

World Journal of *Gastrointestinal Surgery*

World J Gastrointest Surg 2023 June 27; 15(6): 1007-1261



Contents

Monthly Volume 15 Number 6 June 27, 2023

OPINION REVIEW

- 1007 Diverticulitis is a population health problem: Lessons and gaps in strategies to implement and improve contemporary care
Stovall SL, Kaplan JA, Law JK, Flum DR, Simianu VV

REVIEW

- 1020 Distal pancreatectomy with or without radical approach, vascular resections and splenectomy: Easier does not always mean easy
Bencini L, Minuzzo A

MINIREVIEWS

- 1033 Endoscopic ultrasound-guided portal pressure gradient measurement in managing portal hypertension
Lesmana CRA
- 1040 Robotic surgery in elderly patients with colorectal cancer: Review of the current literature
Teo NZ, Ngu JCY
- 1048 Median arcuate ligament syndrome often poses a diagnostic challenge: A literature review with a scope of our own experience
Giakoustidis A, Moschonas S, Christodoulidis G, Chourmouzi D, Diamantidou A, Masoura S, Louri E, Papadopoulos VN, Giakoustidis D
- 1056 Surgical complications of oncological treatments: A narrative review
Fico V, Altieri G, Di Grezia M, Bianchi V, Chiarello MM, Pepe G, Tropeano G, Brisinda G

ORIGINAL ARTICLE

Basic Study

- 1068 Impact of interstitial cells of Cajal on slow wave and gallbladder contractility in a guinea pig model of acute cholecystitis
Ding F, Guo R, Chen F, Liu LP, Cui ZY, Wang YX, Zhao G, Hu H

Retrospective Cohort Study

- 1080 Fascia- vs vessel-oriented lateral lymph node dissection for rectal cancer: Short-term outcomes and prognosis in a single-center experience
Zhao W, Wang ZJ, Mei SW, Chen JN, Zhou SC, Zhao FQ, Xiao TX, Huang F, Liu Q
- 1093 Prognostic value of 11-factor modified frailty index in postoperative adverse outcomes of elderly gastric cancer patients in China
Xu ZY, Hao XY, Wu D, Song QY, Wang XX

Retrospective Study

- 1104** Long-term outcomes and failure patterns after laparoscopic intersphincteric resection in ultralow rectal cancers
Qiu WL, Wang XL, Liu JG, Hu G, Mei SW, Tang JQ
- 1116** Predictors for success of non-operative management of adhesive small bowel obstruction
Ng ZQ, Hsu V, Tee WWH, Tan JH, Wijesuriya R
- 1125** Preoperative albumin-bilirubin score is a prognostic factor for gastric cancer patients after curative gastrectomy
Szor DJ, Pereira MA, Ramos MFKP, Tustumi F, Dias AR, Zilberstein B, Ribeiro Jr U
- 1138** Ability of lactulose breath test results to accurately identify colorectal polyps through the measurement of small intestine bacterial overgrowth
Li L, Zhang XY, Yu JS, Zhou HM, Qin Y, Xie WR, Ding WJ, He XX
- 1149** Treatment outcome analysis of bevacizumab combined with cyclophosphamide and oxaliplatin in advanced pseudomyxoma peritonei
Zhang Y, Zhao X, Gao C, Lin LY, Li Y
- 1159** Surgical management of duodenal Crohn's disease
Yang LC, Wu GT, Wu Q, Peng LX, Zhang YW, Yao BJ, Liu GL, Yuan LW
- 1169** Influences of dexmedetomidine on stress responses and postoperative cognitive and coagulation functions in patients undergoing radical gastrectomy under general anesthesia
Ma XF, Lv SJ, Wei SQ, Mao BR, Zhao XX, Jiang XQ, Zeng F, Du XK
- 1178** Dissimilar survival and clinicopathological characteristics of mucinous adenocarcinoma located in pancreatic head and body/tail
Li Z, Zhang XJ, Sun CY, Li ZF, Fei H, Zhao DB

