**American College of Radiology**
**ACR Appropriateness Criteria®**

# Abnormal Liver Function Tests

## Variant: 1 Abnormal liver function tests. Hepatocellular predominance with mild aminotransferase increase. Initial imaging.

| Procedure | Appropriateness Category | Relative Radiation Level |
|---|---|---|
| US abdomen | Usually Appropriate | O |
| US duplex Doppler abdomen | Usually Appropriate | O |
| US shear wave elastography abdomen | May Be Appropriate | O |
| MR elastography abdomen | May Be Appropriate | O |
| MRI abdomen without and with IV contrast with MRCP | May Be Appropriate | O |
| MRI abdomen without IV contrast with MRCP | May Be Appropriate | O |
| CT abdomen and pelvis without IV contrast | May Be Appropriate | ☢☢☢ |
| US abdomen with IV contrast | Usually Not Appropriate | O |
| CT abdomen and pelvis with IV contrast | Usually Not Appropriate | ☢☢☢ |
| CT abdomen and pelvis without and with IV contrast | Usually Not Appropriate | ☢☢☢☢ |

## Variant: 2 Abnormal liver function tests. Hepatocellular predominance with moderate or severe aminotransferase increase. Initial imaging.

| Procedure | Appropriateness Category | Relative Radiation Level |
|---|---|---|
| US abdomen | Usually Appropriate | O |
| US duplex Doppler abdomen | Usually Appropriate | O |
| CT abdomen and pelvis with IV contrast | Usually Appropriate | ☢☢☢ |
| MRI abdomen without and with IV contrast with MRCP | May Be Appropriate | O |
| MRI abdomen without IV contrast with MRCP | May Be Appropriate | O |
| CT abdomen and pelvis without IV contrast | May Be Appropriate | ☢☢☢ |
| US abdomen with IV contrast | Usually Not Appropriate | O |
| US shear wave elastography abdomen | Usually Not Appropriate | O |
| MR elastography abdomen | Usually Not Appropriate | O |
| CT abdomen and pelvis without and with IV contrast | Usually Not Appropriate | ☢☢☢☢ |

## Variant: 3 Abnormal liver function tests. Cholestatic predominance. Elevated alkaline phosphatase with or without elevated gamma-glutamyl transpeptidase. Initial imaging.

| Procedure | Appropriateness Category | Relative Radiation Level |
|---|---|---|
| US abdomen | Usually Appropriate | O |
| MRI abdomen without and with IV contrast with MRCP | Usually Appropriate | O |
| CT abdomen and pelvis with IV contrast | Usually Appropriate | ☢☢☢ |
| US duplex Doppler abdomen | May Be Appropriate | O |
| MRI abdomen without IV contrast with MRCP | May Be Appropriate | O |
| CT abdomen and pelvis without IV contrast | May Be Appropriate | ☢☢☢ |
| US abdomen with IV contrast | Usually Not Appropriate | O |
| US shear wave elastography abdomen | Usually Not Appropriate | O |
| MR elastography abdomen | Usually Not Appropriate | O |

| | | |
|---|---|---|
| CT abdomen and pelvis without and with IV contrast | Usually Not Appropriate | ☢☢☢☢ |

**Variant: 4 Abnormal liver functions tests. Hyperbilirubinemia. Acute or subacute cholestasis. Conjugated or unconjugated. Initial imaging.**

| Procedure | Appropriateness Category | Relative Radiation Level |
|---|---|---|
| US abdomen | Usually Appropriate | O |
| MRI abdomen without and with IV contrast with MRCP | Usually Appropriate | O |
| MRI abdomen without IV contrast with MRCP | Usually Appropriate | O |
| CT abdomen and pelvis with IV contrast | Usually Appropriate | ☢☢☢ |
| CT abdomen and pelvis without IV contrast | May Be Appropriate | ☢☢☢ |
| US abdomen with IV contrast | Usually Not Appropriate | O |
| US duplex Doppler abdomen | Usually Not Appropriate | O |
| US shear wave elastography abdomen | Usually Not Appropriate | O |
| MR elastography abdomen | Usually Not Appropriate | O |
| CT abdomen and pelvis without and with IV contrast | Usually Not Appropriate | ☢☢☢☢ |

