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Posted Date: 19 January 2026

doi: 10.20944/preprints202601.1414.v1

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Review

# The Expansion of the Role of Endoscopic Ultrasound in the Field of Endohepatology

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## Abstract

**Background/Objective:** Endohepatology has recently emerged as a field combining advanced endoscopy and hepatology. Endoscopic ultrasound (EUS) plays a key role in the management of patients with chronic liver disease. The main objective of this paper is to provide critical review on the recent advances in EUS-based liver diagnostics and therapeutics and how such advances have been central in establishing the field of Endohepatology. **Methods:** We searched the PubMed database for articles published since 1995 focused on the use of EUS in the field of Endohepatology. **Results:** EUS-guided liver biopsy (EUS-LB) now offers diagnostic yield and therapeutic options comparable to those of the percutaneous and/or transjugular approaches. In addition, EUS-guided fine needle biopsy (EUS-FNB) design and suction techniques have further optimized tissue sampling. Furthermore, EUS-guided portal pressure gradient (EUS-PPG) measurement is an alternative to transjugular method. EUS-based elastography enables real-time quantification of liver stiffness and fibrosis and evaluation of space-occupying lesions. Moreover, EUS-guided interventions can play important roles in the management of patients with portal hypertension-related bleeding. Finally, emerging applications include EUS-guided radiofrequency ablation (EUS-RFA), portal venous sampling, and intrahepatic shunt creation, which may further expand minimally invasive treatment options. **Conclusions:** State-of-the-art innovations expanded the role of EUS not only in diagnostics, but also in the therapeutic role of EUS, and provided a new paradigm for the care of patients with liver disease.

**Keywords:** Endoscopic ultrasound; liver disease; biopsy; fine needle aspiration; Endohepatology; portal hypertension; liver transplantation

## 1. Introduction

Endohepatology is defined as the integration of advanced endoscopic techniques, primarily EUS, into the diagnostic, functional, and therapeutic management of patients with liver diseases. This field encompasses EUS-guided interventions for evaluation of the hepatic parenchyma, assessment of portal pressure gradient, and therapeutic procedures such as variceal embolization, abscess drainage, and emerging interventions such as portal vein sampling and shunt creation.[1]

The need for Endohepatology arises from several limitations of traditional approaches. Percutaneous and transjugular techniques for liver biopsy and portal pressure measurement are constrained by patient body habitus, coagulopathy, ascites, and anatomical inaccessibility. Furthermore, they often require more than a single hospital visit. Conventional imaging modalities such as computed tomography (CT), magnetic resonance imaging (MRI), and ultrasound may lack sensitivity for small lesions, real-time vascular assessment, or functional measurements. Moreover, the lack of providing tissue diagnosis or direct therapeutic access in a single session is inconvenient to patients and their caregivers.[1,2]

With the rising global burden of chronic liver diseases, primarily metabolic dysfunction-associated steatotic liver disease (MASLD), there is an increasing demand for minimally invasive,

accurate, and comprehensive diagnostic and therapeutic modalities. EUS-based Endohepatology offers high diagnostic yield, safety, and the ability to combine multiple procedures such as tissue biopsy, portal pressure measurement, detection and sampling of ascites in a single outpatient visit, improving efficiency and patient experience.[1,3] This approach is particularly valuable for complex or fragile patients, where reducing procedural risk and resource utilization is paramount.

## 2. Anatomy and EUS Evaluation of Liver Segments

EUS enables visualization of the liver by placing the echoendoscope in the stomach (transgastric) or duodenum (transduodenal), exploiting the proximity of these organs to the liver. The left lobe is best visualized via the transgastric approach, as the stomach lies adjacent to segments I, II, III, and IV, allowing high-resolution imaging and facilitating interventions such as biopsy, hepatic and portal venous pressure measurement. The right lobe segments V and VI, VII, and VIII, can be accessed via the duodenal bulb, but complete visualization of the segments (VII, VIII) remains technically challenging due to their distance from the duodenum and interposed structures. [4–6]

Technical challenges include limited access to the right posterior segments, suboptimal needle trajectory (especially for deep or posterior lesions), and increased risk of bleeding when traversing vascular structures. Anatomical variations, such as altered liver position or prior surgery, can further complicate access and orientation. The needle path must be carefully planned to avoid major intrahepatic vessels, and real-time Doppler is used to minimize the risk of vascular injury.[4–6]