SYSTEMATIC REVIEWS

- 1191** Gallbladder perforation with fistulous communication
Quiroga-Garza A, Alvarez-Villalobos NA, Muñoz-Leija MA, Garcia-Campa M, Angeles-Mar HJ, Jacobo-Baca G, Elizondo-Omana RE, Guzman-Lopez S

META-ANALYSIS

- 1202** Efficacy of transanal drainage tube in preventing anastomotic leakage after surgery for rectal cancer: A meta-analysis
Fujino S, Yasui M, Ohue M, Miyoshi N

CASE REPORT

- 1211** Percutaneous transhepatic cholangial drainage-guided methylene blue for fistulotomy using dual-knife for bile duct intubation: A case report
Tang BX, Li XL, Wei N, Tao T

- 1216** Optimal resection of gastric bronchogenic cysts based on anatomical continuity with adherent gastric muscular layer: A case report
Terayama M, Kumagai K, Kawachi H, Makuuchi R, Hayami M, Ida S, Ohashi M, Sano T, Nunobe S
- 1224** Intrahepatic cholangiocarcinoma in patients with primary sclerosing cholangitis and ulcerative colitis: Two case reports
Miyazu T, Ishida N, Asai Y, Tamura S, Tani S, Yamade M, Iwaizumi M, Hamaya Y, Osawa S, Baba S, Sugimoto K
- 1232** Massive bleeding from a gastric artery pseudoaneurysm in hepatocellular carcinoma treated with atezolizumab plus bevacizumab: A case report
Pang FW, Chen B, Peng DT, He J, Zhao WC, Chen TT, Xie ZG, Deng HH
- 1240** Bedside ultrasound-guided water injection assists endoscopically treatment in esophageal perforation caused by foreign bodies: A case report
Wei HX, Lv SY, Xia B, Zhang K, Pan CK
- 1247** Modified stomach-partitioning gastrojejunostomy for initially unresectable advanced gastric cancer with outlet obstruction: A case report
Shao XX, Xu Q, Wang BZ, Tian YT
- 1256** Small bowel diverticulum with enterolith causing intestinal obstruction: A case report
Wang LW, Chen P, Liu J, Jiang ZW, Liu XX

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INDEXING/ABSTRACTING

The WJGS is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Current Contents/Clinical Medicine, Journal Citation Reports/Science Edition, PubMed, PubMed Central, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database. The 2022 Edition of Journal Citation Reports® cites the 2021 impact factor (IF) for WJGS as 2.505; IF without journal self cites: 2.473; 5-year IF: 3.099; Journal Citation Indicator: 0.49; Ranking: 104 among 211 journals in surgery; Quartile category: Q2; Ranking: 81 among 93 journals in gastroenterology and hepatology; and Quartile category: Q4.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: Rui-Rui Wu, Production Department Director: Xiang Li, Editorial Office Director: Jia-Ru Fan.

NAME OF JOURNAL

World Journal of Gastrointestinal Surgery

ISSN

ISSN 1948-9366 (online)

LAUNCH DATE

November 30, 2009

FREQUENCY

Monthly

EDITORS-IN-CHIEF

Peter Schemmer

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/1948-9366/editorialboard.htm>

PUBLICATION DATE

June 27, 2023

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INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjgnet.com/bpg/GerInfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>



Endoscopic ultrasound-guided portal pressure gradient measurement in managing portal hypertension

Cosmas Rinaldi Adithya Lesmana

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): A
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): D
Grade E (Poor): E

P-Reviewer: Wondmagegn H, Ethiopia; Yoshida H, Japan; Zhang JW, China

Received: October 28, 2022

Peer-review started: October 28, 2022

First decision: November 14, 2022

Revised: November 30, 2022

Accepted: April 24, 2023

Article in press: April 24, 2023

Published online: June 27, 2023



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Abstract

Portal hypertension (PH) is still a challenging clinical condition due to its silent manifestations in the early stage and needs to be measured accurately for early detection. Hepatic vein pressure gradient measurement has been considered as the gold standard measurement for PH; however, it needs special skill, experience, and high expertise. Recently, there has been an innovative development in using endoscopic ultrasound (EUS) for the diagnosis and management of liver diseases, including portal pressure measurement, which is commonly known as EUS-guided portal pressure gradient (EUS-PPG) measurement. EUS-PPG measurement can be performed concomitantly with EUS evaluation for deep esophageal varices, EUS-guided liver biopsy, and EUS-guided cyanoacrylate injection. However, there are still major issues, such as different etiologies of liver disease, procedural training, expertise, availability, and cost-effectiveness in several situations with regard to the standard management.

