

Distinct ways to perform a liver biopsy: The core technique setups and updated understanding of these modalities

Chao Sun^{1,2}, Xingliang Zhao², Lei Shi³, Xiaofei Fan², Xiaolong Qi^{1,*}

ABSTRACT

There is dramatically increased incidence of several liver diseases worldwide; thus, an unmet need to diagnose and stage these pathological entities heralds the wide application of liver biopsy (LB) techniques. The ways of LB are versatile, including percutaneous LB, transjugular LB, and more recently an approach of minimal invasiveness, that is, EUS-guided LB (EUS-LB). In this review article, we come to the conclusion that EUS-LB may serve as a feasible, reliable, and safe alternative to percutaneous LB and transjugular LB in terms of improved diagnostic yield, excellent sampling performance, and controlled adverse events among patients with focal, infiltrative, and parenchymal liver diseases. Furthermore, extensive efforts have been made to optimize and refine several technical pillars within EUS-LB modality such as the selection of needle size/type, priming manner of biopsy needle, and choice of pass/actuation technique, all of which aim at obtaining better specimen quantity and quality. Another advantageous aspect and unique property pertinent to EUS-guided modality indicate that multiple screening, surveillance, and intervention procedures can be combined into one single endoscopic session. Accordingly, some pilot studies have clarified the clinical usefulness by integrating EUS-LB with simultaneous measurement of portal pressure gradient or examination of liver stiffness. However, more studies, in particular, randomized controlled trials or real-world evidence, are practically warranted to elucidate the validity and safety of EUS-LB as a regular/routine part of managing liver diseases.

Keywords: Liver biopsy; EUS-guided liver biopsy; Focal and parenchymal liver diseases; Percutaneous liver biopsy; Transjugular liver biopsy

INTRODUCTION

In the era of emerging noninvasive approaches, such as ultrasound elastography or serological examination, to diagnose and stage varying liver diseases (eg, fibrosis), the widespread utility of traditional liver biopsy (LB) has been challenged. However, it is our belief that an LB remains the criterion standard aimed at diagnosing/distinguishing a wide array of focal, infiltrative, and parenchymal liver diseases on account of its firm performance and feasibility at daily practice. The routes of LB are versatile, including percutaneous LB (PC-LB), transjugular LB (TJ-LB), and the manner of more invasiveness, via surgical technique.^[1] More recently, another minimally invasive approach, known as EUS-guided LB (EUS-LB), has gained traction among endosonographers, hepatologists, and

general practitioners.^[2] Although extensive attempts have been made to clarify the clinical usefulness of EUS-LB in the context of varying liver diseases and to refine the technical procedures, open questions still exist with regard to optimal indications, suited tissue acquisition modality, selection of processing equipment, and its superiority over other commonly adopted LB methods.

Notably, there is striking increase pertinent to the incidence and prevalence of liver diseases worldwide. For instance, it is proposed that nonalcoholic fatty liver disease (NAFLD), a metabolic disorder in relation to diabetes, dyslipidemia, and hypertension, may affect 29% of the global population.^[3] Furthermore, approximately half of the NAFLD individuals are expected to progress to nonalcoholic steatosis, which is indicative of a pathologically aggressive condition closely linked to the development of liver fibrosis, cirrhosis, and hepatocellular carcinoma. On the other hand, the drug abuse and inappropriate use of dietary supplement and herbal medication give rise to acute liver injury and lethal consequence as acute liver failure in circumstances.^[4,5] Last but not the least, cirrhosis and its associated complications due to portal hypertension account for 39% of annual deaths in the world and bring heavy economic/social burdens on the health care system, taking consideration of limited therapeutic avenue except for liver transplantation. Taken together, it instigates enthusiasms with the purpose of expanding indications for EUS-LB to achieve diagnostic confirmation and disease severity stratification, and this intervention can be combined with concomitant endoscopic procedures such as measurement of portal pressure gradient (PPG) or shear wave elastography (SWE). In this review, we first introduce and compare the clinical utility of multiple LB methods in the context of varying liver diseases through distinct approaching ways and summarize the advantages of EUS-LB compared with its counterparts; next, we concentrate on technical advancement, armamentarium

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requirement, and procedural refinement specific to EUS-LB modality. Last, we come to the current trends of this method in combination with other endoscopic sessions at daily practice.

Comparisons between distinct ways to perform LB

Two mainstays to acquire live tissue for pathological evaluation comprise the PC-LB and TJ-LB methods before the emergence of endoscopic session. Based on the recommendations and endorsements of the American Association for the Study of Liver Diseases and the British Society of Gastroenterology, PC-LB is the most commonly used clinical puncture sampling method.^[6,7] Original PC-LB was used with the guidance of percussion, whereas this modality is thereafter guided by ultrasound or computed tomography imaging techniques.^[8] The needle size of choice covers a wide range from earlier 14-gauge (14G)/16G to recent spring-loaded 18G/20G size.^[9] The preferential access pathways include both subcostal and transthoracic approaches dependent on the volume of the liver (enlarged *vs.* normal/shrinkage). Local anesthesia and moderate consciousness sedation are usually implemented in those conditions. Because PC-LB requires transection against the liver capsule, the major intervention-related complications include but are not limited to postoperative pain, hemorrhage, biopsy trajectory/site infection, hematoma, and pneumothorax.^[10,11] A meta-analysis of 30 studies on complications caused by PC-LB showed that the incidence of major complications of PC-LB was 2.4% (including massive bleeding and hospitalization rate, etc), and that of minor complications (pain) was 9.5%.^[12] As the most widely used modality, PC-LB is considered to be cost-effective, taking consideration of limited procedure time and acceptable recovery time. However, the application of PC-LB has been considerably dampened among individuals with obvious obesity, large volume of ascites, significant problems in relation to coagulopathy, and thrombocytopenia. In addition, even in high-volume centers, the diagnostic efficacy of PC-LB sometimes is constricted because of its inability for bilobar access and restrained field of view pertinent to organs/tissues in the vicinity of targeted liver. For instance, usually a biopsy can be performed only on the right lobe, and focal lesions located in the left lobe may be poorly sampled.