Compared with abdominal ultrasound, CT, and MRI, EUS offers superior spatial resolution for small, subcentimeter lesions, especially in the left lobe and hilum, but is somewhat limited in the assessment of right posterior segments. Cross-sectional imaging such as CT and MRI remain superior for the evaluation of comprehensive segmental mapping and extrahepatic disease. EUS is thus complementary, excelling in targeted evaluation and intervention, but not replacing cross-sectional imaging for full segmental resolution. [7,8]

## 3. EUS-Guided Liver Biopsy

EUS-LB (Figure 1) is increasingly utilized in the evaluation of chronic liver disease, including staging liver fibrosis, diagnosing uncertain etiologies, and assessment in MASLD, autoimmune hepatitis, and cholestatic liver diseases.[9,10] EUS-LB is indicated when histologic diagnosis is required, and noninvasive tests are inconclusive or discordant, or when there is a need for simultaneous endoscopic evaluation or portal pressure measurement, particularly in individuals with suspected advanced liver disease. [10,11]

The advantages of EUS-LB over percutaneous or transjugular liver biopsy include real-time imaging with Doppler to avoid the risk of vascular injury, the ability to sample both hepatic lobes and the option to assess for portal hypertension using EUS-guided portal pressure gradient (EUS-PPG) measurement.[10,11] EUS-LB is associated with comparable specimen adequacy, longer tissue samples, and low rates of adverse events compared to percutaneous approach.[12] The American College of Gastroenterology (ACG) states that EUS-LB achieves high diagnostic yield and specimen adequacy, with a performance target of >85% for adequate samples, and is particularly advantageous when other endoscopic procedures are already planned.[13]

In one of our earlier experiences at our institution, patients who underwent EUS-LB were compared in a 1:2 fashion with an age- and gender-matched group who underwent PC-LB (n = 30 vs. 60 patients).[14] Patients in the EUS-LB compared to those in the PC-LB group had a significantly shorter hospital stay (median time: 3 vs. 4.2 hours) and reported significantly less pain (median pain score: 0 vs. 3.5), respectively.[14] Equally important, the rate of histological diagnosis was comparable in the two groups.[14] Similarly, in a prospective randomized trial of 80 patients comparing EUS-LB and PC-LB (1:1 ratio), both techniques demonstrated comparable diagnostic adequacy (60% of EUS-LB and 75% of PC-LB) met the primary endpoint of  $\geq 11$  complete portal tracts.[15] Despite similar histologic performance, EUS-LB compared to the PC-LB was associated with significantly lower post-

procedure pain (median pain score 2.0 vs 3.0) and a shorter hospital stay (median time 2.0 vs 4.0 hours), respectively.[15] Based on two meta-analyses, EUS-LB compared to PC-LB demonstrated pooled adverse event rates of 2.3% and 3%, respectively, with the most common complications being bleeding, abdominal pain, and pancreatitis.[16,17]

In summary, EUS-LB is a safe, effective, and versatile alternative to percutaneous or transjugular biopsy for patients with chronic liver disease, with specific advantages in procedural integration, sample quality, and patient comfort.[10–13,15,16]

Sampling both lobes of the liver with a bi-lobar biopsy does provide additional diagnostic benefit in a selected patient population due to disease heterogeneity, but the incremental value must be weighed against procedural risks and specimen adequacy. Disease heterogeneity is well-documented in conditions such as autoimmune hepatitis, MASLD, primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC), with studies showing clinically significant discordance in grading and staging between lobes in up to one-third of patients, which can directly impact management decisions.[18–20] For example, in autoimmune hepatitis, bi-lobar sampling altered treatment in 21% of cases due to differences in inflammatory activity or fibrosis stage.[18] Similarly, in NAFLD, overall diagnostic concordance between lobes is high, but fibrosis staging shows poorer agreement, suggesting that single-lobe biopsy may underestimate disease severity in some patients.[17]

EUS-LB enables safe, minimally invasive access to both lobes, with comparable or superior specimen adequacy and safety profiles relative to percutaneous approaches, and no significant increase in adverse events when both lobes are sampled.[10,12] The pilot study referenced found high concordance between left and right lobe specimens for specimen length and portal tracts, supporting the safety and adequacy of left lobe sampling.[21] However, routine bi-lobar biopsy is not universally required if a high-quality, adequately sized specimen is obtained from a single lobe, as recommended by the American Association for the Study of Liver Diseases (AASLD). [20]

In summary, bi-lobar biopsy is most beneficial when disease heterogeneity is suspected or when precise staging will influence management but is not routinely necessary if specimen quality is assured. There is limited large-scale, prospective data directly comparing clinical outcomes of uni-versus bi-lobar biopsy across diverse liver diseases.