Key Words: Portal hypertension; Hepatic vein; Endoscopic ultrasound; Portal pressure

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Core Tip: Portal hypertension (PH) is a challenging clinical condition due to its silent manifestations in the early stage. Hepatic vein pressure gradient measurement is still the gold standard for PH diagnosis; however, it is not recommended for a routine measurement in daily practice. Esophagogastroduodenoscopy is still the main procedure for variceal screening due to PH. Recently, there has been a development in using endoscopic ultrasound (EUS) for managing liver diseases. EUS-guided portal pressure gradient measurement seems to be a promising method in the future for early detection and management of PH.

Citation: Lesmana CRA. Endoscopic ultrasound-guided portal pressure gradient measurement in managing portal hypertension. *World J Gastrointest Surg* 2023; 15(6): 1033-1039

URL: <https://www.wjgnet.com/1948-9366/full/v15/i6/1033.htm>

DOI: <https://dx.doi.org/10.4240/wjgs.v15.i6.1033>

INTRODUCTION

Portal hypertension (PH) is a challenging clinical condition due to its silent manifestations in the early stage and it needs to be measured accurately for early diagnosis. PH is defined when there is an increase of portal pressure above 5 mmHg. Clinically significant PH (CSPH) is defined when the portal pressure reaches 10 mmHg and above. CSPH is an important clinical condition because of its clinical consequences, such as the presence of esophageal and gastric varices, ascites, kidney dysfunction, as well as cardiopulmonary complications. These conditions are mostly observed in liver cirrhotic patients with liver disease progression, even though there are non-cirrhotic conditions with PH[1,2]. Hepatic vein pressure gradient (HVPG) measurement has been considered as the gold standard measurement for PH; however, it needs special skill, experience, and high expertise. This procedure also needs to be performed in a dedicated catheterization procedure room[3]. Esophagogastroduodenoscopy (EGD) is a standard procedure for early detection of PH complications, *i.e.*, the presence of varices[4,5]. A major drawback is that these two procedures might not be performed in the same session. Another issue in clinical practice is that not all cases might have accurate portal pressure measurement through this indirect measurement procedure due to the pathology of the portal vein (PV), which does not include the liver architecture disturbance[6,7]. Recently, there has been innovation for portal pressure measurement through endoscopic ultrasound (EUS). The liver images as well as the liver vascularity will be shown clearly for puncture location. However, it needs special skill and knowledge to perform the procedure[8]. In our center, this procedure is also only performed by endoscopists with more than ten years of clinical experience (Figures 1A and B). This review will discuss the role of EUS in portal pressure measurement and its impact in clinical practice.

PH, portal pressure measurement, and issues in clinical practice

PH has been divided into prehepatic, intrahepatic, and post-hepatic. This condition happens due to increased portal blood flow resistance, where it is mostly caused by intrahepatic vascular resistance in chronic liver disturbances. Imbalanced activation between vasoconstrictors and vasodilators due to liver architectural disturbance is the main key to the development of PH. In non-cirrhotic condition, or commonly known as non-cirrhotic PH (NCPH), PV fibrosis or thrombosis is the main issue[9,10].

