

Expert opinion on bleeding risk from invasive procedures in cirrhosis



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Background & Aims: Despite several recent international guidelines, no consensus exists on the bleeding risk nor haemostatic parameter thresholds that define the safety of invasive procedures in patients with cirrhosis. The aim of this study was to establish a position paper on the bleeding risk associated with invasive procedures in patients with cirrhosis among the experts involved in various guidelines.

Methods: All experts involved in recent guidelines on the management of invasive procedures in patients with cirrhosis were invited to classify 80 procedures as "high risk" or "low risk" with respect to bleeding. Procedures were considered high risk when the estimated risk of major bleeding was 1.5% or more, or when even minor bleeding might lead to significant morbidity or death. The experts were also asked to choose safety thresholds for laboratory test values at which elective invasive procedures could be safely performed. The predetermined threshold considered as "consensus" was $\geq 75\%$ agreement.

Results: Fifty-two experts participated in the study. Out of 80 procedures, a consensus opinion was reached for 52 procedures (65%): 17 procedures were classified as "high risk", primarily interventional endoscopic procedures, percutaneous organ biopsies, or procedures involving the central nervous system; and 35 as "low risk", primarily "diagnostic" procedures. The lowest platelet counts at which performance of a low-risk procedure or a high-risk procedure/surgery were deemed acceptable were $30 \times 10^9/L$ and $50 \times 10^9/L$, respectively. Experts did not believe that international normalised ratio should be considered before performing low-risk procedures; 71% also indicated that it should not be considered before performing high-risk procedures.

Conclusions: This experience-based classification may be helpful to refine future study designs and to guide clinical decision making regarding invasive procedures in patients with cirrhosis.

Impact and implications: Several risk classifications and management guidelines for invasive procedures in patients with cirrhosis have been proposed, but with conflicting recommendations. By providing a position paper, based on the opinion of a broad panel of experts, on the bleeding risk associated with 52 invasive procedures in patients with cirrhosis, this survey will help to provide a framework for future study design. The consensus on platelet count, international normalised ratio, fibrinogen and activated partial thromboplastin time identified in this survey will inform physicians regarding the laboratory test values considered acceptable by the experts prior to the performance of an elective invasive procedure in patients with cirrhosis.

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Introduction

The liver plays a central role in haemostasis by producing most of the pro- and anticoagulant factors present in the body. Consequently, during cirrhosis, the concomitant drop in pro- and

anticoagulant factors leads to a precarious haemostatic balance, which may favour thrombosis and/or bleeding. Bleeding in patients with cirrhosis can be classified into three categories: bleeding due to portal hypertension with little influence from haemostatic mechanisms, bleeding after an invasive procedure (most often associated with vessel rupture/puncture rather than being secondary to haemostatic failure), and bleeding related to premature clot dissolution secondary to hyperfibrinolysis.¹ Procedure-related bleeding occurs in around 7% of patients with cirrhosis and is associated with significantly higher 28-day mortality.² Prevention of such events requires a proper assessment of the bleeding risk based on the medical history of the

Keywords: haemorrhage; coagulation; haemostasis; biopsy; anticoagulant; procedural related bleeding; platelet; INR; aPTT; fibrinogen.

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patient, on the risk of the procedure itself, on the urgency of the procedure and on the results of laboratory tests.^{2,3} Accordingly, multiple recent international guidelines proposed classifications of the bleeding risk associated with invasive procedures.^{1,4–8} Most international guidelines considered a procedure to be high risk if bleeding (major or not) is expected in $\geq 1.5\%$ of procedures, or if even minor bleeding is likely to result in permanent organ damage or death.^{1,6–8} Yet, these guidelines assessed bleeding risk differently for the same procedure, highlighting the need for a broad consensus on this topic (Fig. S1). As an example, the EASL (European Association for the Study of the Liver) guidelines classified both percutaneous and transjugular liver biopsies as low risk, while the AASLD (American Association for the Study of Liver Diseases) guidelines classified both liver biopsy approaches as high risk. ISTH (The International Society on Thrombosis and Haemostasis) classified transjugular liver biopsies as low risk but percutaneous liver biopsies as high risk.^{1,7,8} Likewise, guidelines defined the laboratory threshold values associated with bleeding risk differently.^{1,4–10}

These divergences across guidelines highlighted the need to obtain a broad consensus of experts on the bleeding risk associated with invasive procedures in patients with cirrhosis.

Therefore, the aim of this study was to survey a group of international experts on the bleeding risk associated with invasive procedures in patients with cirrhosis, to establish a position paper on (1) individual procedural risks, and (2) laboratory thresholds at which procedures can be safely performed.

Materials and methods

All experts involved in recent guidelines on the management of invasive procedures in patients with cirrhosis were contacted, namely authors of the AASLD 2021, ACG (American College of Gastroenterology) 2020, AGA (American Gastroenterological Association) 2019, AGA 2021, BSG (British Society of Gastroenterology) 2020 and the ISTH 2022 guidelines, as well as panel and Delphi panel members of the EASL 2022 guidelines and of the ongoing AASLD guidelines.^{1,4–10}

As a first step, experts were invited to classify 80 procedures as being associated with a “high risk” or “low risk” of bleeding. Procedures included those performed in patients with cirrhosis in the area of digestive endoscopy, hepatology, vascular procedures, pulmonary medicine, neurology, urology and nephrology, gynaecology and others (questionnaire presented in Supplementary Text 1). These procedures were derived from the ones included in recent guideline classifications, with some added according to expert opinion (Fig. S1). Procedures were considered high risk when the estimated risk of major bleeding was 1.5% or more, or when even minor bleeding might lead to significant morbidity or death, such as with intracranial bleeding.^{1,4,6–8} Percentage of agreement was calculated without taking into account the experts who responded “I don’t know”. The predetermined threshold considered as “consensus” was 75% agreement or more.

As a second step, the same experts were asked to choose thresholds of laboratory test values at which they considered it acceptable to perform an elective invasive procedure (low risk or high risk according to the consensus obtained in step one) or a surgical procedure considered by the surgeon as being associated with a high risk of bleeding, in patients with cirrhosis not taking anticoagulants, anti-platelet agents, and without active bacterial infection or acute kidney failure (questionnaire presented in

Supplementary Text 2). Percentage of agreement was calculated after excluding the experts who answered “I don’t know” to the particular question. When the experts answered “I do not recommend this parameter to judge bleeding risk in this setting in patients with cirrhosis”, it was considered as “any of the laboratory test values”, as it reflects that the experts do not take into account the result of the laboratory test before performing the procedure. The predetermined threshold considered as “consensus” was $\geq 75\%$ agreement.

Results

Experts’ characteristics

Out of a total of 72 invited experts, 52 participated in the study (72%): 35 from Europe, 16 from the USA, and one from Asia. Of those who did not participate, one was more laboratory oriented and was not involved in patient care; one had retired from clinical practice; and 18 declined to respond (Fig. 1). All the experts had participated or are currently involved in drafting recommendations on procedural bleeding risk in patients with cirrhosis.^{1,4,5,7–10} Those who participated were specialists in gastroenterology/hepatology (n = 36; 69%), radiology (n = 4; 8%), anesthesiology or intensive care medicine (n = 3; 6%), haematology/haemostasis (n = 8; 15%), or internists (n = 1; 2%) (Table 1).