Taking into account aforesaid contraindications and shortcomings of PC-LB, another less invasive modality, that is, TJ-LB, has been developed to foster liver tissue acquisition in special settings. Notably, this procedure can be done among individuals with sizable body habitus as well as those having massive ascites and coagulopathy, because the liver capsule integrity is preserved. In many clinical practices, patients at high risk for complications requiring LB are often referred for TJ-LB. It has been found to have relatively low complication rates and mortality.^[13] From technical perspective of view, the puncture needle is cannulated to the internal jugular vein and then advanced toward one of the hepatic veins by fluoroscopic guidance. Both unilobar and bilobar trajectories can be accessible, whereas the right lobe is of common choice on account of its anatomic feasibility and relatively optimal size (larger than the left lobe). Furthermore, the evaluation of portal hypertension can be accomplished (*e.g.*, hepatic venous pressure gradient [HVPG]) with concomitant TJ-LB in a wide spectrum of liver diseases including sinusoidal obstruction syndrome, acute liver failure, noncirrhotic portal fibrosis, and cirrhosis.^[14-16] The major complications of TJ-LB encompass pain, bleeding, ventricular arrhythmia, and hematoma.^[13] The drawbacks pertinent to TJ-LB should be noted as sampling variability, requirement for trained hands, and failure to launch focal hepatic lesion because of restricted view of the proximal anatomy.

In parallel with the advent of endosonography, a novel endoscopic intervention EUS-LB, which is characterized by minimal invasiveness, has emerged as an alternative to traditional LB modalities with the purpose of diagnosing and staging various focal, infiltrative, and parenchymal liver diseases. This technique was initially depicted by Mathew^[17] in 2007. The advantages of EUS-LB are described as follows. It provides more visualized lesions of targeted liver to aid in subsequent biopsy processing. As for real-time image guidance, critical adverse events can be subverted by avoiding any large blood vessel or biliary tract on the needle passages/trajectories. In addition, EUS-LB is simultaneously accessible to both hepatic lobes and allows for better examination of surrounding structures, which may enhance the sampling accuracy and diminish the sampling errors. A recent meta-analysis reported that the histological diagnosis rate of EUS-LB was 93.9%.^[18] Last but not the least, this procedure can be accompanied by other endoscopic sessions at the same time, such as screening for gastroesophageal varices, measurement for portosystemic pressure, or examination for liver stiffness. Moreover, patients undergoing EUS-LB benefit from shorter recovery time (*e.g.*, 3 *vs.* 4.2 hours required for PC-LB, $P = 0.004$) and postprocedural discomfort of lesser degree (*e.g.*, pain scores 0/10 *vs.* 3.5/10 for PC-LB, $P < 0.001$).^[19,20] The main disadvantages of EUS-LB comprise the requirement of remarkable expertise, infeasibility among individuals with significant coagulopathy, and inevitable risks in relation to deep sedation/anesthesia. Oh and colleagues^[21] compared the EUS-guided fine-needle aspiration (EUS-FNA) results of the left and right lobes of the liver. Neither the size nor the number of needle passes of the lesions was significantly different between the left and right lobes on EUS. In the right lobe and left lobe, the liver mass was 2.3 cm and 1.6 cm away from the transducer, respectively. Right lobe liver mass distances from transducer were significantly longer than the left ($P = 0.01$), but both lobes had similar technical success rates (30/30 [100%] *vs.* 16/17 [94.1%], $P = 0.2$). The detailed comparisons between distinct ways to perform LB are illustrated in Figure 1.

Parameters to assess LB specimen adequacy

The histologic yield pertinent to LB technique can be determined by several metrics: sample size, intact specimen length, total specimen length (TSL), and the number of complete portal tracts (CPTs). A CPT indicates the complete procurement encompassing all 3 portal structures, including hepatic artery, portal vein branch, and bile duct. However, no consensus has been reached on the “best adequate” specimen: the Royal College of Pathologists suggests that adequate LB specimen is greater than 10 mm in length and consisting of at least 6 CPTs, whereas the American Association for the Study of Liver Diseases guidelines define adequacy as being at least 15 mm in length and presenting with more than 11 CPTs.^[6,7]

Comparisons between EUS-LB and other LB methods

Taking into account the rapid development and progression of EUS-LB technique and armamentarium, it is justified to compare the diagnostic performance between EUS-LB and PC-LB aimed at promoting clinical practice. Chandan and colleagues^[22] noted that the rates of overall adverse events were similar between EUS-LB and PC-LB. Notably, Facciorusso and colleagues^[23] showed that both PC-LB and EUS-LB yielded similar results concerning a spectrum of metrics including TSL, CPTs, and sampling adequacy. Furthermore, two 2022 meta-analyses have come to the conclusion that aforesaid 2 modalities exhibited no significant differences pertinent to diagnostic performance and safety profile.^[23,24] DeWitt and colleagues^[2] suggested that EUS-LB may have fewer contraindications