HVPG measurement is the gold standard for PH assessment. This measurement technique is considered safer than direct measurement *via* transhepatic or transvenous catheterization because a more advanced approach to the inferior vena cava will be required for portal pressure gradient (PPG) measurement. HVPG has been considered as a safe procedure. However, there are several patient conditions which need special attention, such as cardiopulmonary disorders, hepatic encephalopathy, history of cardiac arrhythmias, and evidence of vena cava thrombosis. There are also some possible conditions which can happen during the procedure itself, such as allergic reaction to contrast agent, cardiac arrhythmia during catheter insertion *via* the transjugular route, and bleeding in patients with a very low platelet count or prolonged international normalized ratio[11,12]. On the other hand, this procedure is preferable in patients with significant ascites[3]. Based on HVPG measurement, the strategy of further management has been clearly defined with possible mortality rate. In the early stage, CSPH complications can be prevented with early medication. A randomized controlled trial of carvedilol *vs* endoscopic band ligation (EBL) by Tripathi *et al*[4] has showed that carvedilol has the same efficacy as EBL primary prophylaxis in terms of bleeding prevention. This study has also been supported by another more recent study by Shah *et al*[13] in a multicentre randomized controlled trial. A recent systematic review and meta-analysis by Dwinata *et al*[14] showed that carvedilol had similar efficacy to EBL for primary variceal bleeding prevention. Follow-up HVPG value can also be used to determine the response to the treatment and change to another strategy if needed. In the late stage of the disease or decompensated condition, more advanced complication prevention or advanced mana-



Figure 1 Endoscopic ultrasound procedure. A: Endoscopic ultrasound evaluation in a liver cirrhosis patient with portal hypertension; B: Endoscopic ultrasound-guided portal pressure gradient measurement. Non-surgical Integrated Procedural Room, Hepatobiliary Endoscopy Unit, Dr. Cipto Mangunkusumo National General Hospital, Jakarta, Indonesia.

gement can be decided based on HVPg value[2]. Moitinho *et al*[15] showed the usefulness of early portal pressure measurement in acute variceal bleeding scenario. This prospective study concluded that higher HVPg value is associated with a longer interval between each hospital admission and lower mortality rate. Another study conducted by Ripoll *et al*[16] on 213 liver cirrhosis (LC) patients within a 6-year period showed that HVPg value with a 10 mmHg cut-off can be a good predictor of liver decompensation. The hazard ratio for liver decompensation of HVPg is higher than those of albumin level and model for end-stage liver disease score.

There has been a development of non-invasive methods for PH assessment. A prospective study by Bureau *et al*[17] on the use of transient elastography for PH prediction showed that there was a good correlation between liver stiffness and HVPg ($P < 0.001$). However, based on further analysis, the sensitivity and specificity were becoming higher in line with the increase of the liver stiffness. The main issues were the high value of liver stiffness due to the severity of liver fibrosis condition and varied etiologies of liver diseases[17]. Another prospective study conducted by Palaniyappan *et al*[18] on patients with advanced liver disease using magnetic resonance imaging (MRI) parameters, where the patients also underwent liver stiffness measurement (LSM) before the MRI examination, showed that two MRI parameters, *i.e.*, liver T1 relaxation time and splenic artery velocity, were significantly associated with HVPg values ($r = 0.90$, $P < 0.001$). Even though the LSM was significantly correlated to HVPg ($r = 0.791$, $P < 0.001$), no significant correlation was found in the subgroup of patients with an HVPg value more than 10 mmHg[18]. Another innovation of non-invasive method for assessing PH in clinical practice has been showed in a study by Frankova *et al*[19], where liver stiffness measured by ultrasound-based shear-wave elastography has been correlated well with HVPg values in all LC patients as well as in a subgroup of patients. The liver stiffness values of 16 and 20 mmHg were considered as the best predictive values associated with HVPg. In daily practice, non-invasive methods are still debatable due to their different study results and early detection for PH. MRI examination is also a major issue at present as a routine follow-up examination due to its cost, availability, and patients' comfort[20].

Metabolic condition, such as non-alcoholic fatty liver disease (NAFLD), now well-known as metabolic dysfunction associated fatty liver disease, might be a new challenge in the field of hepatology. It has been postulated that this condition might not have liver fibrosis progression and PH condition in the same line[21]. A prospective study published by Hirooka *et al*[22] revealed that there was a hemodynamic change in early course of the disease process in NAFLD patients, where patients were still in the early liver fibrosis condition based on the median hepatic arteriportal ratio together with splenic elasticity evaluation. Another database study conducted by Mendes *et al*[23] on 354 NAFLD patients showed that 6% of NAFLD patients without evidence of LC had PH complications. NCPH is another issue, where HVPg measurement may not be as good as it is. The complexity of the vascular system and liver pathology assessment for confirming diagnosis have been a challenging issue in clinical practice[24].