Classification of invasive procedures

Out of the 80 procedures, a consensus opinion ($\geq 75\%$ agreement) was reached for 52 procedures (65%): 17 procedures were classified as “high risk” and 35 as “low risk”. A consensus could not be reached for 28 procedures (Fig. 2 and Table S1). Vascular procedures were almost all classified as low risk except for three procedures for which a consensus could not be reached (arterial line placement; therapeutic coronary angiography; and angiography or venography with intervention), though the majority favoured these procedures as low risk. For

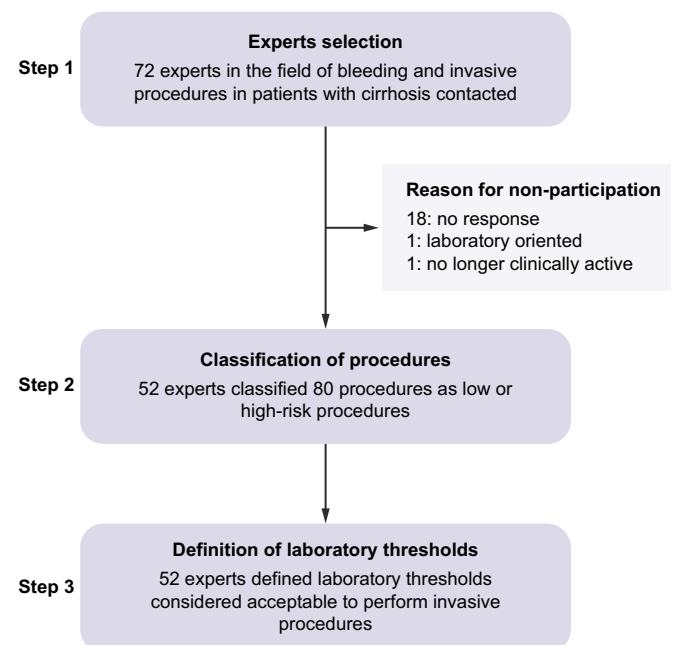


Fig. 1. Summary of the position paper process.

Table 1. Experts' characteristics

Characteristics of the experts	n	%
Gender		
Woman	20	38
Man	32	62
Country where currently working		
Austria	1	2
France	6	11
Germany	1	2
India	1	2
Italy	9	17
Malta	1	2
Netherlands	1	2
Romania	1	2
Spain	4	8
Switzerland	2	4
Sweden	1	2
United Kingdom	8	15
United States of America	16	31
Medical specialty		
Gastroenterology/hepatology	36	69
Radiology	4	8
Anesthesiology or intensive care medicine	3	6
Hematology/haemostasis	8	15
Internal medicine	1	2
Guideline in which expert was involved ^a		
American Association for the Study of Liver Diseases (AASLD) 2021 ¹	9	17
American College of Gastroenterology (ACG) 2020 ⁹	5	10
American Gastroenterological Association (AGA) 2019 ⁵	4	8
American Gastroenterological Association (AGA) 2021 ⁶	0	0
American Gastroenterological Association (AGA) 2021 ⁴	2	4
British Society of Gastroenterology (BSG) 2020 ¹⁰	5	10
European Association for the Study of the Liver (EASL) 2022 ⁷	34	65
International Society on Thrombosis and Haemostasis (ISTH) 2022 ⁸	4	8
Other ongoing initiative	3	6
Number of articles (co)authored on topic of bleeding risk from invasive procedures in patients with cirrhosis ^b		
<6	4	8
6-20	18	35
21-50	20	38
>50	10	19

^a 10 experts were involved in 2 guidelines or more.

^b Research for the articles (co) authored by the expert was conducted on Pubmed by searching: ((XX[Author]) AND ((coagulation[Title/Abstract]) OR (hemostasis[Title/Abstract]) OR (haemostasis[Title/Abstract]) OR (anticoagulant[Title/Abstract]) OR (anticoagulation[Title/Abstract]) OR (bleeding[Title/Abstract]) OR (hemorrhage[Title/Abstract]) OR (haemorrhage[Title/Abstract]) OR (anticoagulation[Title/Abstract]) OR (DOAC[Title/Abstract]) OR (DOACS[Title/Abstract]) OR (VKA[Title/Abstract]) OR (LMWH[Title/Abstract]) OR (thrombin[Title/Abstract]) OR (biopsy[Title/Abstract]) OR (invasive procedure[Title/Abstract]) OR (procedure related bleeding[Title/Abstract]))) AND ((cirrhosis[Title/Abstract]) OR (liver[Title/Abstract]) OR (hepatitis[Title/Abstract]) OR (acute decompensation of cirrhosis[Title/Abstract])).

endoscopic procedures, a consensus of low risk of bleeding was established for 13 procedures, mainly diagnostic procedures, *i.e.* diagnostic endoscopy (colonoscopy, upper endoscopy, upper or lower ultrasound without fine needle aspiration, video-capsule), endoscopy with polypectomy <1 cm and endoscopic retrograde cholangiopancreatography (ERCP) without sphincterotomy. Nine procedures were considered high risk, mostly interventional endoscopic procedures such as endoscopy with polypectomy >1 cm, submucosal dissection or mucosal resection, cystogastrostomy and percutaneous gastrostomy.

Among procedures frequently performed in hepatology, paracentesis (both diagnostic and therapeutic) was classified as low risk, as were transjugular liver biopsy and hepatic venous pressure gradient measurement. However, no consensus was obtained for percutaneous liver biopsy and TIPS (transjugular intrahepatic portosystemic shunt), although there was a trend towards classifying these procedures as high risk for bleeding.

In pulmonary medicine, urology, nephrology, and gynaecology, diagnostic endoscopic procedures were classified as low risk

for bleeding, while solid organ biopsies were classified as high risk. Two out of three neurological procedures were classified as high risk.

Determination of laboratory test thresholds at which invasive procedures can be safely performed

The lowest platelet counts at which performance of a low-risk procedure or a high-risk procedure/surgery were deemed acceptable by the experts were $30 \times 10^9/L$ and $50 \times 10^9/L$, respectively. The experts did not believe that international normalised ratio (INR) should be considered before performing low-risk procedures, nor high-risk procedures, although the 75% agreement threshold was not reached for the latter (71% agreement). The highest acceptable value was 2 for high-risk surgeries. The lowest acceptable values for fibrinogen for low-risk procedures, high-risk procedures and high-risk surgeries were 60 mg/dl, 100 mg/dl and 120 mg/dl, respectively. Experts did not believe that activated partial thromboplastin time should be considered before performing any type of procedure,