The 19-gauge needle is not universally superior to the 22-gauge needle. Recent studies demonstrate that both 19G and 22G needles can achieve similar rates of specimen adequacy and diagnostic yield when advanced sampling techniques, such as hydrostatic sampling, are employed; notably, 22G needles may result in less blood contamination, which can be advantageous for histopathologic interpretation in certain scenarios.[22].

Some evidence suggests that 19G needles may yield longer core samples and more complete portal tracts, but this is often accompanied by increased fragmentation and bloodiness, with no clear advantage in clinical outcomes for most indications.[23,24] The clinical impact of these differences in specimen quality remains undetermined, and further research is needed to clarify whether larger samples translate into improved diagnostic or therapeutic outcomes.

#### 4. Evaluation of Portal Hypertension & Ascites Sampling

EUS can be used to sample ascites, particularly when fluid collections are small, loculated, or inaccessible to percutaneous approaches. EUS-guided paracentesis allows for targeted sampling of ascitic fluid for cytology and biochemistry, which is especially valuable in patients with suspected malignancy or infection, and can detect small-volume ascites not seen on cross-sectional imaging.[25,26] EUS-guided ascitic fluid sampling is safe and effective, and can be performed during the same session as EUS evaluation of gastrointestinal malignancies or liver disease.

For localization of fluid collections, EUS provides high-resolution, real-time imaging, enabling precise identification and access to peritoneal fluid, even in challenging anatomical locations or in the presence of adhesions.[25,26] This is particularly useful for diagnostic and therapeutic interventions.



However, EUS-guided paracentesis may carry a risk of self-limited fever, reported in approximately 3% of patients in one study.[27]

Regarding imaging of varices and portal hypertensive gastropathy, EUS offers superior visualization of peri- and para-esophageal and gastric varices, as well as collateral veins, compared to standard endoscopy (Figure 2). EUS can assess the size, number, and hemodynamics of varices and collaterals, and can guide therapeutic interventions such as coil or glue injection for gastric varices.[28–30] EUS also allows for the assessment of portal hypertensive gastropathy and can be used to evaluate portal hemodynamics, including direct portal pressure measurements.[29]

The AASLD recommends standard paracentesis for ascitic fluid evaluation, but EUS-guided approaches are increasingly used in specialized settings for difficult-to-access or small-volume ascites, and for comprehensive assessment of portal hypertension.[31]

## 5. EUS-Guided Elastography

Shear wave measurement (SWM) by endoscopic ultrasound-guided elastography (EUS-SWE) correlates strongly with stage of fibrosis in MASLD, and has been found to have a superior diagnostic accuracy compared to vibration-controlled transient elastography (VCTE), especially in patients with obesity.[32,33] EUS-SWE provides reliable liver stiffness measurement (LSM) that correlate with histologic stage of fibrosis, and is also correlates with the degree of portal hypertension, as higher LSM values predict portal hypertension and esophageal varices (Figure 3(A) and 3(B)).[34]

For MASLD features, liver stiffness measured by SWE is primarily a marker of fibrosis, but can be modestly influenced by inflammation; shear wave dispersion slope (SWDS) and attenuation imaging can improve detection of steatosis and inflammation. SWDS correlates with lobular inflammatory activity, and attenuation coefficient correlates with grade of steatosis.[35,36] Severe steatosis may lead to overestimation of LSM, particularly in early stages of fibrosis, reducing specificity for detection of fibrosis.[37] In a recent single-center study, EUS-SWE was significantly higher in patients with significant fibrosis compared to those without significant fibrosis (30.0 vs 15.6 kPa;  $p = 0.02$ ) and in patients with advanced fibrosis compared to those without advanced fibrosis (32.0 vs 18.8 kPa;  $p = 0.04$ ), supporting its utility in assessment of fibrosis.[38]

