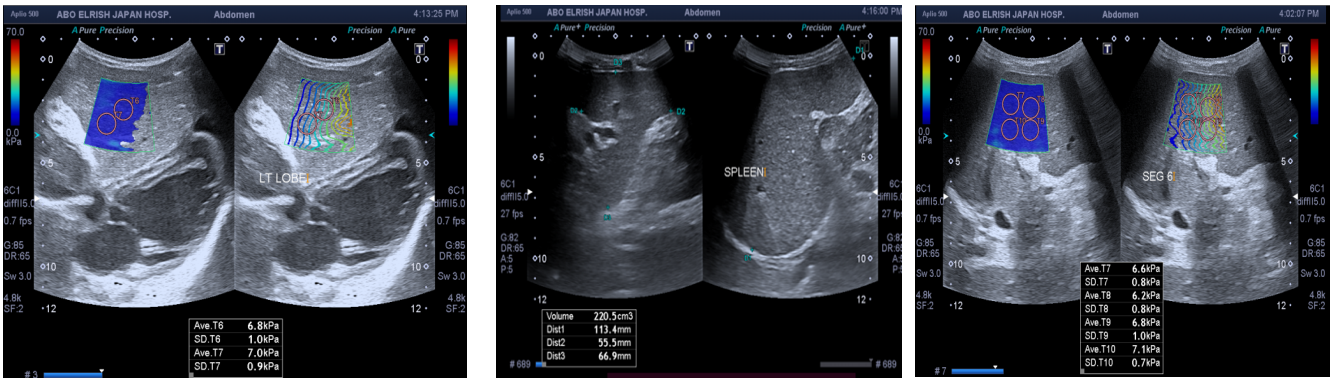

Figure 4. Liver elastography and spleen volume and elastography in 4 years old patient with EHPV. He had chronically occluded portal with cavernoma transformation as well as splenomegaly by ultrasonography. Right lobe METAVIR score <7 kPa (no fibrosis). Left lobe METAVIR score 7–9 kPa (mild fibrosis). There was no history of upper GIT bleeding. No history of NICU admission, or other risk factors. His platelet count =119,000/mlL. Upper endoscopy revealed grade II oesophageal varices and one fundal extension.

Discussion

Shear wave elastography detected subclinical hepatic stiffness of right lobe in 64% and left lobe in 73.3% of the studied children with EHPVT, which was associated with increased C:RL that was significantly higher than that of the accepted norms ($p < 0.001$) (*16*). The EHPVT is associated by hepatic hypoperfusion as the portal vein supplies 70-75% of the blood supply and 50% of oxygen supply (*23*, *24*), hence the stiffness detected by the shear wave elastography might be related to a grade of hepatic ischemia. The stiffness of the spleen seems to be related to its degree of resilience and expandability as a reservoir of the portal blood (*25*) that was not able to bypass the portal obstruction and move through the multiple channels of the portal cavernoma. The increase in stiffness of liver or spleen did not correlate with the grade or recent bleeding of esophageal varices. Hence, the stiffness might prove to be related to the low-grade ischemia as a result of long-standing portal hypertension and not logarithmic related to the pressure building with port-systemic circulation. The development of varices and their grade seem to be multifactorial (*26*). As none of the children were currently on beta-blockers, the stiffness is not related to the intake of beta-blockers that are known to produce hepatic fibrosis and hypoperfusion (*27*). It is interesting however that not all children had stiffness, hence it seems that the hypoperfusion is not the only factor dictating the hepatic fibrosis.

The spleen function as a reservoir seems to be protective against variceal congestion as the splenic size was dramatically higher in patients who has no varices (1965.5 cm^3) (both cases were 17 years old), while the remaining subjects in the other grades showed an average volume between 403.5 and 631cm^3, and seems to be an initiator of spontaneous opening of lienorenal shunt (*25*, *28*). The spontaneous lienorenal shunts were associated with less incidence of recent bleeding varices (*29*). Yet, our study was a cross-sectional and not a prospective one, so we did not compare before and after bleeding size of spleen or its stiffness. The spleen size might be related to its ability to expand, previous infarcts or previous peri-splenitis (*30*). More studies are needed to highlight its role in diagnosis and follow up.