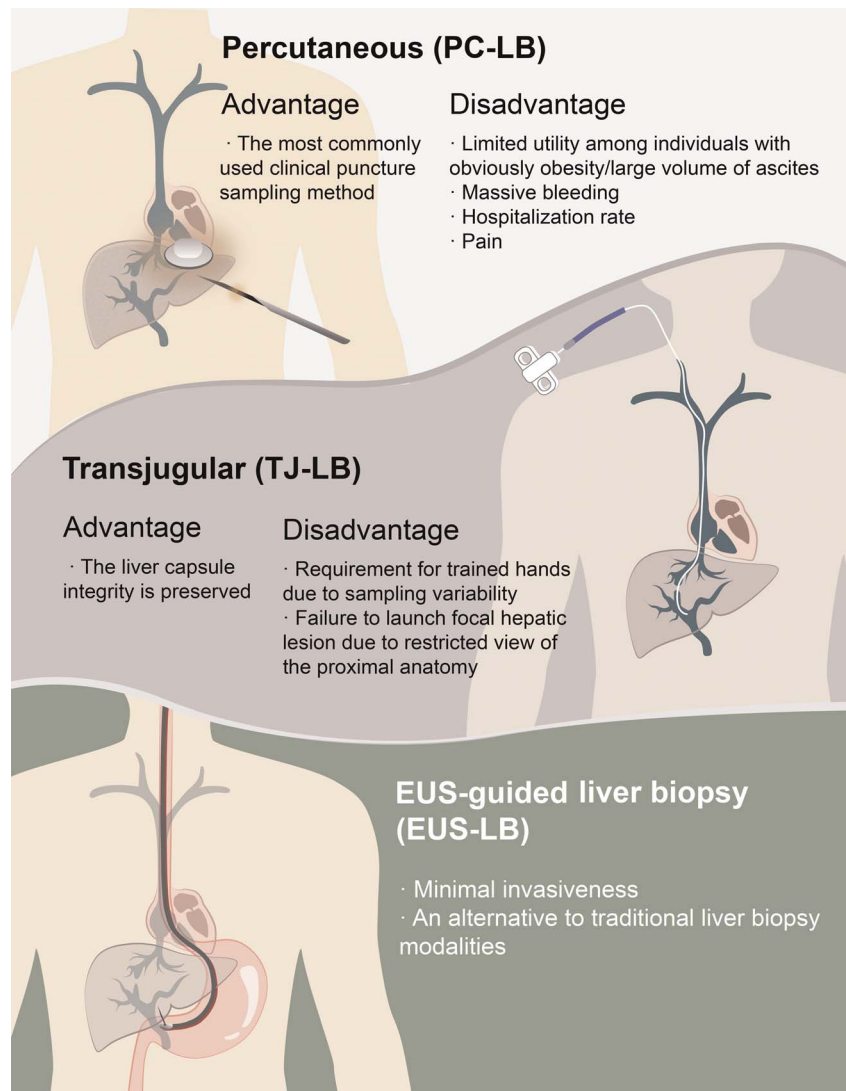


Figure 1. The detailed comparisons between distinct ways to perform liver biopsy.

than the traditional PC-LB techniques. Despite that no direct comparisons have been used, Zeng and colleagues^[24] stated that the overall rates of diagnostic yield and specimen adequacy of EUS-LB were 95% and 84%, respectively, as high as those of PC-LB. Moreover, another previous meta-analysis also found that EUS-LB was comparable to another 2 biopsy routes (*i.e.*, PC-LB and TJ-LB) in terms of sampling adequacy and adverse event, but this report was lacking of randomized trials.^[25] Taken together, further randomized controlled trials are urgently needed to validate those results.

Comparisons within EUS-LB modality

Comparison between distinct needle types

In fact, a variety of designs of needles has been developed; the first used tools were FNA needles.^[26] In the existing literature, the reported EUS-FNA biopsy success rates range from 88% to 98% with the purpose of consequent histologic diagnosis.^[27–29] However, it is also suggested that FNA needles may result in cellular sample and inadequate tissue architecture for cytological examination, giving rise to the advent of fine-needle biopsy (FNB) needles.

There are 3 distinct types of FNB needles commercially available: Procore reverse-bevel, SharkCore Fork tip (Medtronic, Minneapolis, MN) and Acquire Franseen tip (Boston Scientific, Natick, MA). The Fork tip encompasses a modified tip of 6 cutting-edge surfaces to achieve intact sample architecture with tissue-cohesive units; the Franseen tip facilitates tissue capture in addition to decreased specimen fragmentation.^[30]

Theoretically, FNB needles would provide longer intact cores on account of improved sampling capability. Actually, a discrepancy exists in the literature with regard to the superiority of FNB versus FNA based on lately published meta-analyses. A 2017 meta-analysis by Khan and colleagues^[31] analyzing 15 studies of 1024 patients showed that FNB was associated with a better diagnostic accuracy compared with FNA except for the scenario indicative of combined FNA and the rapid on-site evaluation. As for parenchymal liver diseases, Baran and colleagues^[32] reported that FNB core needles provided more CPTs along with similar TSL relative to standard 19G FNA needles. In addition, a 2022 meta-analysis by Zeng and colleagues^[24] found that no significant differences were observed between FNA and FNB needles

in terms of sampling performance. The novel innovation/advancement in EUS-FNB technique, such as 1-pass, 1-actuation wet suction technique, may account for those heterogeneous findings by minimizing adverse events but inevitably impairing the specimen quality.^[33] On the other hand, the needle size is considered as one influencing factor on sampling performance (see statement below), because both FNA and FNB are of various sizes (19G, 20G, and 22G).^[34] Notably, another study implicated that FNA needles were inferior to equally sized FNB needles in terms of the length of the longest piece of tissue, obtained CPTs, and TSL.^[35] Accordingly, a latest investigation by Gheorghiu and colleagues^[36] conducted a prospective head-to-head comparison between 22G Franseen needle and 22G FNA needle (Expect; Boston Scientific, Marlborough, MA) with 1 pass in focal liver lesions. Their results revealed the EUS-FNB samples to be more histologic adequacy, with longer tissue aggregates and more cellularity, relative to the EUS-FNA samples (100% *vs.* 86.7%, $P = 0.039$) and without serious postoperative complications. Notably, another recent study by Mok and colleagues^[37] evaluated the tissue yields with a 22G FNB and a 19G FNA needle, and they found the tissue adequacy was higher for the 19G FNA. However, a major limitation of the aforesaid study was that the authors compared 2 different types of needles and 2 different gauges, making it difficult to conclude that the observed results were due to differences in gauges rather than a composite of these 2 variables.

At present, EUS-LB technique using QuickCore Tru-Cut needle is out of the market because of the technical difficulties and relatively low success rates, particularly in not well-trained hands, which is regarded as a disadvantageous aspect of EUS-LB modality.^[38] As for the reverse-bevel structure of the Procore needle, aforesaid innovations such as Fork or Franseen tip may outperform this earlier design. However, a 2021 study by Kongkam and colleagues^[39] explored the diagnostic rate of a newly designed 20G Echotip Procore needle with an antegrade core trap (Cook Medical, Winston Salem, NC, United States) as compared with the original 22G reverse-bevel needle for liver masses. Their results denoted that EUS-LB procurement using the antegrade-bevel needle provided longer length of the biopsied tissue than its counterparts.