Limitations of EUS-SWE worth noting may include:

- Calibration and vendor-specific cutoffs: LSM thresholds vary by instrument and must be interpreted accordingly.[39]
- Operator dependency: Technical expertise is required for proper region-of-interest selection and avoidance of vascular/biliary structures; however, interobserver reproducibility is generally excellent when performed by skilled operators.[40,41]
- Attenuation by ascites or obesity: While EUS-SWE is less affected by ascites and obesity than VCTE, extreme obesity and large-volume ascites can impair signal transmission and measurement reliability. The AASLD notes that SWE is relatively robust but not immune to these confounders.[39]

Other confounding factors include rapid diaphragmatic movements, acute hepatitis, congestion, and biliary obstruction, which can increase measured shear wave velocity independent of fibrosis.[41] In summary, EUS-SWE is a robust tool for assessment of fibrosis and portal hypertension in patients with MASLD, but interpretation requires awareness of technical and biological limitations.

## 6. EUS-Guided Portal Pressure Gradient (PPG) Measurement

Building on the consensus regarding safety and feasibility, recent clinical studies have demonstrated that EUS-PPG measurement achieves high technical success rates, with direct access to the portal vein, hepatic vein, or inferior vena cava using fine-needle aspiration (FNA) needle and a compact manometry setup (Figure 4(A) & 4(B); Figure 5(A)& 5(B)). In multiple studies, EUS-PPG values have shown strong correlation with clinical markers of portal hypertension, such as the presence of varices, portal hypertensive gastropathy, and thrombocytopenia, as well as with

histologic features of cirrhosis.[11,38,42–44] In our recent retrospective study (n = 25 patients), patients with significant fibrosis ( $F \geq 2$ ) had a higher mean EUS-PPG (5.9 vs 2.8 mmHg;  $p = 0.003$ ) compared to the nonsignificant fibrosis ( $F < 2$ ) group. Similarly, patients with advanced fibrosis ( $F \geq 3$ ) had a higher mean EUS-PPG (6.0 vs 3.4 mmHg;  $p = 0.01$ ) compared to the nonadvanced fibrosis ( $F < 3$ ) group.[38] Notably, EUS-PPG can be performed in a single session alongside EUS-LB and variceal screening, streamlining the diagnostic workflow for chronic liver disease.[42–44]

Comparative studies in both animal models and human subjects have confirmed that EUS-PPG measurements are highly concordant with the traditional transjugular hepatic venous pressure gradient (HVPG), with correlation coefficients exceeding 0.9 and mean gradients differing by less than 1 mmHg in most cases.[49] This direct approach is particularly advantageous in patients with Budd-Chiari syndrome or presinusoidal portal hypertension, where HVPG may be technically challenging or less accurate.[45] The ability to obtain real-time pressure tracings and perform concurrent interventions, such as variceal banding, further supports the clinical utility of EUS-PPG in both inpatient and outpatient settings.[43]

While procedural complexity and operator dependence remain challenges, published data consistently reports low rates of adverse events. Multiple studies, including over 180 patients, have reported no major adverse events, with only one mild adverse event of abdominal pain reported.[11,43,46] The integration of EUS-PPG into routine practice is expected to expand, especially as standardization and multicenter validation studies progress.[47]

## 7. EUS-Guided Embolization & Cyanoacrylate Injection for Portal Hypertension and Variceal Bleeding

Building on the guideline-based recommendations, recent clinical trials and meta-analyses have further clarified the comparative efficacy and safety of EUS-guided coil plus cyanoacrylate injection (Figure 6(A) & 6(B)) versus conventional endoscopic cyanoacrylate injection (ECI) for gastric varices. Multiple randomized and observational studies demonstrate that EUS-guided therapy, particularly the combination of coil embolization and cyanoacrylate, results in lower rates of recurrent bleeding and reintervention compared to ECI alone, without a significant increase in adverse events such as pulmonary embolism or procedure-related pain.[48–50] A recent meta-analysis found that EUS-guided coil plus glue injection was associated with a markedly reduced odds of recurrent bleeding (OR 0.22; 95% CI 0.10–0.45;  $p < 0.001$ ) and reintervention rates (OR 0.29; 95% CI 0.09–0.89;  $p = 0.03$ ) compared to ECI, with similar rates of technical success and mortality.[49]

EUS guidance allows for precise targeting of both the gastric varix and perivascular feeding collaterals (perforating veins), which is thought to improve obliteration rates and reduce the risk of glue embolization by providing a coil scaffold for thrombosis and glue retention.[50,51] The addition of coils appears to enhance the durability of variceal obliteration and extend the time to reintervention, as shown in randomized studies.[48,51] Furthermore, EUS enables real-time Doppler assessment, facilitating confirmation of flow cessation and allowing for tailored therapy based on variceal anatomy.