Platelet retainment in the spleen or hypersplenism, was noted among 16 (88.8%) of the studied children with EHPVT (*31*). None had purpura or was at more risk of bleeding. The platelets (margination or migration) in the spleen seems to be a matter of parking there and not of increased destruction.

Ultrasound shear wave elastography is a promising non-invasive technique in assessment of liver fibrosis and spleen stiffness that clearly outlines that the liver and spleen suffer from mild fibrosis from the long-standing hepatic hypo-perfusion, which is contrary to our previous convictions that EHPVT has no influence on the liver tissue. We did not study the inter-operator variability; hence, more studies are needed to quantify its objectivity. The hepatic fibrosis questions the role of beta-blockers that are used off-label to reduce splanchnic circulation and reduce hepatic perfusion. SWE sensitivity and specificity in detection of stiffness was beyond the scope of this study as we did not compare the findings with fibroscan or liver biopsy histopathology. Upper GIT endoscopy remains the golden standard for diagnosis of esophageal bleeding (*32*).

Conclusion

Shear wave elastography detected hepatic and splenic stiffness among children associated with EHPVT compared to the control group. The detected stiffness was not associated with a risk of upper GIT variceal grade or bleeding. Development of spontaneous lienorenal shunts seems to deflate porto-systemic shunt pressure and reduce risk of variceal bleeding.

Author Contributions: All authors searched medical literature, databases, conceptualized, conducted the case review and reviewed the final manuscript. All authors have read and agreed to the published version of the manuscript.

FUNDING

Authors declare there was no extramural funding provided for this study.

CONFLICT OF INTEREST

The authors declare no conflict of interest in connection with the reported study. Authors declare veracity of information.

References

1. S. Tenny, M. Varacallo, *Evidence Based Medicine.* (StatPearls Publishing; Treasure Island (FL), 2020; https://www.ncbi.nlm.nih.gov/books/NBK470182/).
2. C. A. Chapin, L. M. Bass, Cirrhosis and Portal Hypertension in the Pediatric Population. *Clin. Liver Dis.* **22**, 735–752 (2018).
3. P. M. Ferri, A. R. Ferreira, E. D. T. Fagundes, S. M. Liu, M. L. V. Roquete, F. J. Penna, Portal vein thrombosis in children and adolescents: 20 years experience of a pediatric hepatology reference center. *Arq. Gastroenterol.* **49**, 69–76 (2012).
4. A. Grama, A. Pîrvan, C. Sîrbe, L. Burac, H. Ştefănescu, O. Fufezan, M. A. Bordea, T. L. Pop, Extrahepatic Portal Vein Thrombosis, an Important Cause of Portal Hypertension in Children. *J. Clin. Med.* **10** (2021).
5. R. Khanna, S. K. Sarin, Noncirrhotic Portal Hypertension: Current and Emerging Perspectives. *Clin. Liver Dis.* **23**, 781–807 (2019).
6. V. Young, S. Rajeswaran, Management of Portal Hypertension in the Pediatric Population: A Primer for the Interventional Radiologist. *Semin. Interv. Radiol.* **35**, 160–164 (2018).
7. Amani M. Ibrahim , Elsayed A. Kalil , Maha R Habeeb, Predictors of early re-bleeding and mortality in patients with first attack of gastric variceal hemorrhage. *Med. J. Viral Hepat. MJVH*, 14–21 (2021).
8. M. Ali, M. Afify, O. Abdelrazek, M. Elfeshawy, A. Abdelnaby, Multi-detector Computed Tomography Versus Upper Gastrointestinal Endoscopy in Diagnosis and Grading of Esophageal Varices in Egyptian Cirrhotic Patients. *Al-Azhar Int. Med. J.* **3**, 35–43 (2022).
9. C.-X. Zhang, J.-M. Xu, J.-B. Li, D.-R. Kong, L. Wang, X.-Y. Xu, D.-M. Zhao, Predict esophageal varices via routine trans-abdominal ultrasound: A design of classification analysis model: Predict EV via routine TUS. *J. Gastroenterol. Hepatol.* **31**, 194–199 (2016).
10. M. Danish, H. Ismail, R. Tulsi, N. Mehmood, S. M. Laeeq, N. Hassan Luck, Liver Elastography as a Predictor of Esophageal Varices in Patients With Cirrhosis. *Cureus*, doi: 10.7759/cureus.18593 (2021).
11. R. Paternostro, T. Reiberger, T. Bucsics, Elastography-based screening for esophageal varices in patients with advanced chronic liver disease. *World J. Gastroenterol.* **25**, 308–329 (2019).
12. World Medical Association, WMA Declaration of Helsinki- Ethical Principles for Medical Research Involving Human Subjects (2013). https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/2013/.
13. Buscarini E, Lutz H, Mirk P, World Health Organization, World Federation for Ultrasound in Medicine and Biology, "Manual of diagnostic ultrasound" (World Health Organization, Geneva, Switzerland; https://apps.who.int/iris/bitstream/handle/10665/85386/9789241548540_engch5.pdf?sequence=6&isAllowed=y).