		Procedure	Voting percentage	
			Low risk	High risk
Digestive endoscopy	ERCP	Without sphincterotomy	90%	10%
		With biliary or pancreatic sphincterotomy	12%	88%
		With papillary balloon dilatation without sphincterotomy	67%	33%
		With biliary or pancreatic stent placement without sphincterotomy	80%	20%
	Upper and lower	Mucosal resection	25%	75%
		Submucosal dissection	8%	92%
		Hemostasis with argon plasma coagulation	92%	8%
		Radiofrequency ablation	67%	33%
		Video capsule	100%	0%
		Ultrasound without fine-needle aspiration	98%	2%
		Ultrasound with fine-needle aspiration	59%	41%
		Stricture dilatation (pneumatic or bougie)	32%	68%
		Stricture dilatation (balloon)	38%	63%
		Enteral stent deployment	77%	23%
	Upper	Cystogastrostomy	13%	87%
		Polypectomy <1 cm	76%	24%
		Polypectomy >1 cm	12%	88%
		Diagnostic (with or without biopsy)	98%	2%
		Variceal ligation	71%	29%
		Glue injection of gastric varices	54%	46%
		Peroral endoscopic myotomy	7%	93%
		Ampullary resection	6%	94%
		Percutaneous gastrostomy or jejunostomy placement	22%	78%
		Diagnostic balloon-assisted enteroscopy	90%	10%
	Therapeutic balloon-assisted enteroscopy	64%	36%	
	Push enteroscopy	88%	12%	
	Lower	Polypectomy <1 cm	78%	22%
		Polypectomy >1 cm	10%	90%
		Flexible sigmoidoscopy (with or without biopsy)	96%	4%
		Diagnostic colonoscopy (with or without biopsy)	92%	8%
Vascular	Central venous catheter placement	81%	19%	
	Peripherally-inserted central catheter line placement	90%	10%	
	Arterial line placement	73%	27%	
	Central line removal	94%	6%	
	Cardiac catheterization	82%	18%	
	Transesophageal echocardiography	94%	6%	
	Diagnostic coronary angiography	90%	10%	
	Therapeutic coronary angiography	66%	34%	
	Angiography or venography with intervention	60%	40%	
	Inferior vena cava filter placement	87%	13%	

		Procedure	Voting percentage	
			Low risk	High risk
Hepatology	Percutaneous liver biopsy		33%	67%
	Transjugular liver biopsy		83%	17%
	Laparoscopic liver biopsy		46%	54%
	Hepatic venous pressure gradient measurement		92%	8%
	Portal recanalization		40%	60%
	Transjugular intrahepatic portosystemic shunt		38%	62%
	Transcatheter arterial chemoembolization or radioembolization		62%	38%
	Percutaneous ablation of liver cancer		40%	60%
	Cholecystostomy or percutaneous biliary drain placement		22%	78%
	Diagnostic paracentesis		98%	2%
	Therapeutic paracentesis		96%	4%
	Tunneled ascitic drain placement		59%	41%
Pulmonary medicine	Thoracentesis		78%	22%
	Bronchoscopy without biopsy		96%	4%
	Bronchoscopy with biopsy		29%	71%
	Therapeutic bronchoscopy		26%	74%
	Intrathoracic organ biopsy		9%	91%
	Tunneled pleural drain placement		44%	56%
Urology and nephrology	Prostate biopsy		25%	75%
	Cystoscopy		100%	0%
	Ureteroscopy		98%	2%
	Lithotripsy (kidney, bladder, ureter)		59%	41%
	Percutaneous kidney biopsy		10%	90%
	Transjugular kidney biopsy		61%	39%
Nephrostomy tube placement		24%	76%	
Neurology	Lumbar puncture		41%	59%
	Epidural catheter placement		23%	77%
	Central nervous system procedure		2%	98%
Gynecology	Colposcopy with cervical biopsy		79%	21%
	Diagnostic hysteroscopy		100%	0%
	Hysteroscopy with biopsy		64%	36%
Miscellaneous	Amniocentesis		38%	62%
	Dental cleaning		100%	0%
	Dental extraction		45%	55%
	Intra-articular puncture		65%	35%
	Intra-articular injection		77%	23%
	Lymph node percutaneous biopsy		83%	17%
	Non-liver intra-abdominal solid-organ biopsy		15%	85%
	Skin biopsy		98%	2%
	Drainage catheter exchange		98%	2%

Consensus for a procedure to be at "low bleeding risk"
 Consensus for a procedure to be at "high bleeding risk"
 No consensus

Fig. 2. Classification of the bleeding risk associated with invasive procedures. Green and purple colours indicate when a consensus ($\geq 75\%$ agreement) was reached for low-risk or high-risk procedures, respectively. White colour indicates that a consensus was not reached.

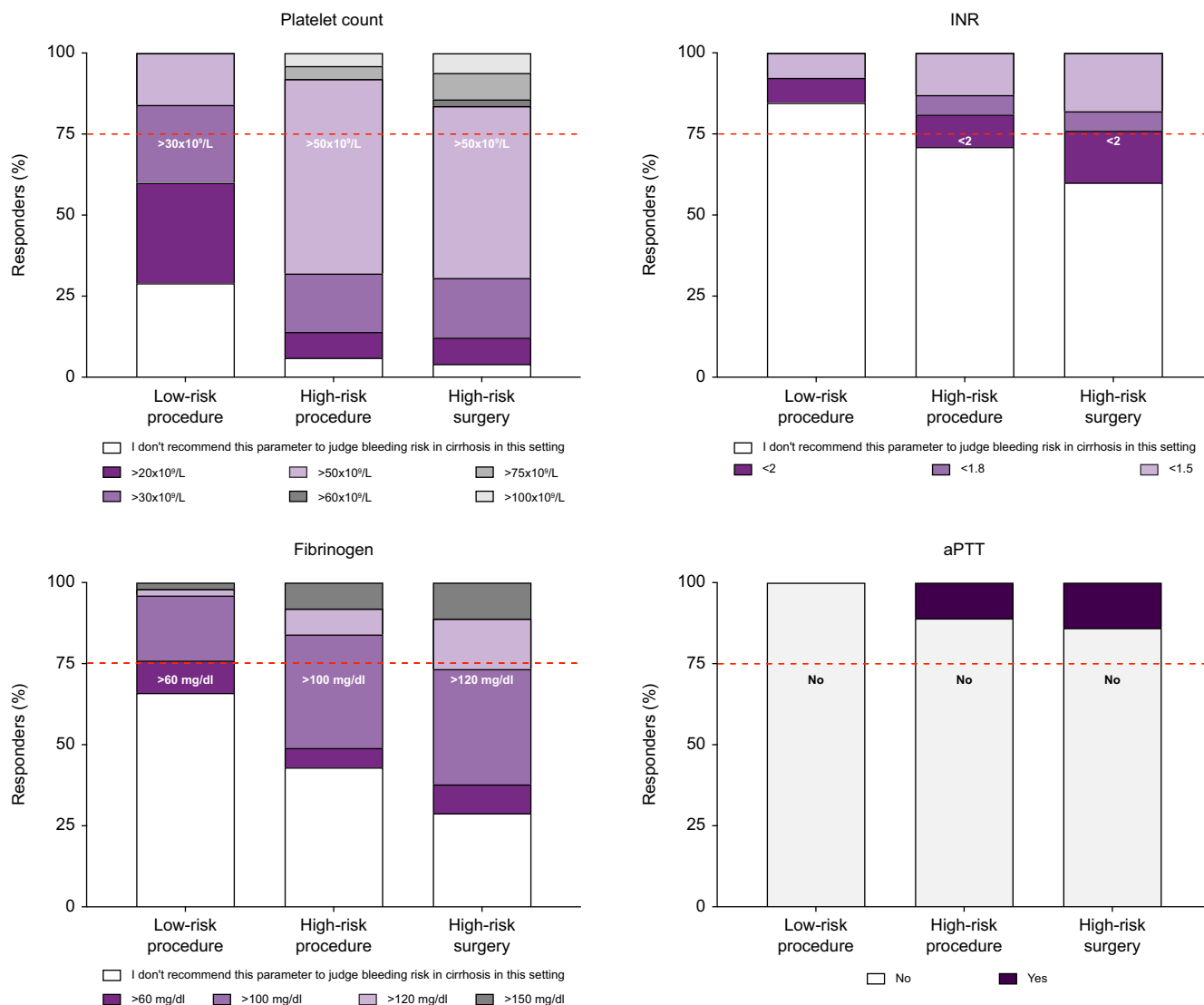


Fig. 3. Results of the survey for laboratory tests thresholds considered safe prior to low-risk and high-risk procedure or high-risk surgery. Percentage of agreement was calculated without taking into account the experts who answered "I don't know". To define a threshold, the responses "I do not recommend this parameter to judge bleeding risk in this setting in patients with cirrhosis" were considered as any of the blood test values. aPTT, activated partial thromboplastin time; INR, international normalised ratio.

namely low- or high-risk procedures or high-risk surgery (Fig. 3 and Table S2). It should be emphasized that determining the specific circumstances and modalities for correcting INR, platelets, and fibrinogen to threshold levels was not part of the survey.