Within the setup of newly developed SharkCore and Acquire FNB needles, a meta-analysis based on two 2021 pilot studies concluded that the latter yielded greater CPTs, lengthier aggregate specimens, and more intact cores.^[24,40,41]

Comparison between distinct needle sizes

The impact of distinct needle sizes on sampling performance seems to be heterogeneous. Historically, 14G to 16G spring-loaded cutting needles had been applied with widely estimated diagnostic yield ranging from 29% to 100%.^[42,43] Nowadays, the 19G needle has dominated the clinical utility to some extent, since accumulating evidence unveils noninferiority of the smaller-gauge needles in relation to their 14G–16G counterparts. More recently, a single-center study showed that EUS-FNB using a 19G Acquire needle had similar success rates (100% *vs.* 95%, $P = 1$), surface area of liver tissue, and the numbers of CPTs (29 *vs.* 25, $P = 0.916$) when compared with PC-LB using a spring-loaded 16G needle among patients with diffuse liver diseases.^[44] Another study conducted by Schulman and colleagues^[30] illustrated that the 19G Fork-tip EUS-LB needle outperformed the 18G PC-LB needle in terms of histologic field.

Intriguingly, a meta-analysis conducted by Zeng and colleagues^[24] showed a nonsignificant trend of 19G needles pertinent to sampling capability in relation to 22G counterparts. The authors extrapolated

that various needle types (both FNA and FNB encompassing 19/22G size) may account for these findings in addition to reduced specimen ability following 1-pass, 1-actuation wet suction via 19G procurement. Notably, Patel and colleagues^[34] showed that 19G Procore needle was superior to the 22G Franseen tip needle in terms of specimen adequacy (82.1% *vs.* 66.7%). Another study also demonstrated that EUS-LB using a 19G core needle yielded better performance in terms of tissue acquisition and specimen adequacy as compared with 22G core needle.^[45] In contrast, Hasan and colleagues^[46] reported that adequacy of the specimen for histology interpretation was obtained in 100% of patients undergoing EUS-FNB due to abnormal liver function. However, the aforementioned study applied bilobar specimen procurement with 3 passes and without controls.

Comparison between other influencing factors

Extensive efforts have been made to refine the EUS-LB procedure, because this modality has proved to be highly dependent on the expertise of the operator and technical manipulation. Accordingly, multiple tissue acquisition techniques have been developed pertinent to EUS-LB modality.^[26] Suction can be implemented in a dry or wet fashion. Dry suction is done by applying a 10- to 20-mL syringe to maintain suction following the needle insertion into the liver parenchyma, whereas the wet suction indicates removal of the needle stylet and then priming the needle cavity with fluid ahead of attaching the vacuum syringe. The available priming fluids encompass saline and heparin in the existing literature. On contrary, the operator can also obtain samples without using suction via stylet designated as “slow-pull” technique. The meta-analysis by Baran and colleagues^[32] revealed that EUS-FNB without (no stylet or slow-pull) or with suction yielded comparable pooled TSL (44.3 *vs.* 53.9 mm, $P = 0.4$) but higher CPTs (30 *vs.* 14.6, $P < 0.001$). The underlying reasons can be attributed to decreased fragmentation in the samples stemming from lower negative pressure under the slow-pull manner. Mok and colleagues^[47] conducted a prospective crossover study to assess wet heparinized suction for EUS-LB in parenchymal liver diseases. Further analyses unveiled that the specimen adequacy was improved pertinent to longer TSL (49.2 *vs.* 23.9 mm, $P = 0.003$), greater CPTs (7 *vs.* 4, $P = 0.01$), and less fragmentation for wet suction when compared with dry needle technique. The authors hold the promise that heparin priming can foster sampling adequacy and cellularity through multiple ways including the prevention of blood clot formation, stabilization of tissue fragments, and improvement in diagnostic yield. A 2022 study further compared the performance between EUS-LB wet suction with heparin versus saline techniques.^[48] The preliminary results showed that the specimen adequacy was similar between those 2 groups, which was indicative of comparable aggregate specimen length (heparin: 43 mm, saline: 40 mm; $P = 0.16$) and longest piece length (heparin: 10 mm, saline: 8 mm; $P = 0.19$). As expected, wet heparin EUS-LB gave rise to fewer frequencies of clots as compared with its opponent using wet saline (18% *vs.* 53%, $P < 0.0001$).

The predominance regarding needle pass/actuation in the field of EUS-LB is the 1-pass (single puncture of the liver capsule) and 1-actuation (single back-and-forth motion) technique.^[49,50] Although data are scant pertinent to comparison between distinct pass/actuation modes, Ching-Companioni and colleagues^[51] implicated that 1-pass, 3-actuation technique resulted in greater CPTs (24.5 *vs.* 17.3, $P < 0.008$) and longer aggregate specimen length (12.9 *vs.* 6.9 cm, $P < 0.001$) as compared with its opponent (*i.e.*, 1-pass, 1-actuation) when performing EUS-LB for parenchymal

liver diseases. In addition, the safety profile of pain experience was not significantly different between those techniques.

EUS-LB accompanied by other endoscopic procedures

One advantageous aspect of EUS-LB indicates that this procedure can facilitate multiple endoscopic evaluation/treatment during the same endoscopic session, which is a common requirement among individuals with liver diseases [Figure 2]. Considering a lower overall cost of the EUS strategy, this technique may be more suited on account of limited health care resources.^[52]

EUS-guided PPG

It is widely accepted that portal hypertension represents the major complication of cirrhosis, which is in close relation to the advent/development of gastroesophageal varices, portal hypertensive gastropathy, hepatorenal syndrome, and refractory ascites. Therefore, it is pivotal to accurately determine portal hypertension with the purpose of clarifying the stage and keeping surveillance on the disease progression among cirrhosis. The common measurement of HVPG via transjugular manner indirectly reflects the portal vein pressure, which is relatively invasive along with risk of radiologic exposure and intravenous contrast. Notably, the feasibility of HVPG is negatively influenced in the scenario of prehepatic portal hypertension (*e.g.*, portal vein thrombosis) or presinusoidal hepatic portal hypertension (*e.g.*, myeloproliferative disorders).^[53–55] Collectively, it is justified to develop and introduce novel method to

directly measure portal hypertension. Accordingly, Choi and colleagues^[56] intended to elucidate the feasibility and safety pertinent to combined EUS-guided measurement of PPG (EUS-PPG) applying a 25G needle/compact manometer with concomitant EUS-LB among patients with chronic liver diseases. Data analyses implicated that 100% (83/83) technique success rate of EUS-PPG and 98.6% (70/71) specimen adequacy rate were observed among the study population without severe adverse events. Moreover, the retrieved PPGs correlated well with biomarkers of portal hypertension including the chance of varices, thrombocytopenia, and the presence of portal hypertensive gastropathy; this method provides a significant advance in the field of “endo-hepatology.” Intriguingly, the same research group reported that EUS-PPG metrics also represented excellent correlations with a spectrum of variables pertinent to hepatic histological fibrosis stages.^[57] This comprehensively endoscopic evaluation was successfully performed in the entire cohort without major adverse events. Similarly, another lately published work demonstrated that the technical success rates regarding measurement of the portosystemic pressure gradient and simultaneous EUS-LB were 96% and 100%, respectively; only mild adverse event was encountered.^[58] Their findings indicated that assessed portosystemic pressure gradient values were significantly associated with transient elastography (TE)-defined liver stiffness and fibrosis-4 score.