14. Hemeda MS, Kotb MA, Hamad KS, Mohamed MA., "Hepatomegaly: Comparing Sonography and Clinical Evaluation in Infancy and Pre-school Children," thesis, Faculty of Medicine, Azhar University, Egypt (2016).
15. H. Awaya, D. G. Mitchell, T. Kamishima, G. Holland, K. Ito, T. Matsumoto, Cirrhosis: Modified Caudate–Right Lobe Ratio. *Radiology* **224**, 769–774 (2002).
16. Ibrahim Hassan Ibrahim, Morphological Variations and Measurements of the Caudate Lobe of the Human Liver: A Cadaveric Study. *Med. J. Cairo Univ.* **88**, 155–160 (2020).
17. E. K. Hong, Y. H. Choi, J.-E. Cheon, W. S. Kim, I.-O. Kim, S. Y. Kang, Accurate measurements of liver stiffness using shear wave elastography in children and young adults and the role of the stability index. *Ultrasonography* **37**, 226–232 (2018).
18. R. G. Barr, G. Ferraioli, M. L. Palmeri, Z. D. Goodman, G. Garcia-Tsao, J. Rubin, B. Garra, R. P. Myers, S. R. Wilson, D. Rubens, D. Levine, Elastography Assessment of Liver Fibrosis: Society of Radiologists in Ultrasound Consensus Conference Statement. *Radiology* **276**, 845–861 (2015).
19. E. Fitzpatrick, A. Quaglia, S. Vimalesvaran, M. S. Basso, A. Dhawan, Transient Elastography Is a Useful Noninvasive Tool for the Evaluation of Fibrosis in Paediatric Chronic Liver Disease. *J. Pediatr. Gastroenterol. Nutr.* **56**, 72–76 (2013).
20. BSPGHAN, Assessment and Management of Oesophageal Varices in Children V2: Joint Guideline of the Children's Specialised Liver Services at King's, Birmingham, and Leeds (2021). https://bspghan.org.uk/wp-content/uploads/2021/12/Varices-guideline_BSPGHAN_v2.pdf.
21. P. Virtanen, R. Gommers, T. E. Oliphant, M. Haberland, T. Reddy, D. Cournapeau, E. Burovski, P. Peterson, W. Weckesser, J. Bright, S. J. van der Walt, M. Brett, J. Wilson, K. J. Millman, N. Mayorov, A. R. J. Nelson, E. Jones, R. Kern, E. Larson, C. J. Carey, İ. Polat, Y. Feng, E. W. Moore, J. VanderPlas, D. Laxalde, J. Perktold, R. Cimrman, I. Henriksen, E. A. Quintero, C. R. Harris, A. M. Archibald, A. H. Ribeiro, F. Pedregosa, P. van Mulbregt, A. Vijaykumar, A. Pietro Bardelli, A. Rothberg, A. Hilboll, A. Kloeckner, A. Scopatz, A. Lee, A. Rokem, C. N. Woods, C. Fulton, C. Masson, C. Häggström, C. Fitzgerald, D. A. Nicholson, D. R. Hagen, D. V. Pasechnik, E. Olivetti, E. Martin, E. Wieser, F. Silva, F. Lenders, F. Wilhelm, G. Young, G. A. Price, G. L. Ingold, G. E. Allen, G. R. Lee, H. Audren, I. Probst, J. P. Dietrich, J. Silterra, J. T. Webber, J. Slavič, J. Nothman, J. Buchner, J. Kulick, J. L. Schönberger, J. V. de Miranda