Establishment of an algorithm for the management of bleeding risk following invasive procedures and surgeries in patients with cirrhosis

Following the results obtained for the classification of invasive procedures and laboratory tests thresholds, an algorithm was established by consensus to help clinicians in their daily management of patients with cirrhosis subjected to invasive procedures or high-risk surgeries (Fig. 4). Green boxes indicate when a consensus was strong and that the procedure could be performed without need for prophylactic measures. As experts were not questioned about correcting platelet count and/or

fibrinogen concentration and/or INR, patients in the grey squares (intermediate-risk group) should not routinely receive prophylactic measures to correct haemostasis. Regarding the INR to determine bleeding risk in patients with cirrhosis undergoing high-risk procedures, it is worth noting that – even though the 75% threshold was not reached – 71% of the experts did not recommend its measurement (explaining why INR has been put in brackets in the algorithm). This algorithm is not put forward as a guideline, but rather represents the consensus opinion of established investigators in this field.

Discussion

The present study, involving a large panel of recognised international experts, was designed to overcome the heterogeneity across international guidelines regarding the classifications of bleeding risk associated with invasive procedures in patients

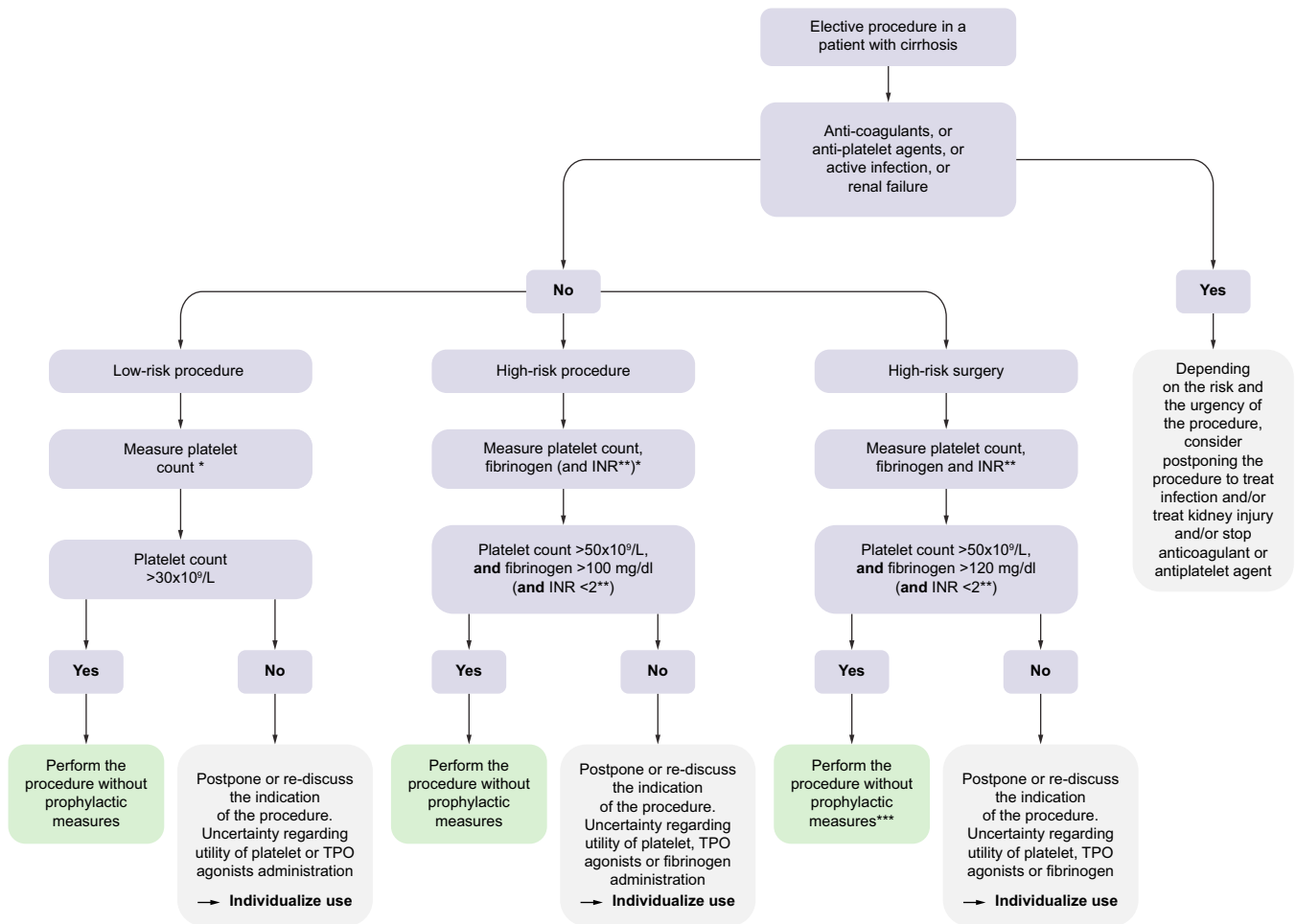


Fig. 4. Proposed algorithm based on the results of the present survey to stratify and manage bleeding risk following invasive procedures and surgeries in patients with cirrhosis. *If the patient has reasonably recent laboratory test results, re-measuring might not be needed. **Assessing INR to predict procedure-related bleeding may rely more on customary practices than on recent data regarding INR in cirrhosis. Moreover, recent guidelines recommended not to correct a prolonged INR (BSG 2020, ACG 2020, AASLD 2021, AGA 2021, ISTH 2022, EASL 2022). *** The decision to proceed with surgery must carefully balance the patient's individual risks, such as the severity of liver disease and any comorbidities, against the potential harm of foregoing the procedure. INR, international normalised ratio; TPO, thrombopoietin.

with cirrhosis. This survey also aimed to identify laboratory thresholds at which the experts, based on their practice, considered it safe to proceed with low-risk and high-risk procedures, as well as high-risk surgeries in patients with cirrhosis.