Rectal varices are common in patients with cirrhosis and portal hypertension, reported in 38% to 94%. However, rectal variceal bleeding is rare, reported in ~ 5% of patients.[52] EUS is helpful in differentiating rectal varices from hemorrhoids, identifying in- and out-flow veins and target perforator veins. The published literature on EUS-guided injection of rectal and ectopic varices is limited to small case.[53–57]

While EUS-guided embolization is not yet universally adopted as first-line therapy, accumulating evidence supports its use in expert centers for patients with high-risk or recurrent gastric varices, especially when conventional endoscopic approaches are suboptimal or technically challenging.[48–51] The American Gastroenterology Association (AGA) Clinical Practice Update recommends EUS-guided coil and glue injection for gastric varices at centers of expertise.[53] The optimal technique, including the number and size of coils, volume of cyanoacrylate, and targeting of

collaterals, remains under investigation, but current data favor combination therapy for improved outcomes.

## 8. EUS-Guided Portosystemic Shunt (EUS-IPS)

Endoscopic ultrasound-guided intrahepatic portosystemic shunt (EUS-IPS) is technically feasible in animal models, specifically in porcine studies. [58,59] The procedure involves EUS-guided puncture of the hepatic vein (or inferior vena cava) and portal vein, followed by deployment of a self-expanding metal stent to establish a portosystemic shunt. Patency of the shunt is confirmed by portal venography and EUS Doppler, with documented portosystemic flow and direct portal pressure measurements before and after shunt.[58–60]

Technical feasibility is high, with successful shunt reported in the majority of studied animals (success rates up to 91%).[60] The mean procedure time duration was approximately 43 minutes in one study, and the technical demand is considered manageable for experienced endoscopists.[58] Shunt Patency can be demonstrated immediately in short-term survival models, with functional flow confirmed in 81% of cases in one series. However, some stents may become thrombosed or malpositioned, indicating the need for further device/technique optimization.[60]

Safety in animal models is acceptable, with no major bleeding or organ injury observed in most studies. Reported morbidity includes hemoperitoneum, hemothorax, and pneumothorax in a minority of cases (overall reported morbidity ~14%).[60] No procedure-related deaths were reported in short-term follow-up.[58–60] These data support the technical feasibility, short-term patency, and acceptable safety profile of EUS-IPS in animal models. However, further studies are required to assess long-term outcomes, device improvements, and applicability in models of portal hypertension before clinical translation.[60]

## 9. EUS and Hepatocellular Carcinoma Screening

EUS has no established role in hepatocellular carcinoma (HCC) screening and is not endorsed by the society guidelines for HCC surveillance.[61,62] Both the National Comprehensive Cancer Network (NCCN) and the AASLD recommend transabdominal ultrasound plus alpha-fetoprotein at 6-month intervals as the standard surveillance strategy for patients at risk of HCC.[61,62]

The fundamental limitation that precludes EUS from serving as a screening modality is that EUS is invasive and resource intensive.[7] Unlike transabdominal ultrasound, which can visualize the entire liver parenchyma, EUS provides limited visualization of the entire hepatic lobe segments, making comprehensive entire liver assessment impossible.[7] Beyond anatomic limitations, EUS requires endoscopy with sedation, making it impractical for the semi-annual surveillance required in at-risk populations, where non-invasive imaging modalities are preferred for repeated examinations over many years.[2] The requirement for specialized endoscopic expertise, limited availability compared to standard ultrasound, operator dependency, and lack of cost-effectiveness data for surveillance populations further compound these limitations.[2,6]