Cardoso, J. Reimer, J. Harrington, J. L. C. Rodríguez, J. Nunez-Iglesias, J. Kuczynski, K. Tritz, M. Thoma, M. Newville, M. Kümmerer, M. Bolingbroke, M. Tartre, M. Pak, N. J. Smith, N. Nowaczyk, N. Shebanov, O. Pavlyk, P. A. Brodtkorb, P. Lee, R. T. McGibbon, R. Feldbauer, S. Lewis, S. Tygier, S. Sievert, S. Vigna, S. Peterson, S. More, T. Pudlik, T. Oshima, T. J. Pingel, T. P. Robitaille, T. Spura, T. R. Jones, T. Cera, T. Leslie, T. Zito, T. Krauss, U. Upadhyay, Y. O. Halchenko, Y. Vázquez-Baeza, SciPy 1.0: fundamental algorithms for scientific computing in Python. *Nat. Methods 2020 173* **17**, 261–272 (2020).
22. G. H. Alhashmi, A. Gupta, A. T. Trout, J. R. Dillman, Two-dimensional ultrasound shear wave elastography for identifying and staging liver fibrosis in pediatric patients with known or suspected liver disease: a clinical effectiveness study. *Pediatr. Radiol.* **50**, 1255–1262 (2020).
23. C. Eipel, Regulation of hepatic blood flow: The hepatic arterial buffer response revisited. *World J. Gastroenterol.* **16**, 6046 (2010).
24. Kotb MA, El-Koofy N, Lotfi WN, Kamal N., Doppler assessed haemodynamic changes in infants and children suffering cholestasis. *Gaz. Egypt. Pediatr. Assoc.* **48**, 345–56 (2000).
25. C. V. Greenway, G. E. Lister, Capacitance effects and blood reservoir function in the splanchnic vascular bed during non-hypotensive haemorrhage and blood volume expansion in anaesthetized cats. *J. Physiol.* **237**, 279–294 (1974).
26. Meseeha M, Attia M., Esophageal Varices., *In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing;* (2023). https://www.ncbi.nlm.nih.gov/books/NBK448078/.
27. P. S. Ge, B. A. Runyon, The changing role of beta-blocker therapy in patients with cirrhosis. *J. Hepatol.* **60**, 643–653 (2014).
28. M. El-Feky, Y. Weerakkody, "Splenorenal shunt" in *Radiopaedia.Org* (Radiopaedia.org, 2012; http://radiopaedia.org/articles/19361).
29. S. Rajesh, C. A. Philips, R. Ahamed, J. K. Abduljaleel, D. C. Nair, P. Augustine, Friend or Foe? Spontaneous Portosystemic Shunts in Cirrhosis—Current Understanding and Future Prospects. *Can. J. Gastroenterol. Hepatol.* **2021**, 1–19 (2021).
30. D. Bell, M. Agha, "Perisplenitis" in *Radiopaedia.Org* (Radiopaedia.org, 2017; http://radiopaedia.org/articles/51762).

31. Y. Lv, W. Y. Lau, Y. Li, J. Deng, X. Han, X. Gong, N. Liu, H. Wu, Hypersplenism: History and current status. *Exp. Ther. Med.* **12**, 2377–2382 (2016).
32. S. Pallio, G. Melita, E. Shahini, A. Vitello, E. Sinagra, B. Lattanzi, A. Facciorusso, D. Ramai, M. Maida, Diagnosis and Management of Esophagogastric Varices. *Diagnostics* **13**, 1031 (2023).