The first main finding of this study is a consensus of 52 experts on the assessment of bleeding risk associated with 80 invasive procedures frequently performed in patients with cirrhosis. A consensus could be reached for 52 procedures, including 17 high-risk procedures and 35 low-risk procedures. Low-risk procedures were primarily “diagnostic” procedures, whereas high-risk procedures were primarily interventional endoscopic procedures, percutaneous organ biopsies, or procedures involving the central nervous system. Out of these 52 procedures for which a consensus was reached among experts, an agreement between guidelines was already present for 21 procedures, the procedure-related risk was not mentioned in more than one guideline for 22 procedures, while no consensus between guidelines was available for nine procedures, namely ERCP with or without sphincterotomy, upper and lower endoscopy with polypectomy <1 cm, diagnostic balloon assisted

enteroscopy, transjugular liver biopsy, cystogastrostomy, percutaneous gastrostomy or jejunostomy placement and non-liver intra-abdominal solid organ biopsy. Of note, three procedures (endoscopy with haemostasis with argon plasma coagulation, ERCP with biliary/pancreatic stent placement without sphincterotomy and intra-articular injection) were previously classified in guidelines as high risk but were considered by experts as low risk. While this position paper will be a valuable tool to help homogenise further studies on invasive procedures in patients with cirrhosis, it should be noted that the rate of bleeding and the risk of bleeding are not interchangeable concepts.¹¹

The second important finding of this position paper concerns the thresholds for laboratory tests at which invasive procedures can be considered safe. The highest acceptable value for the INR to perform high-risk surgeries was 2, but the majority of experts determined that INR should not be taken into account before performing low-risk and high-risk procedures, although the 75% agreement threshold was not reached in the latter case. This opinion is in line with the results of a recent multicentre prospective study including 1,187 patients with cirrhosis undergoing

3,006 non-surgical procedures, where no association between procedure-related bleeding and INR was found.² Indeed, the INR does not reflect the haemostatic state of patients with cirrhosis as it is only a measure of pro-coagulant factor activity and not anticoagulant factors (*i.e.* protein C, antithrombin) that are also decreased in patients with cirrhosis. Therefore, correction using fresh frozen plasma or prothrombin complex concentrate is not recommended as they are associated with important side effects while their effect on preventing procedure-related bleeding is debatable (Fig. 4).¹² Regarding platelet count, a consensus was reached for a threshold of $30 \times 10^9/L$ for low-risk procedures and $50 \times 10^9/L$ for high-risk procedures or high-risk surgeries. Of note, about 30% of the experts did not consider platelet count measurements before low-risk procedures, and another 33% required a lower threshold of only $20 \times 10^9/L$ for low-risk procedures. As the ability of platelets to predict procedure-related bleeding is not proven,² the use of thrombopoietin agonists or platelet transfusion should be decided on a case-by-case basis.² There was consensus that measurement of activated partial thromboplastin time was not required prior to performing an invasive procedure. Still, it should be highlighted that haemostasis does not fully explain post-procedural bleeding, which is often the consequence of a dual mechanism including vascular injury and disturbed haemostasis.¹ It is also important to stress that the algorithm presented in Fig. 4 is based on expert opinion, and – while it may help practitioners in their day-to-day practice – validation by *ad hoc* prospective studies is required.

There are, however, certain limits to this position paper that must be emphasised. Firstly, this study is not evidence based, but rather reflects the opinion of well-known experts with publications in this field; 58% had over 20 publications on the

topic. Secondly, the experts who took part in this position paper are mainly from Europe and North America and were mainly hepatologists. As a consequence, the opinion expressed here might not be representative of practices in other parts of the world or in other specialties, especially the specialists who might carry out the procedure, such as surgeons. Moreover, clinical expertise of hepatologists for certain procedures (*e.g.* intra-articular injection or lymph node percutaneous biopsy) might be limited. Future recommendations will need to involve a more diverse range of specialists to ensure a well-rounded perspective on the subject. Thirdly, a consensus could not be reached for 28 procedures (including TIPS placement, variceal ligation or percutaneous liver biopsy), although some tendency towards categorisation as high risk or low risk was observed. Fourthly, the current classification does not consider the severity of the underlying liver disease, which has recently been confirmed to be a risk factor for post-procedural bleeding.² Severity of liver disease influences not only the risk of post-procedural bleeding, but also the consequences of this bleeding for the patient.

In conclusion, we have provided a position paper, based on the opinions of 52 published experts, on the assessment of bleeding risk associated with a variety of invasive procedures in patients with cirrhosis, and the suggested laboratory thresholds at which physicians can proceed with high-risk and low-risk procedures, as well as high-risk surgeries. While prospective studies that include various potential interventions and individual susceptibility are necessary (though difficult to carry out) to make more definitive recommendations, this experience-based classification may be helpful to refine future study design and to inform clinical decision making for invasive procedures in patients with cirrhosis.

Abbreviations

ERCP, endoscopic retrograde cholangiopancreatography; INR, international normalised ratio.

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Conflicts of interest

The authors of this study declare that they do not have any conflict of interest.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

A. Riescher-Tuczkiwicz and P.E. Rautou analyzed the data and wrote the manuscript.

P.E. Rautou, E. Villa, S. Caldwell and P.S. Kamath designed and supervised the research and revised manuscript. All authors reviewed and approved the final version of the manuscript.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supplementary data

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Supplemental information

Expert opinion on bleeding risk from invasive procedures in cirrhosis

Alix Riescher-Tuczkiwicz, Stephen H. Caldwell, Patrick S. Kamath, Erica Villa, Pierre-Emmanuel Rautou, and on behalf of the Bleeding in liver diseases investigators

Supplementary Material

Classification of bleeding risk from invasive procedures in patients with cirrhosis: an expert consensus

Alix Riescher-Tuczkiwicz¹, Stephen H Caldwell², Patrick S Kamath³, Erica Villa⁴,
Pierre-Emmanuel Rautou^{1,5}

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Supplementary text 1.

Questionnaire to define the bleeding risk associated with 80 invasive procedures frequently performed in patients with cirrhosis

Note for the experts:

In this questionnaire, we listed the procedures performed in patients with cirrhosis and would like to ask you to rank those procedures as at low or high risk of major bleeding. The procedures are grouped into different categories: hepatology, digestive endoscopy, cardiovascular, pneumology, urology, neurology, gynecology and miscellaneous.

Procedures should be considered at high-risk when the estimated bleeding risk is $\geq 1.5\%$, or when even minor bleeding may lead to severe consequences, or death. Procedures are considered at low-risk when the expected occurrence of bleeding is $< 1.5\%$.

The predetermined threshold that we consider for consensus is 75%. If the 75% threshold is not reached, the conclusion will be "we could not reach a consensus on the risk of this procedure".

Hepatology

Percutaneous liver biopsy

- High risk procedure
- Low risk procedure
- Do not know

Transjugular liver biopsy

- High risk procedure
- Low risk procedure
- Do not know

Laparoscopic liver biopsy

- High risk procedure
- Low risk procedure
- Do not know

Hepatic venous pressure gradient measurement

- High risk procedure
- Low risk procedure
- Do not know

Portal recanalization

- High risk procedure
- Low risk procedure
- Do not know

Transjugular intrahepatic portosystemic shunt

- High risk procedure

- Low risk procedure
- Do not know

Transcatheter arterial chemoembolization / radioembolization

- High risk procedure
- Low risk procedure
- Do not know

Percutaneous ablation of liver cancer

- High risk procedure
- Low risk procedure
- Do not know

Biliary intervention (cholecystostomy or percutaneous biliary drain placement)

- High risk procedure
- Low risk procedure
- Do not know

Diagnostic paracentesis

- High risk procedure
- Low risk procedure
- Do not know

Therapeutic paracentesis

- High risk procedure
- Low risk procedure
- Do not know

Tunneled ascitic drain placement

- High risk procedure
- Low risk procedure
- Do not know

Digestive endoscopy

Endoscopic retrograde cholangiopancreatography without sphincterotomy

- High risk procedure
- Low risk procedure
- Do not know

Endoscopic retrograde cholangiopancreatography with biliary or pancreatic sphincterotomy