EUS has been shown to detect small hepatic lesions missed by cross-sectional imaging, supporting that EUS approach can detect small lesions missed by CT or MRI and can be used as an adjunct exam in the management of selected patient populations.[63] Singh et al. conducted a prospective study of 17 high-risk patients and found that EUS detected significantly more nodular lesions than transabdominal ultrasound, CT, and MRI, with a diagnostic accuracy of 94% when combined with EUS-guided fine needle aspiration.[64] However, this small single-center study evaluated EUS as a diagnostic tool in patients already suspected of having HCC rather than as a screening modality in asymptomatic at-risk populations, and the authors recommended EUS for suspected HCC, particularly in cases being considered for liver transplantation.[64]

In summary, currently, EUS has no validated role in HCC screening. When standard ultrasound surveillance is suboptimal, guidelines recommend contrast-enhanced MRI or multiphase CT as

alternative surveillance modalities.[61,62] EUS remains confined to diagnostic problem-solving in select cases where standard imaging is inconclusive.[2,7]

## 10. EUS- Guided Evaluation, Radiofrequency Ablation & Treatment of Focal Liver Lesions

Indeterminate focal liver lesions represent a diagnostic challenge, as exclusion of malignancy is often required for clinical decision-making. EUS enables high-resolution evaluation of focal liver lesions and permits targeted tissue acquisition, with particular utility for lesions in the left hepatic lobe and caudate region, which are anatomically favorable for transgastric EUS access and may be challenging for percutaneous access.[2,6] In a systematic review and meta-analysis of EUS-guided tissue acquisition for focal liver lesions, pooled diagnostic accuracy ranged from 90% to 94%, with adverse event rates of 3%, demonstrating favorable diagnostic performance and safety in mixed patient populations.[2] Transplant-focused reviews describe the use of EUS as a problem-solving tool when cross-sectional imaging is inconclusive, and additional lesion characterization is required to inform transplant candidacy.[65]

EUS-RFA is a minimally invasive technique that utilizes real-time EUS to guide the placement of a radiofrequency ablation probe into focal liver lesions. This approach has evolved from its initial use in pancreatic lesions to selected hepatic applications, particularly for patients who are not candidates for surgical resection or percutaneous ablation due to comorbidities, lesion location, or anatomical constraints. [66,67] EUS-RFA is primarily considered in cases where lesions are accessible via the gastrointestinal tract wall, such as the left lobe of the liver adjacent to the stomach or duodenum.[66]

### 10.1. Applications of Endoscopic Ultrasound-Guided Radiofrequency Ablation for Specific Liver Lesions

- **Neuroendocrine Tumors:** EUS-RFA has demonstrated efficacy in the management of hepatic metastases from gastroenteropancreatic neuroendocrine tumors, particularly in the setting of oligoprogression. Local thermal ablation, including RFA, can provide focal growth control and prolong progression-free survival, delaying the need for escalation of systemic therapy. In retrospective series, thermal ablation was well tolerated and resulted in a median progression-free survival of 62 weeks per procedure, with most patients experiencing delayed disease progression.[68] NCCN recognizes locoregional therapies, including ablation, as preferred options for patients not amenable to surgery or transplantation.[69]

- **Dysplastic Nodules:** RFA for high-grade dysplastic nodules (HGDNs) in chronic liver disease achieves high technical effectiveness and low local tumor progression rates, with 1-year effectiveness rates approaching 100%. However, modeling studies and guideline recommendations from the AASLD state that there is no definitive evidence that RFA of HGDNs provides additional long-term overall survival benefit compared to regular follow-up and timely treatment by resection.[70]

- **Small HCC:** For HCC  $\leq 3$  cm, RFA is considered a potentially curative option, especially in patients who are not surgical candidates. The AASLD and NCCN guidelines state that ablation alone may be curative for tumors  $\leq 3$  cm, with overall 3-year survival of 76% and recurrence-free survival of 46%. EUS-RFA is particularly relevant for lesions in locations accessible via the GI tract wall, such as the left hepatic lobe. [61,62]

### 10.2. Endoscopic Ultrasound-Guided Radiofrequency Ablation

EUS-guided RFA for focal liver lesions, including HCC, is mainly case reports and small case series, and broader reviews of EUS-guided intrabdominal tumors. EUS-guided RFA is best suited as an adjunct option for lesions that are difficult to reach percutaneously (especially hepatic segments II and III, and the caudate lobe). [71–73]