Gastric variceal hemorrhage occurs in approximately 20% of patients with portal hypertension. It has been proved that EUS can be used to accurately evaluate gastric varices (GVs).^[59] Yokoyama

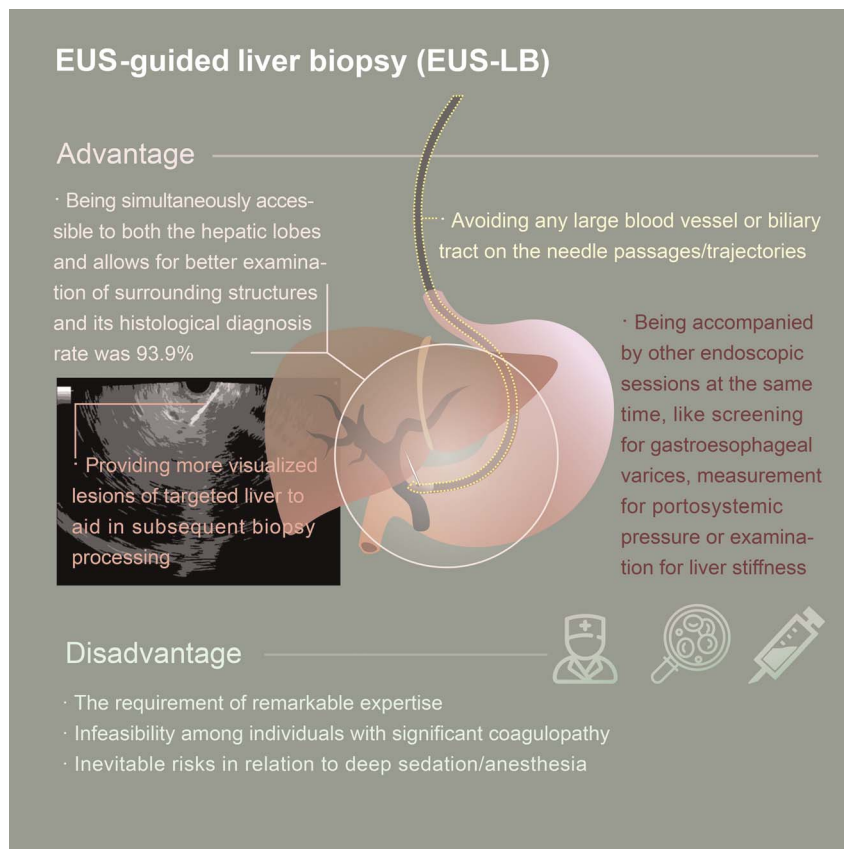


Figure 2. Clarification pertinent to the clinical usefulness of EUS-guided liver biopsy.

and colleagues^[60] evaluated the effectiveness of forward visual EUS (FV-EUS) for GVs by retrospectively analyzing 4 cases. Forward visual EUS can display endoscopic and ultrasound images in real time during the treatment. When there is distance between the mucosal surface and vascular lumen or the blood flow site requires puncture as an additional treatment, FV-EUS demonstrates higher success rate and effect than oblique viewing therapy.^[60] EUS-guided treatment of GVs is not widely used, but the implementation of the FV-EUS might facilitate the approach.^[61]

EUS-guided SWE

Nowadays, multiple noninvasive imaging approaches can be used to assess liver stiffness in terms of quantified parenchymal stiffness. The SWE results from acoustically generated shear wave propagation velocity to measure liver tissue stiffness, advantageous in concomitant B-mode ultrasound imaging anatomically.^[62] On the other hand, TE represents a nonimaging elastographic modality. Transient elastography measures the stiffness of the liver by a mechanical thrust to obtain the intrinsic physical properties of the liver parenchyma.^[63] However, TE has not been considered the best elastography method for diagnosing parenchymal fibrosis because it overestimates the stage of fibrosis in the subject of histological analysis.^[64] Besides, because ascites can attenuate mechanical waves, TE cannot be used in patients with ascites.^[65] Furthermore, one proposed limitation pertinent to the percutaneous elastography modality lies on its access to the right hepatic lobe in most cases, but substantial variations of fibrotic changes have been depicted between the right and left lobes in the liver.^[66] To our knowledge, ultrasound endoscopy plays an important role in the diagnosis and treatment of the gastrointestinal tract and adjacent organs. EUS has better sensitivity in identifying subtle lesions in the liver compared with conventional imaging such as computed tomography.^[67] The noninvasive SWE combined with EUS can assess the severity of fibrosis in the target organ by measuring its degree of elasticity, which increases the diagnostic value of EUS.^[68,69] The technique advancement and innovation in the field of endo-hepatology facilitate the real-time visualization of liver parenchyma through transgastric trajectory, that is, EUS-SWE along with simultaneous endoscopic examinations. Compared with static elastography, EUS-SWE does not rely on the manual application of pressure to induce liver tissue deformation, as well as to some extent avoiding significant alterations in the results due to physiological motion artifacts. This means that EUS-SWE has a broad diagnostic utility for liver fibrosis.^[70] This novel approach enables access to both the right and left hepatic lobes and can be applied in patients with morbid obesity.^[71,72] Most recently, a prospective tandem study by Kohli and colleagues^[73] compared the diagnostic accuracy of EUS-SWE in comparison to vibration-controlled TE (VCTE) among patients susceptible for the presence of NAFLD. In particular, EUS-LB was done immediately after EUS-SWE by using a heparinized 19G Acquire biopsy needle, both of which were performed bilobarly via transgastric approach.^[2] Analyses showed that EUS-SWE correlated well with liver fibrosis stages and may serve as a safe and reliable alternative to evaluate liver histology on account of comparable diagnostic accuracy to VCTE. Moreover, the EUS-SWE had achieved technical success in the whole study population, whereas VCTE failed in some cases.