- High risk procedure
- Low risk procedure
- Do not know

Endoscopic retrograde cholangiopancreatography with papillary balloon dilatation without sphincterotomy

- High risk procedure
- Low risk procedure

- Do not know

Endoscopic retrograde cholangiopancreatography with biliary or pancreatic stent placement without sphincterotomy

- High risk procedure
- Low risk procedure
- Do not know

Endoscopic (both upper and lower) mucosal resection

- High risk procedure
- Low risk procedure
- Do not know

Endoscopic (both upper and lower) submucosal dissection

- High risk procedure
- Low risk procedure
- Do not know

Endoscopic (both upper and lower) hemostasis with argon plasma coagulation

- High risk procedure
- Low risk procedure
- Do not know

Endoscopic (both upper and lower) radiofrequency ablation

- High risk procedure
- Low risk procedure
- Do not know

Endoscopic (both upper and lower) video-capsule

- High risk procedure
- Low risk procedure
- Do not know

Endoscopic (both upper and lower) ultrasound without fine-needle aspiration

- High risk procedure
- Low risk procedure
- Do not know

Endoscopic (both upper and lower) ultrasound with fine-needle aspiration

- High risk procedure
- Low risk procedure
- Do not know

Endoscopic (both upper and lower) stricture dilatation (pneumatic or bougie)

- High risk procedure
- Low risk procedure
- Do not know

Endoscopic (both upper and lower) stricture dilatation (balloon)

- High risk procedure

- Low risk procedure
- Do not know

Endoscopic (both upper and lower) enteral stent deployment

- High risk procedure
- Low risk procedure
- Do not know

Upper endoscopy: cystogastrostomy

- High risk procedure
- Low risk procedure
- Do not know

Upper endoscopy: polypectomy < 1cm

- High risk procedure
- Low risk procedure
- Do not know

Upper endoscopy: polypectomy > 1cm

- High risk procedure
- Low risk procedure
- Do not know

Upper endoscopy: diagnostic (with or without biopsy)

- High risk procedure
- Low risk procedure
- Do not know

Upper endoscopy: variceal ligation

- High risk procedure
- Low risk procedure
- Do not know

Upper endoscopy: glue injection of gastric varices

- High risk procedure
- Low risk procedure
- Do not know

Upper endoscopy: peroral endoscopic myotomy (POEM)

- High risk procedure
- Low risk procedure
- Do not know

Upper endoscopy: ampullary resection

- High risk procedure
- Low risk procedure
- Do not know

Upper endoscopy: percutaneous gastrostomy or jejunostomy placement

- High risk procedure

- Low risk procedure
- Do not know

Upper endoscopy: diagnostic balloon assisted enteroscopy

- High risk procedure
- Low risk procedure
- Do not know

Upper endoscopy: therapeutic balloon assisted enteroscopy

- High risk procedure
- Low risk procedure
- Do not know

Upper endoscopy: push enteroscopy

- High risk procedure
- Low risk procedure
- Do not know

Lower endoscopy: polypectomy <1cm

- High risk procedure
- Low risk procedure
- Do not know

Lower endoscopy: polypectomy > 1cm

- High risk procedure
- Low risk procedure
- Do not know

Lower endoscopy: flexible sigmoidoscopy (with or without biopsy)

- High risk procedure
- Low risk procedure
- Do not know

Lower endoscopy: diagnostic colonoscopy (with or without biopsy)

- High risk procedure
- Low risk procedure
- Do not know

Vascular

Central venous catheter placement

- High risk procedure
- Low risk procedure
- Do not know

Peripherally inserted central catheter line placement

- High risk procedure
- Low risk procedure
- Do not know

Arterial line placement

- High risk procedure
- Low risk procedure
- Do not know

Central line removal

- High risk procedure
- Low risk procedure
- Do not know

Cardiac catheterization

- High risk procedure
- Low risk procedure
- Do not know

Transesophageal echocardiography

- High risk procedure
- Low risk procedure
- Do not know

Diagnostic coronary angiography

- High risk procedure
- Low risk procedure
- Do not know

Therapeutic coronary angiography

- High risk procedure
- Low risk procedure
- Do not know

Angiography or venography with intervention

- High risk procedure
- Low risk procedure
- Do not know

Inferior vena cava filter placement

- High risk procedure
- Low risk procedure
- Do not know

Pneumology

Thoracentesis

- High risk procedure
- Low risk procedure
- Do not know

Bronchoscopy without biopsy

- High risk procedure

- Low risk procedure
- Do not know

Bronchoscopy with biopsy

- High risk procedure
- Low risk procedure
- Do not know

Therapeutic bronchoscopy

- High risk procedure
- Low risk procedure
- Do not know

Intrathoracic organ biopsy

- High risk procedure
- Low risk procedure
- Do not know

Tunneled pleural drain placement

- High risk procedure
- Low risk procedure
- Do not know

Urology

Prostate biopsy

- High risk procedure
- Low risk procedure
- Do not know

Cystoscopy

- High risk procedure
- Low risk procedure
- Do not know

Ureteroscopy

- High risk procedure
- Low risk procedure
- Do not know

Lithotripsy (kidney, bladder, ureter)

- High risk procedure
- Low risk procedure
- Do not know

Percutaneous kidney biopsy

- High risk procedure
- Low risk procedure
- Do not know

Transjugular kidney biopsy

- High risk procedure
- Low risk procedure
- Do not know

Nephrostomy tube placement

- High risk procedure
- Low risk procedure
- Do not know

Neurology

Lumbar puncture

- High risk procedure
- Low risk procedure
- Do not know

Epidural catheter placement

- High risk procedure
- Low risk procedure
- Do not know

Central nervous system procedure

- High risk procedure
- Low risk procedure
- Do not know

Gynecology

Colposcopy with cervical biopsy

- High risk procedure
- Low risk procedure
- Do not know

Diagnostic hysteroscopy

- High risk procedure
- Low risk procedure
- Do not know

Hysteroscopy with biopsy

- High risk procedure
- Low risk procedure
- Do not know

Amniocentesis

- High risk procedure
- Low risk procedure
- Do not know

Miscellaneous

Dental cleaning

- High risk procedure
- Low risk procedure
- Do not know

Dental extraction

- High risk procedure
- Low risk procedure
- Do not know

Intra-articular puncture

- High risk procedure
- Low risk procedure
- Do not know

Intra-articular injection

- High risk procedure
- Low risk procedure
- Do not know

Lymph node percutaneous biopsy

- High risk procedure
- Low risk procedure
- Do not know

Non liver intraabdominal solid-organ biopsy

- High risk procedure
- Low risk procedure
- Do not know

Skin biopsy

- High risk procedure
- Low risk procedure
- Do not know

Drainage catheter exchange

- High risk procedure
- Low risk procedure
- Do not know

Supplementary text 2.

Questionnaire to define thresholds of laboratory test values considered acceptable to perform an elective invasive procedure or surgical procedure

Low-risk non-surgical procedures

The following questions concern patients with cirrhosis who are neither taking anti-platelet agents nor anticoagulants, who do not have an active bacterial infection or an acute kidney failure, and who are about to undergo a low-risk procedure according to the classification made in the attached letter.

Q1. Assuming other parameters are acceptable, what is the lowest platelet count you are conformable with to perform a low-risk procedure, without prophylactic measures/intervention, in a patient with cirrhosis

- 20 G/L
- 30 G/L
- 50 G/L
- 60 G/L
- 75 G//L
- 100 G/L
- I don't recommend this parameter to judge bleeding risk in cirrhosis in this setting
- Do not know

Q2. Assuming other parameters are acceptable, what is the highest INR you are conformable with to perform a low-risk procedure, without prophylactic measures/intervention, in a patient with cirrhosis.