## 11. EUS in Liver Transplantation



EUS has become increasingly relevant in liver transplantation as part of the evolving endohepatology framework, with applications spanning pre-transplant evaluation and post-transplant complication management. Rather than serving as a routine screening modality, EUS is most impactful when applied at specific clinical decision points, including exclusion criteria during transplant candidate workup, characterization of biliary pathology underlying graft dysfunction, and minimally invasive management of post-transplant collections. When used selectively within a multidisciplinary transplant pathway, EUS complements established diagnostic and therapeutic strategies and can directly influence transplant-related decision-making.[65,74]

#### A. Pre-Transplant Applications

##### 1. Portal hypertension assessment and risk stratification

As we stated, EUS-PPG measurement has been described as a minimally invasive alternative to transjugular HVPG assessment, with potential relevance in selected liver transplant candidates.[11,47]

In the transplant setting, EUS-PPG is discussed as a complementary hemodynamic assessment rather than a replacement for HVPG. Reviews highlight its potential value in candidates with discordant clinical findings or suspected presinusoidal portal hypertension, a scenario in which HVPG may underestimate portal pressure.[47] An additional consideration relevant to pre-transplant evaluation is the ability to integrate portal pressure assessment with other endohepatology applications during a single EUS session, including evaluation of portosystemic collaterals and EUS-LB when indicated.[3,47] However, transplant-specific outcome data remain limited, and the role of EUS-PPG in transplant listing decisions or prognostication has not been validated in dedicated liver transplant cohorts; consequently, its use in the transplant setting remains center- and expertise-dependent.[47]

##### 2. Lymph node staging in transplant protocols for perihilar cholangiocarcinoma

Among transplant-specific indications, EUS has a defined role in staging candidates with unresectable perihilar cholangiocarcinoma undergoing transplant-based protocols.[75] In a multicenter cohort study, EUS-guided sampling of nonregional lymph nodes identified metastatic disease in approximately 4% of evaluated candidates.[75] Although the diagnostic yield is modest, identification of nodal metastasis excludes transplantation and prevents futile neoadjuvant therapy or surgical exploration.[75]

#### B. Post-Transplant Applications

##### 1. Post-liver transplant biliary complications (diagnostic adjunct to ERCP)

Biliary complications remain a major source of morbidity following liver transplantation.[76] In a cohort of liver transplant recipients, EUS demonstrated high diagnostic performance for biliary complications, with reported sensitivity and overall accuracy in the 90%'s range.[76] EUS was particularly useful for detecting biliary casts and ischemic-type cholangiopathy, entities that may be incompletely characterized by cholangiography alone and that carry prognostic significance.[76] While ERCP remains central for therapeutic biliary intervention and for evaluation of anastomotic strictures, EUS is considered as a complementary diagnostic modality in selected cases of unexplained cholestasis or graft dysfunction. [65,76]

##### 2. Post-transplant collections and EUS-guided drainage

Bilomas and other infected hepatic fluid collections are important complications after liver transplantation. [77,78] EUS-guided transluminal drainage has been reported as technically feasible for bilomas adjacent to the gastrointestinal lumen, providing an internal drainage option and an alternative to percutaneous or surgical drainage in selected cases.[79] In broader (non-transplant-specific) liver disease evidence, a systematic review and meta-analysis reported high technical and clinical success for EUS-guided liver abscess drainage (90.7%) with low complication rates, supporting the general feasibility of EUS-guided drainage approaches when anatomy is favorable and expertise is available. [2] Transplant-focused reviews describe therapeutic EUS, including drainage interventions, as an emerging option in post-transplant care, with utilization largely dependent on local expertise and case selection.[65]

### 3. Histological evaluation of graft dysfunction

EUS-LB is described as an alternative diagnostic approach when graft dysfunction, suspected rejection, or recurrent liver disease requires histologic confirmation and percutaneous biopsy is limited by ascites, anticoagulation, or altered post-surgical anatomy. [6,65] Systematic reviews of EUS-LB, derived predominantly from mixed liver disease populations that include post-transplant recipients, report specimen adequacy rates exceeding 85%–90% with low adverse event rates.[2,6]

On this basis, transplant-focused reviews support the selective use of EUS-LB in post-transplant recipients who are already undergoing endoscopic evaluation, rather than its routine use as a first-line biopsy modality. [65]