SUMMARY AND CONCLUSION

Given the epidemic of a variety of metabolic disorders such as obesity, diabetes mellitus, and dyslipidemia, the landscape of liver diseases has dramatically changed with alarmingly increased incidence of NAFLD

and nonalcoholic steatosis.^[74] Therefore, it is an urgent and unmet need to accurately diagnose, histologically stage, and clinically differentiate individuals with suspected liver diseases. Traditionally, the diagnosis of liver diseases is dependent on an LB via percutaneous or transjugular routes along with other clinical, laboratory, and imaging information. As the rapid progression and subsequently wide utility of EUS for diagnostic as well as therapeutic purposes, a novel subspecialty coined “endo-hepatology” has recently emerged.^[75] In this review article, we come to the conclusion that EUS-LB may serve as a feasible, reliable, and safe alternative to PC-LB and TJ-LB in terms of improved diagnostic yield, excellent sampling performance, and controlled adverse events among patients with focal, infiltrative, and parenchymal liver diseases. Furthermore, extensive efforts have been made to optimize and refine several technical pillars within EUS-LB modality such as the selection of needle size/type, priming manner of biopsy needle, and choice of pass/actuation technique, all of which aim at obtaining better specimen quantity and quality. Another advantageous aspect and unique property pertinent to EUS-guided modality indicates that multiple screening, surveillance, and intervention procedures can be combined into a single endoscopic session. Accordingly, some pioneers have applied EUS-LB with simultaneous measurement of PPG or examination of liver stiffness. However, more studies, in particular, randomized controlled trials or real-world evidence, are practically warranted to clarify the validity and safety of EUS-LB as a regular/routine part of managing liver diseases.

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Conflict of Interest

The authors declare that they have no financial conflict of interest with regard to the content of this report.

Author Contributions

Chao Sun, Lei Shi, and Xiaolong Qi designed the study, analyzed the data and prepared the original draft. Xingliang Zhao and Xiaofei Fan analyzed the data and reviewed the manuscript. Xiaolong Qi and Lei Shi made critical revisions of the manuscript. All authors have approved the final draft submitted.

References

1. Madhok IK, Parsa N, Nieto JM. Endoscopic ultrasound-guided liver biopsy. *Clin Liver Dis* 2022;26:127–138.
2. DeWitt JM, Arain M, Chang KJ, et al. Interventional endoscopic ultrasound: current status and future directions. *Clin Gastroenterol Hepatol* 2021;19:24–40.
3. Liu J, Tian Y, Fu X, et al. Estimating global prevalence, incidence, and outcomes of non-alcoholic fatty liver disease from 2000 to 2021: systematic review and meta-analysis. *Chin Med J (Engl)* 2022;135:1682–1691.