- 1.5
- 1.8
- 2
- I don't recommend this parameter to judge bleeding risk in cirrhosis in this setting
- Do not know

Q3. Assuming other parameters are acceptable, what is the lowest fibrinogen concentration you are conformable with to perform a low-risk procedure, without prophylactic measures/intervention, in a patient with cirrhosis.

- 60 mg/dL
- 100 mg/dL
- 120 mg/dL
- 150 mg/dL
- I don't recommend this parameter to judge bleeding risk in cirrhosis in this setting
- Do not know

Q4. Assuming other parameters are acceptable, do you think that aPTT result should be taken into account before performing a low-risk procedure in a patient with cirrhosis

- Yes
- No
- Do not know

High-risk non-surgical procedures

The following questions concern patients with cirrhosis who are neither taking anti-platelet agents nor anticoagulants, who do not have an active bacterial infection or an acute kidney failure, and who are about to undergo a high-risk procedure according to the classification made in the attached letter.

Q5. Assuming other parameters are acceptable, what is the lowest platelet count you are conformable with to perform a high-risk procedure, without prophylactic measures/intervention, in a patient with cirrhosis

- 20 G/L
- 30 G/L
- 50 G/L
- 60 G/L
- 75 G//L
- 100 G/L
- I don't recommend this parameter to judge bleeding risk in cirrhosis in this setting
- Do not know

Q6. Assuming other parameters are acceptable, what is the highest INR you are conformable with to perform a high-risk procedure, without prophylactic measures/intervention, in a patient with cirrhosis.

- 1.5
- 1.8
- 2
- I don't recommend this parameter to judge bleeding risk in cirrhosis in this setting
- Do not know

Q7. Assuming other parameters are acceptable, what is the lowest fibrinogen concentration you are conformable with to perform a high-risk procedure, without prophylactic measures/intervention, in a patient with cirrhosis.

- 60 mg/dL
- 100 mg/dL
- 120 mg/dL
- 150 mg/dL
- I don't recommend this parameter to judge bleeding risk in cirrhosis in this setting
- Do not know

Q8. Assuming other parameters are acceptable, do you think that aPTT result should be taken into account before performing a high-risk procedure in a patient with cirrhosis

- Yes
- No
- Do not know

Surgical procedures

The following questions concern patients with cirrhosis who are neither taking anti-platelet agents nor anticoagulants, who do not have an active bacterial infection or an acute kidney failure, and who are about to undergo a surgical procedure, considered by the surgeon as at high-risk of bleeding. Please assess your response from the perspective of a consultant making recommendations.

Q9. Assuming other parameters are acceptable, what is the lowest platelet count you are conformable with to perform a surgical procedure, considered by the surgeon as at high-risk of bleeding, without prophylactic measures/intervention, in a patient with cirrhosis?

- 20 G/L
- 30 G/L
- 50 G/L
- 60 G/L
- 75 G//L
- 100 G/L
- I don't recommend this parameter to judge bleeding risk in cirrhosis in this setting
- Do not know

Q10. Assuming other parameters are acceptable, what is the highest INR you are conformable with to perform a surgical procedure, considered by the surgeon as at high-risk of bleeding, without prophylactic measures/intervention, in a patient with cirrhosis?

- 1.5
- 1.8
- 2
- I don't recommend this parameter to judge bleeding risk in cirrhosis in this setting
- Do not know

Q11. Assuming other parameters are acceptable, what is the lowest fibrinogen concentration you are conformable with to perform a surgical procedure, considered by the surgeon as at high-risk of bleeding, without prophylactic measures/intervention, in a patient with cirrhosis?

- 60 mg/dL
- 100 mg/dL
- 120 mg/dL
- 150 mg/dL
- I don't recommend this parameter to judge bleeding risk in cirrhosis in this setting
- Do not know

Q12. Assuming other parameters are acceptable, do you think that aPTT result should be taken into account before performing a surgical procedure, considered by the surgeon as at high-risk of bleeding, in a patient with cirrhosis?

- Yes

- No
- Do not know

Procedure	AASLD 2021 ¹	ACG 2020 ⁹	AGA 2019 ^b	AGA 2021 ⁶	AGA 2021 ⁴	BSG 2020 ¹⁰	EASL 2022 ⁷	ISTH 2022 ⁸
Pulmonary medicine	Thoracentesis	Low risk	-	Low risk	Low risk	Low risk	-	Low risk
	Bronchoscopy without biopsy	Low risk	-	-	-	-	-	-
	Bronchoscopy with biopsy	High risk	-	-	-	-	-	High risk
	Therapeutic bronchoscopy	High risk	-	-	-	-	-	-
	Intrathoracic organ biopsy	High risk	-	-	-	-	-	-
	Tunnelled pleural drain placement	-	-	-	-	-	-	High risk
Urology and nephrology	Prostate biopsy*	-	-	-	-	-	-	-
	Cystoscopy*	-	-	-	-	-	-	-
	Ureteroscopy*	-	-	-	-	-	-	-
	Lithotripsy (kidney, bladder or ureter)*	-	-	-	-	-	-	-
	Percutaneous kidney biopsy*	-	-	-	-	-	-	-
	Transjugular kidney biopsy*	-	-	-	-	-	-	-
Neurology	Nephrostomy tube placement	High risk	-	-	-	-	-	-
	Lumbar puncture	High risk	-	Intermediate risk	High risk	High risk	-	-
	Epidural catheter placement	High risk	-	-	-	-	-	-
Gynecology	Central nervous system procedures	High risk	-	-	-	-	-	High risk
	Colposcopy with cervical biopsy*	-	-	-	-	-	-	-
	Diagnostic hysteroscopy*	-	-	-	-	-	-	-
	Hysteroscopy with biopsy*	-	-	-	-	-	-	-
	Amniocentesis*	-	-	-	-	-	-	-
Miscellaneous	Dental cleaning	Low risk	-	-	-	-	-	Low risk
	Dental extraction	High risk	-	Low risk	Low risk	Low risk	High risk	Low risk
	Intra-articular puncture*	-	-	-	-	-	-	-
	Intra-articular injection	High risk	-	-	-	-	-	-
	Lymph node percutaneous biopsy*	-	-	-	-	-	-	-
	Nonliver intraabdominal solid-organ biopsy	High risk	-	Intermediate risk	High risk	High risk	-	-
	Skin biopsy	Low risk	-	-	-	-	-	Low risk
Drainage catheter exchange	Low risk	-	-	-	-	-	-	

* Additional procedures included in the present study following the experts' opinion

Abbreviations: AASLD: American Association for the Study of Liver Diseases; ACG: American College of Gastroenterology; AGA: American Gastroenterological Association; BSG: British Society of Gastroenterology; EASL: European Association for the Study of the Liver; ISTH: International Society on Thrombosis and Haemostasis;

Supplementary table 1.