EGD is still the main procedure in daily practice to diagnose PH condition based on the presence of esophageal or gastric varices[25,26]. However, luminal evaluation does not always show a significant parameter for the presence of PH as well as in further management for PH[27].

EUS-PPG measurement in PH

Recently, there has been an innovative development in using EUS for diagnosis and management of liver diseases. It has been proposed as “endo-hepatology”, where endoscopic technique innovation can be used in the field of hepatology. It is started from EUS-guided liver biopsy, followed by the use of

EUS for abdominal fluid paracentesis, portal circulation, and EUS-guided intravascular injection for gastroesophageal varices[28,29].

The initial animal study by Lai *et al*[30] on feasibility of EUS-guided PV catheterization showed a good correlation between PV pressure (PVP) obtained through EUS procedure and *via* the transhepatic route ($r = 0.91$). Giday *et al*[31] conducted EUS-guided direct PVP measurement in pigs, and this study showed that there has been consistency in the pressure results, and no evidence of complications was recorded. Another pioneered animal study which used a novel device (compact manometer) was published by Huang *et al*[32], where the authors were able to show a good correlation between EUS approach and transjugular approach for right hepatic vein, PV, and aorta pressure measurements ($r = 0.985$). An innovative animal study on EUS-PPG measurement using a digital pressure wire showed that this method was safe, and there were no complications such as thrombus or bleeding[33]. A human pilot study was subsequently published by Huang *et al*[34], where 28 patients underwent EUS-PPG without any complications. The technical success rate was 100% and the PPG had a good correlation with varices ($P = 0.002$), low platelet count ($P = 0.036$), and gastropathy ($P = 0.007$). A recent study was conducted by Zhang *et al*[35] on the role of EUS-PPG measurement in patients with acute or subacute PH. In this study, the technical success was achieved in 91.7% of the cases, where EUS-PPG measurement had a higher success rate than HVPG measurement. A good correlation was showed through the manometry result between EUS-PPG value and HVPG value ($r = 0.852$). No adverse events were observed during examination. Recently, a retrospective study conducted by Choi *et al*[36] was looking at the correlation between portal pressure and clinical manifestations of PH. In that study, the PPG value was significantly higher in patients with LC (9.46 *vs* 3.61 mmHg; $P < 0.0001$), presence of gastroesophageal varices (13.88 *vs* 4.34 mmHg; $P < 0.0001$), and low platelet count (9.25 *vs* 4.71 mmHg; $P = 0.0022$). Seventy-one of 83 subjects underwent liver biopsy through EUS. No adverse events or complications were observed during and after the procedures. Lesmana[37] has recently published a technique innovation where EUS-PPG was conducted by using a standard manometer set in 13 patients diagnosed with PH. In this case series, two LC patients with Child-Pugh C liver function were included. One patient was diagnosed with NCPH. There were no adverse events or complications occurring during and after the procedure. Another more recent case report using a standard pressure monitor was published just to show the procedural steps and safety[38]. A systematic review and meta-analysis on EUS-PPG to diagnose cirrhosis showed that successful portal pressure measurement was achieved in 91.61% of the cases, with no post-procedural complications, such as bleeding, perforation, and infection (95% confidence interval: 0-2.85). However, based on pooled analysis, abdominal pain developed in 6.15% of cases, emergency department visit in 3.11%, and sore throat in 2.82%[39]. A very recent publication from Lei *et al*[40] on EUS-PPG in 52 LC patients showed that this method was successfully performed in 98% of the cases. The authors showed an innovative puncture location, *i.e.*, transduodenal route, where it can be an alternative location if conventional puncture location was difficult. This study also showed that none of the patients experienced any adverse event (Table 1).