4. Benic MS, Nezcic L, Vujic-Aleksic V, et al. Novel therapies for the treatment of drug-induced liver injury: a systematic review. *Front Pharmacol* 2021;12:785790.
5. Mueller S, Chen C, Mueller J, Wang S. Novel insights into alcoholic liver disease: Iron overload, sensing and hemolysis. *J Transl Intern Med* 2022;10:92–124.
6. Rockey DC, Caldwell SH, Goodman ZD, et al. Liver biopsy. *Hepatology* 2009;49:1017–1044.
7. Neuberger J, Patel J, Caldwell H, et al. Guidelines on the use of liver biopsy in clinical practice from the British Society of Gastroenterology, the Royal College of Radiologists and the Royal College of Pathology. *Gut* 2020;69:1382–1403.
8. Gilmore IT, Burroughs A, Murray-Lyon IM, et al. Indications, methods, and outcomes of percutaneous liver biopsy in England and Wales: an audit by the British Society of Gastroenterology and the Royal College of Physicians of London. *Gut* 1995;36:437–441.
9. Diehl DL. Endoscopic ultrasound-guided liver biopsy. *Gastrointest Endosc Clin N Am* 2019;29:173–186.
10. Chi H, Hansen BE, Tang WY, et al. Multiple biopsy passes and the risk of complications of percutaneous liver biopsy. *Eur J Gastroenterol Hepatol* 2017;29:36–41.
11. Lavian JD, Thornton LM, Zybulewski A, et al. Safety of percutaneous versus transjugular liver biopsy: a propensity score matched analysis. *Eur J Radiol* 2020;133:109399.
12. Thomaidis-Brears HB, Alkhoury N, Allende D, et al. Incidence of complications from percutaneous biopsy in chronic liver disease: a systematic review and meta-analysis. *Dig Dis Sci* 2022;67:3366–3394.
13. Kalambokis G, Manousou P, Vibhakorn S, et al. Transjugular liver biopsy—indications, adequacy, quality of specimens, and complications—a systematic review. *J Hepatol* 2007;47:284–294.
14. Gressens SB, Cazals-Hatem D, Lloyd V, et al. Hepatic venous pressure gradient in sinusoidal obstruction syndrome: diagnostic value and link with histological lesions. *JHEP Rep* 2022;4:100558.
15. Lal BB, Sood V, Rastogi A, et al. Safety, feasibility, yield, diagnostic and prognostic implications of transjugular liver biopsy in children and adolescents. *J Pediatr Gastroenterol Nutr* 2021;73:e109–114.
16. Ferral H, Fimmel CJ, Sonnenberg A, et al. Transjugular liver biopsy with hemodynamic evaluation: correlation between hepatic venous pressure gradient and histologic diagnosis of cirrhosis. *J Clin Imaging Sci* 2021;11:25.
17. Mathew A. EUS-guided routine liver biopsy in selected patients. *Am J Gastroenterol* 2007;102:2354–2355.
18. Mohan BP, Shakhatreh M, Garg R, et al. Efficacy and safety of EUS-guided liver biopsy: a systematic review and meta-analysis. *Gastrointest Endosc* 2019;89:238–246.e3.
19. Ali AH, Panchal S, Rao DS, et al. The efficacy and safety of endoscopic ultrasound-guided liver biopsy versus percutaneous liver biopsy in patients with chronic liver disease: a retrospective single-center study. *J Ultrasound* 2020;23:157–167.
20. Shuja A, Alkhasawneh A, Fialho A, et al. Comparison of EUS-guided versus percutaneous and transjugular approaches for the performance of liver biopsies. *Dig Liver Dis* 2019;51:826–830.
21. Oh D, Seo DW, Hong SM, et al. Endoscopic ultrasound-guided fine-needle aspiration can target right liver mass. *Endosc Ultrasound* 2017;6:109–115.
22. Chandan S, Deliwala S, Khan SR, et al. EUS-guided versus percutaneous liver biopsy: a comprehensive review and meta-analysis of outcomes. *Endosc Ultrasound* 2022;12:171–180.
23. Facciorusso A, Crino SF, Ramai D, et al. Diagnostic yield of endoscopic ultrasound-guided liver biopsy in comparison to percutaneous liver biopsy: a systematic review and meta-analysis. *Expert Rev Gastroenterol Hepatol* 2022;16:51–57.
24. Zeng K, Jiang Z, Yang J, et al. Role of endoscopic ultrasound-guided liver biopsy: a meta-analysis. *Scand J Gastroenterol* 2022;57:545–557.
25. McCarty TR, Bazarbashi AN, Njei B, et al. Endoscopic ultrasound-guided, percutaneous, and transjugular liver biopsy: a comparative systematic review and meta-analysis. *Clin Endosc* 2020;53:583–593.
26. Vozzo C, Saleh MA, Drake R, et al. Endoscopic ultrasound-guided liver biopsy: needle types and suction methods. *VideoGIE* 2021;6:485–486.
27. Akay E, Atasoy D, Altinkaya E, et al. Endoscopic ultrasound-guided fine needle aspiration using a 22-G needle for hepatic lesions: single-center experience. *Clin Endosc* 2021;54:404–412.
28. Ichim VA, Chira RI, Nagy GA, et al. Endoscopic ultrasound-guided biopsy of liver tumors. *In Vivo* 2022;36:890–897.
29. Möller K, Zadeh ES, Görg C, et al. Focal liver lesions other than hepatocellular carcinoma in cirrhosis: Diagnostic challenges. *J Transl Intern Med* 2022;10:308–327.
30. Schulman AR, Thompson CC, Odze R, et al. Optimizing EUS-guided liver biopsy sampling: comprehensive assessment of needle types and tissue acquisition techniques. *Gastrointest Endosc* 2017;85:419–426.
31. Khan MA, Grimm IS, Ali B, et al. A meta-analysis of endoscopic ultrasound-fine-needle aspiration compared to endoscopic ultrasound-fine-needle biopsy: diagnostic yield and the value of onsite cytopathological assessment. *Endosc Int Open* 2017;5:E363–375.
32. Baran B, Kale S, Patil P, et al. Endoscopic ultrasound-guided parenchymal liver biopsy: a systematic review and meta-analysis. *Surg Endosc* 2021;35:5546–5557.
33. Nieto J, Dawod E, Deshmukh A, et al. EUS-guided fine-needle core liver biopsy with a modified one-pass, one-actuation wet suction technique comparing two types of EUS core needles. *Endosc Int Open* 2020;8:E938–943.
34. Patel HK, Saxena R, Rush N, et al. A comparative study of 22G versus 19G needles for EUS-guided biopsies for parenchymal liver disease: are thinner needles better? *Dig Dis Sci* 2021;66:238–246.
35. Ching-Companioni RA, Diehl DL, Johal AS, et al. 19 G aspiration needle versus 19 G core biopsy needle for endoscopic ultrasound-guided liver biopsy: a prospective randomized trial. *Endoscopy* 2019;51:1059–1065.
36. Gheorghiu M, Seicean A, Bolboaca SD, et al. Endoscopic ultrasound-guided fine-needle biopsy versus fine-needle aspiration in the diagnosis of focal liver lesions: prospective head-to-head comparison. *Diagnostics (Basel)* 2022;12.
37. Mok SRS, Diehl DL, Johal AS, et al. Endoscopic ultrasound-guided biopsy in chronic liver disease: a randomized comparison of 19-G FNA and 22-G FNB needles. *Endosc Int Open* 2019;7:E62–71.
38. Parekh PJ, Majithia R, Diehl DL, et al. Endoscopic ultrasound-guided liver biopsy. *Endosc Ultrasound* 2015;4:85–91.
39. Kongkam P, Nalinthassanai N, Prueksapanich P, et al. A comparison of the antegrade core trap and reverse bevel needles for EUS-guided fine-needle biopsy sampling of liver mass: a prospective randomized cross over study. *HPB (Oxford)* 2022;24:797–805.
40. Aggarwal SN, Magdaleno T, Klocksieben F, et al. A prospective, head-to-head comparison of 2 EUS-guided liver biopsy needles in vivo. *Gastrointest Endosc* 2021;93:1133–1138.
41. Hashimoto R, Lee DP, Samarasena JB, et al. Comparison of two specialized histology needles for endoscopic ultrasound (EUS)-guided liver biopsy: a pilot study. *Dig Dis Sci* 2021;66:1700–1706.
42. Dewitt J, McGreevy K, Cummings O, et al. Initial experience with EUS-guided Tru-Cut biopsy of benign liver disease. *Gastrointest Endosc* 2009;69:535–542.
43. Gleeson FC, Clayton AC, Zhang L, et al. Adequacy of endoscopic ultrasound core needle biopsy specimen of nonmalignant hepatic parenchymal disease. *Clin Gastroenterol Hepatol* 2008;6:1437–1440.
44. Matsumoto K, Doi S, Watanabe A, et al. Quantitative analysis of tissue area of endoscopic ultrasound-guided liver biopsy specimens using 19-gauge fine-needle biopsy needle in patients with diffuse liver disease: a single-center retrospective study. *J Hepatobiliary Pancreat Sci* 2022;30:678–685.
45. Shah RM, Schmidt J, John E, et al. Superior specimen and diagnostic accuracy with endoscopic ultrasound-guided liver biopsies using 19-gauge versus 22-gauge core needles. *Clin Endosc* 2021;54:739–744.
46. Hasan MK, Kadkhodayan K, Idrisov E, et al. Endoscopic ultrasound-guided liver biopsy using a 22-G fine needle biopsy needle: a prospective study. *Endoscopy* 2019;51:818–824.
47. Mok SRS, Diehl DL, Johal AS, et al. A prospective pilot comparison of wet and dry heparinized suction for EUS-guided liver biopsy (with videos). *Gastrointest Endosc* 2018;88:919–925.
48. Saraireh H, Abdelfattah T, Hassouneh R, et al. “Wet heparin” and “wet saline” EUS-guided liver biopsy techniques both provide high rates of specimen adequacy for benign parenchymal liver disease. *Dig Dis Sci* 2022;67:5256–5261.
49. Nieto J, Khaleel H, Challita Y, et al. EUS-guided fine-needle core liver biopsy sampling using a novel 19-gauge needle with modified 1-pass, 1 actuation wet suction technique. *Gastrointest Endosc* 2018;87:469–475.
50. Tejedor-Tejada J, Nieto J, Deshmukh A, et al. EUS-guided fine-needle liver biopsy in pediatric patients using a modified technique with one-pass, one-actuation wet suction. *Rev Esp Enferm Dig* 2022;114:575–579.
51. Ching-Companioni RA, Johal AS, Confer BD, et al. Single-pass 1-needle actuation versus single-pass 3-needle actuation technique for EUS-guided liver biopsy sampling: a randomized prospective trial (with video). *Gastrointest Endosc* 2021;94:551–558.
52. Diehl DL. Top tips regarding EUS-guided liver biopsy. *Gastrointest Endosc* 2022;95:368–371.
53. Chawla YK, Bodh V. Portal vein thrombosis. *J Clin Exp Hepatol* 2015;5:22–40.
54. Nakhleh RE. The pathological differential diagnosis of portal hypertension. *Clin Liver Dis (Hoboken)* 2017;10:57–162.
55. Yan M, Geyer H, Mesa R, et al. Clinical features of patients with Philadelphia-negative myeloproliferative neoplasms complicated by portal hypertension. *Clin Lymphoma Myeloma Leuk* 2015;15:e1–5.