Number of expert respondents to the questionnaire aimed at defining the bleeding risk associated with 80 invasive procedures frequently performed in patients with cirrhosis

Procedure	Experts' responses	
	High or low-bleeding risk	Do not know
Endoscopic Retrograde Cholangiopancreatography without sphincterotomy	51 (98)	1 (2)
Endoscopic Retrograde Cholangiopancreatography with biliary or pancreatic sphincterotomy	52 (100)	0
Endoscopic Retrograde Cholangiopancreatography with papillary balloon dilatation without sphincterotomy	49 (94)	3 (6)
Endoscopic Retrograde Cholangiopancreatography with biliary / pancreatic stent placement without sphincterotomy	51 (98)	1 (2)
Endoscopic (both upper and lower) mucosal resection	51 (98)	1 (2)
Endoscopic (both upper and lower) submucosal dissection	50 (96)	2 (4)
Endoscopic (both upper and lower) hemostasis with argon plasma coagulation	49 (94)	3 (6)
Endoscopic (both upper and lower) radiofrequency ablation	43 (83)	9 (17)
Endoscopic (both upper and lower) video-capsule	52 (100)	0
Endoscopic (both upper and lower) ultrasound without fine-needle aspiration	51 (98)	1 (2)
Endoscopic (both upper and lower) ultrasound with fine-needle aspiration	51 (98)	1 (2)
Endoscopic (both upper and lower) stricture dilatation (pneumatic or bougie)	47 (90)	5 (10)
Endoscopic (both upper and lower) stricture dilatation (balloon)	48 (92)	4 (8)
Endoscopic (both upper and lower) enteral stent deployment	47 (90)	5 (10)
Upper endoscopy : cystogastrostomy	45 (87)	7 (13)
Upper endoscopy : polypectomy < 1cm	48 (92)	4 (8)
Upper endoscopy : polypectomy > 1cm	49 (94)	3 (6)
Upper endoscopy : diagnostic (with or without biopsy)	52 (100)	0
Upper endoscopy : variceal ligation	52 (100)	0
Upper endoscopy : glue injection of gastric varices	51 (98)	1 (2)
Upper endoscopy : peroral endoscopic myotomy (POEM)	41 (79)	11 (21)
Upper endoscopy : ampullary resection	49 (94)	3 (6)
Upper endoscopy : percutaneous gastrostomy or jejunostomy placement	51 (98)	1 (2)
Upper endoscopy : diagnostic balloon assisted enteroscopy	50 (96)	2 (4)
Upper endoscopy : therapeutic balloon assisted enteroscopy	39 (75)	13 (25)
Upper endoscopy : push enteroscopy	43 (83)	9 (17)
Lower endoscopy : polypectomy < 1cm	51 (98)	1 (2)
Lower endoscopy : polypectomy > 1cm	51 (98)	1 (2)
Lower endoscopy : flexible sigmoidoscopy (with or without biopsy)	52 (100)	0
Lower endoscopy : diagnostic colonoscopy (with or without biopsy)	52 (100)	0
Central venous catheter placement	52 (100)	0
Peripherally inserted central catheter line placement	52 (100)	0
Arterial line placement	52 (100)	0
Central line removal	52 (100)	0
Cardiac catheterization	50 (96)	2 (4)
Transesophageal echocardiography	52 (100)	0
Diagnostic coronary angiography	51 (98)	1 (2)
Therapeutic coronary angiography	50 (96)	2 (4)
Angiography or venography with intervention	48 (92)	4 (8)

Inferior vena cava filter placement	52 (100)	0
Percutaneous liver biopsy	52 (100)	0
Transjugular liver biopsy	52 (100)	0
Laparoscopic liver biopsy	50 (96)	2 (4)
Hepatic venous pressure gradient measurement	51 (98)	1 (2)
Portal recanalization	47 (90)	5 (10)
Transjugular intrahepatic portosystemic shunt	52 (100)	0
Transcatheter arterial chemoembolization / radioembolization	52 (100)	0
Percutaneous ablation of liver cancer	52 (100)	0
Biliary intervention (cholecystostomy or percutaneous biliary drain placement)	50 (96)	2 (4)
Diagnostic paracentesis	52 (100)	0
Therapeutic paracentesis	51 (98)	1 (2)
Tunneled ascitic drain placement	47 (90)	5 (10)
Thoracentesis	51 (98)	1 (2)
Bronchoscopy without biopsy	52 (100)	0
Bronchoscopy with biopsy	49 (94)	3 (6)
Therapeutic bronchoscopy	46 (88)	6 (12)
Intrathoracic organ biopsy	46 (88)	6 (12)
Tunneled pleural drain placement	48 (92)	4 (8)
Prostate biopsy	44 (85)	8 (15)
Cystoscopy	49 (94)	3 (6)
Ureteroscopy	49 (94)	3 (6)
Lithotripsy (kidney, bladder, ureter)	46 (88)	6 (12)
Percutaneous kidney biopsy	50 (96)	2 (4)
Transjugular kidney biopsy	46 (88)	6 (12)
Nephrostomy tube placement	45 (87)	7 (13)
Lumbar puncture	51 (98)	1 (2)
Epidural catheter placement	49 (94)	3 (6)
Central nervous system procedure	44 (85)	8 (15)
Colposcopy with cervical biopsy	48 (92)	4 (8)
Diagnostic hysteroscopy	49 (94)	3 (6)
Hysteroscopy with biopsy	48 (92)	4 (8)
Amniocentesis	45 (87)	7 (13)
Dental cleaning	52 (100)	0
Dental extraction	51 (98)	1 (2)
Intra-articular puncture	48 (92)	4 (8)
Intra-articular injection	47 (90)	5 (10)
Lymph node percutaneous biopsy	49 (94)	3 (6)
Nonliver intraabdominal solid-organ biopsy	47 (90)	5 (10)
Skin biopsy	51 (98)	1 (2)
Drainage catheter exchange	47 (90)	5 (10)

Data are expressed as absolute value (percentage).

Supplementary table 2.

Number of expert respondents to the questionnaire aimed at defining thresholds of laboratory test values considered acceptable to perform an elective invasive procedure or surgical procedure

	Low risk procedure	High-risk procedure	High-risk surgery
Plaquettes			
> 20G/L	16 (31)	4 (8)	4 (8)
> 30G/L	12 (23)	9 (17)	9 (16)
> 50G/L	8 (15)	30 (57)	26 (50)
> 60G/L	0	0	1 (2)
> 75G/L	0	2 (4)	4 (8)
> 100G/L	0	2 (4)	3 (6)
I don't recommend this parameter to judge bleeding risk in cirrhosis in this setting	15 (29)	3 (6)	2 (4)
I don't know	1 (2)	2 (4)	3 (6)
INR			
< 2	4 (8)	5 (10)	8 (15)
< 1.8	0	3 (6)	3 (6)
< 1.5	4 (8)	7 (13)	9 (17)
I don't recommend this parameter to judge bleeding risk in cirrhosis in this setting	44 (84)	37 (71)	30 (58)
I don't know	0	0	2 (4)
Fibrinogen			
> 60mg/dL	5 (10)	3 (6)	4 (8)
> 100mg/dL	10 (19)	17 (32)	16 (31)
> 120mg/dL	1 (2)	4 (8)	7 (13)
> 150mg/dL	1 (2)	4 (8)	5 (10)
I don't recommend this parameter to judge bleeding risk in cirrhosis in this setting	33 (63)	21 (40)	13 (25)
I don't know	2 (4)	3 (6)	7 (13)
aPTT			
Yes	0	5 (10)	6 (12)
No	47 (90)	41 (79)	36 (69)
I don't know	5 (10)	6 (11)	10 (19)

Data are expressed as absolute value (percentage).

Abbreviations: aPTT: activated partial thromboplastin time; INR: International Normalized Ratio