Future directions

EUS-PPG measurement is a better method in portal pressure measurement and diagnosing all PH conditions, not limited to chronic liver disease patients only. However, there are several issues that still need to be discussed before it becomes a clinical recommendation in daily practice. First, EUS-PPG measurement can be performed concomitantly with EUS evaluation for the presence of deep esophageal varices or gastroesophageal varices. The clinical impact of EUS evaluation in the presence of deep esophageal varices in naïve patients as well as in patients with recurrent esophageal varices has been reported in several studies[41-43]. However, whether EUS evaluation is needed in the first setting in all patients with LC for deep varices evaluation is still debatable because there is no strong clinical evidence yet regarding its impact as the first-line examination, and there is a different course of liver disease progression based on each etiology. Second, EUS-PPG measurement can be performed together with EUS-guided liver biopsy; however, EUS-guided liver biopsy is not considered as a routine procedure yet in clinical practice due to the unavailability of standard training, limited experience and availability, and high cost when compared to percutaneous liver biopsy[44,45]. Last but not least, EUS-PPG measurement can be performed and then followed by EUS-guided cyanoacrylate injection for large or deep gastroesophageal varices as well as isolated gastric varices[37,46]. However, the need of EUS approach in acute variceal bleeding and the impact of interventional radiology procedures, such as transjugular intrahepatic porto-systemic shunt or balloon-occluded retrograde transvenous obliteration, are still becoming a long way discussion for managing PH complications[30,47].

CONCLUSION

EUS-PPG is a promising method in future clinical practice for managing PH condition and complications. However, it needs further studies and re-evaluation before it can be recommended as a routine clinical procedure.

Table 1 Endoscopic ultrasound portal pressure gradient study for portal hypertension assessment

Ref.	Type of study	Study design	Results	Technical success rate	Adverse events
Lai <i>et al</i> [30], 2004	Animal	Experimental	EUS-PVP correlated well with transhepatic catheterization ($r = 0.91$)	100%	None
Giday <i>et al</i> [31], 2008	Animal	Experimental	Consistent results of portal pressure measurements for 1 h	100%	None
Huang <i>et al</i> [32], 2016	Animal	Experimental	Excellent correlation between EUS and IR methods in all pressure range ($r = 0.985-0.99$)	100%	None
Schulman <i>et al</i> [33], 2017	Animal	Experimental	EUS-PPG results did not differ from transhepatic portal venule measurement	100%	None
Huang <i>et al</i> [34], 2017	Human ($n = 28$)	Pilot	EUS-PPG had an excellent correlation with clinical parameters of portal hypertension ($P < 0.05$)	100%	None
Zhang <i>et al</i> [35], 2021	Human ($n = 12$)	Cohort prospective	Good correlation between EUS-PPG and HVPG ($r = 0.923$)	91.7%	None
Choi <i>et al</i> [36], 2022	Human ($n = 83$)	Retrospective	EUS-PPG correlates well with clinical markers of portal hypertension ($P < 0.05$)	100%	None
Lesmana[37], 2022	Human ($n = 13$)	Case series	EUS-PPG showed consistent pattern of portal pressure	100%	None
Reddy <i>et al</i> [39], 2022	Human ($n = 128$)	Systematic review and meta-analysis	Good correlation between clinical portal hypertension and portal pressure gradients	91.61%	None
Lei <i>et al</i> [40], 2023	Human ($n = 52$)	Case series	EUS-PPG results are significantly higher in patients with a history of gastro-esophageal bleeding ($P < 0.05$)	98%	None

EUS-PPG: Endoscopic ultrasound portal pressure gradient; HVPG: Hepatic vein pressure gradient; PVP: Portal vein pressure; IR: Interventional radiology.

ACKNOWLEDGEMENTS

I would like to thank Prof. Rino Alvani Gani, MD, PhD, FINASIM who has given a big support for EUS-PPG development at Hepatobiliary Division, Department of Internal Medicine, Dr. Cipto Mangunkusumo National General Hospital, Medical Faculty Universitas Indonesia, Jakarta.

FOOTNOTES

Author contributions: Lesmana CRA conceptualized the idea and wrote the manuscript.

Conflict-of-interest statement: The author reports no relevant conflicts of interest for this article.

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Country/Territory of origin: Indonesia

ORCID number: Cosmas Rinaldi Adithya Lesmana 0000-0002-8218-5971.

S-Editor: Wang JJ

L-Editor: Wang TQ

P-Editor: Yu HG

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