56. Choi AY, Kolb J, Shah S, et al. Endoscopic ultrasound-guided portal pressure gradient with liver biopsy: 6 years of endo-hepatology in practice. *J Gastroenterol Hepatol* 2022;37:1373–1379.
57. Choi AY, Chang KJ, Samarasekera JB, et al. Endoscopic ultrasound-guided porto-systemic pressure gradient measurement correlates with histological hepatic fibrosis. *Dig Dis Sci* 2022;67:5685–5692.
58. Hajifathalian K, Westerveld D, Kaplan A, et al. Simultaneous EUS-guided portosystemic pressure measurement and liver biopsy sampling correlate with clinically meaningful outcomes. *Gastrointest Endosc* 2022;95:703–710.
59. Binmoeller KF, Weilert F, Shah JN, et al. EUS-guided transesophageal treatment of gastric fundal varices with combined coiling and cyanoacrylate glue injection (with videos). *Gastrointest Endosc* 2011;74:1019–1025.
60. Yokoyama K, Miyayama T, Uchida Y, et al. Novel endoscopic therapy for gastric varices using direct forward-viewing endoscopic ultrasonography. *Case Rep Gastroenterol* 2021;15:28–34.
61. Fuccio L, Attili F, Larghi A. Forward-viewing linear echoendoscope: a new option in the endoscopic ultrasound armamentarium (with video). *J Hepatobiliary Pancreat Sci* 2015;22:27–34.
62. Ferraioli G, Tinelli C, Dal Bello B, et al. Accuracy of real-time shear wave elastography for assessing liver fibrosis in chronic hepatitis C: a pilot study. *Hepatology* 2012;56:2125–2133.
63. Castera L. Invasive and non-invasive methods for the assessment of fibrosis and disease progression in chronic liver disease. *Best Pract Res Clin Gastroenterol* 2011;25:291–303.
64. Llop E, Iruzubieta P, Perello C, et al. High liver stiffness values by transient elastography related to metabolic syndrome and harmful alcohol use in a large Spanish cohort. *United Eur Gastroenterol J* 2021;9:892–902.
65. Barr RG. Shear wave liver elastography. *Abdom Radiol (NY)* 2018;43:800–7.
66. Samir AE, Dhyani M, Vij A, et al. Shear-wave elastography for the estimation of liver fibrosis in chronic liver disease: determining accuracy and ideal site for measurement. *Radiology* 2015;274:888–896.
67. Singh P, Mukhopadhyay P, Bhatt B, et al. Endoscopic ultrasound versus CT scan for detection of the metastases to the liver: results of a prospective comparative study. *J Clin Gastroenterol* 2009;43:367–373.
68. Jeong JY, Kim TY, Sohn JH, et al. Real time shear wave elastography in chronic liver diseases: accuracy for predicting liver fibrosis, in comparison with serum markers. *World J Gastroenterol* 2014;20:13920–13929.
69. Cui XW, Chang JM, Kan QC, et al. Endoscopic ultrasound elastography: current status and future perspectives. *World J Gastroenterol* 2015;21:13212–13224.
70. Patel K, Sebastiani G. Limitations of non-invasive tests for assessment of liver fibrosis. *JHEP Rep* 2020;2:100067.
71. Schulman AR, Lin MV, Rutherford A, et al. A prospective blinded study of endoscopic ultrasound elastography in liver disease: towards a virtual biopsy. *Clin Endosc* 2018;51:181–185.
72. Song JE, Lee DW, Kim EY. Endoscopic ultrasound real-time elastography in liver disease. *Clin Endosc* 2018;51:118–119.
73. Kohli DR, Mettman D, Andraws N, et al. Comparative accuracy of endosonographic shear wave elastography and transcutaneous liver stiffness measurement: a pilot study. *Gastrointest Endosc* 2023;97:35–41.e1.
74. Kaya E, Yilmaz Y. Metabolic-associated fatty liver disease (MAFLD): a multi-systemic disease beyond the liver. *J Clin Transl Hepatol* 2022;10:329–338.
75. Dhar J, Samanta J. Role of endoscopic ultrasound in the field of hepatology: recent advances and future trends. *World J Hepatol* 2021;13:1459–1483.