### 4. Portal hypertension–related varices after liver transplantation

Although liver transplantation usually results in resolution of portal hypertension, persistent or recurrent portal hypertension has been described in a subset of recipients, most commonly in association with portal vein thrombosis, vascular anastomotic complications, or persistent portosystemic collateralization.[80,81] In this context, gastric or ectopic variceal bleeding may occur despite preserved graft function.[80]

EUS-guided therapy has been evaluated for the management of gastric varices in patients with complex portal hypertension anatomy. A systematic review and meta-analysis demonstrated lower rates of recurrent bleeding and reintervention with EUS-guided coil-plus-cyanoacrylate injection compared with endoscopic glue injection alone, without differences in mortality or major procedure-related complications.[49] These findings are supported by an international multicenter propensity-matched study reporting reduced rebleeding with EUS-guided coil-and-glue therapy.[50] Transplant-focused and post-transplant EUS reviews describe EUS-guided variceal therapy as a targeted option for selected post-transplant patients when conventional endoscopic approaches are limited or unsuccessful.[65]

## 12. Limitations of Endoscopic Ultrasound in the Study of Liver Disease

We acknowledge that EUS assessment of the liver is not devoid from limitations. EUS examination of the hepatic lobe segments can be hampered by the presence of pneumobilia from previous biliary intervention or surgical anastomosis. Significant calcifications in the gallbladder from calcified stones or calcified wall render attenuation of ultrasound beams. Moreover, hydropic gallbladder may impede the echoendoscope approximation at the duodenum. The presence of biliary metal stents causes significant echosonographic artifacts. Body habitus and increase in visceral abdominal fat as well as severe hepatic steatosis impedes acoustic coupling. Altered anatomy in patients with hepaticojejunostomy after liver transplantation can also put a challenge on endoscopic examination of the hepatic parenchyma.

**Supplementary Materials:** None.

**Author Contributions:** MM drafted the first draft of the manuscript. EI edited the first draft. AHA edited the final draft. GMH drafted the framework of the manuscript, provided key insights into the content of the manuscript, added figures to the manuscript, and edited the first and final drafts. All authors approved of the final draft.

**Funding:** None.

**Institutional Review Board Statement:** Not applicable.

**Informed Consent Statement:** Not applicable.

**Data Availability Statement:** Not applicable.

**Conflicts of Interest:** All authors have nothing to disclose.

## Abbreviations

The following abbreviations are used in this manuscript:

|         |                                                               |
|---------|---------------------------------------------------------------|
| AASLD   | American Association for the Study of Liver Disease           |
| ACG     | American College of Gastroenterology                          |
| AGA     | American Gastroenterology Association                         |
| CI      | Confidence interval                                           |
| CT      | Computed tomography                                           |
| ERCP    | Endoscopic retrograde cholangiopancreatography                |
| EUS     | Endoscopic ultrasound                                         |
| EUS-IPS | Endoscopic ultrasound-guided intrahepatic portosystemic shunt |
| EUS-FNB | Endoscopic ultrasound-fine-needle biopsy                      |
| EUS-LB  | Endoscopic ultrasound-guided liver biopsy                     |
| EUS-PPG | Endoscopic ultrasound-guided portal pressure gradient         |
| EUS-RFA | Endoscopic ultrasound-guided radiofrequency ablation          |
| EUS-SWM | Endoscopic ultrasound-guided shear wave measurement           |
| EUS-SWE | Endoscopic ultrasound-guided shear wave elastography          |
| HCC     | Hepatocellular carcinoma                                      |
| HGDNs   | High-grade dysplastic nodules                                 |
| HVPG    | Hepatic venous pressure gradient                              |
| kPa     | Kilopascals                                                   |
| LSM     | Liver stiffness measurement                                   |
| MASLD   | Metabolic dysfunction-associated steatotic liver disease      |
| MRI     | Magnetic resonance imaging                                    |
| NCCN    | National Comprehensive Cancer Network                         |
| OR      | Odds ratio                                                    |
| PBC     | Primary biliary cholangitis                                   |
| PC-LB   | Percutaneous-guided liver biopsy                              |
| PSC     | Primary sclerosing cholangitis                                |
| SWDS    | Shear wave dispersion slope                                   |
| VCTE    | Vibration-controlled transient elastography                   |

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