**Panel Members**

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**Summary of Literature Review**

**Introduction/Background**

Liver function tests are often obtained as part of standard laboratory panels in asymptomatic and symptomatic patients. Alteration in the biochemical markers of hepatocyte damage or bile flow indicate hepatobiliary insult rather than a measurement of liver function. Routine liver chemistries include alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), and bilirubin. On the contrary, albumin and prothrombin time are actual markers of hepatocellular synthetic function.

Hepatocellular predominant abnormal liver function tests are reflected as an increase in aminotransferases, ALT, and AST. Hepatocytic injury and necrosis caused by diffuse hepatic infiltration (fat, copper, or iron), acute hepatitis, or toxic or ischemic injury can lead to leakage of these enzymes from liver cells into serum. Because both aminotransferases (AST and ALT) are concentrated in the liver, their elevations are indicative of liver damage. However, an increase in AST could be due to disorders involving the heart, skeletal muscle, kidneys, brain, and red blood cells. ALT elevations, on the other hand, are specific for liver injury owing to low concentrations in skeletal muscle and kidney. Normal ALT levels are 29 to 33 IU/L (0.48-0.55 µkat/L) in men and 19 to 25 IU/L (0.32-0.42 µkat/L) in women [1-3].

The severity of abnormal aminotransferase can be classified as 1) mild: <5 times the upper reference limit, 2) moderate: 5 to 10 times the upper reference limit, or 3) severe: >10 times the upper reference limit. Moderate and severe are discussed collectively as significant clinical overlap exists between these 2 categories.

Pathologically increased levels of ALP may occur in cholestatic liver disease, which can show elevated ALP with or without elevated bilirubin. Cholestasis can be due to obstruction of biliary outflow or impairment in bilirubin uptake. If abnormal ALP levels are seen without impairment of other liver enzymes, the etiology is suspected to be cholestatic in origin. If ALP is elevated in isolation, a confirmation with gamma-glutamyl transpeptidase (GGT) or fractionated ALP isoenzyme helps to differentiate hepatic from nonhepatic etiologies, such as bone disease. GGT can be elevated in nonhepatic diseases such as myocardial infarction, renal failure, diabetes, pulmonary, and pancreatic disorders; therefore, it is not used in isolation to assess for liver disease when other liver function tests are normal [1].

Bilirubin is produced by the breakdown of heme. Following conjugation within the liver to increase water solubility, bilirubin is excreted into bile. Conjugated (direct) bilirubin is rapidly excreted in the alimentary tract; thus, bilirubin amounts are negligible in serum in healthy individuals. A rise in levels of conjugated bilirubin in the serum is an indicator of impaired liver excretion. Conjugated hyperbilirubinemia can occur because of impaired bilirubin transport into the intrahepatic bile ducts or downstream obstruction of the biliary tract from intrinsic or extrinsic causes.

Serum unconjugated (indirect) bilirubin can be increased in hemolysis or Gilbert syndrome, which is diagnosed when unconjugated hyperbilirubinemia is the only abnormal liver function test and conjugated bilirubin and complete blood count are normal.

**Initial Imaging Definition**

Initial imaging is defined as imaging at the beginning of the care episode for the medical condition defined by the variant. More than one procedure can be considered usually appropriate in the initial imaging evaluation when:

- There are procedures that are equivalent alternatives (ie, only one procedure will be ordered to provide the clinical information to effectively manage the patient's care)

OR

- There are complementary procedures (ie, more than one procedure is ordered as a set or simultaneously where each procedure provides unique clinical information to effectively manage the patient's care).

**Discussion of Procedures by Variant**
**Variant 1: Abnormal liver function tests. Hepatocellular predominance with mild aminotransferase increase. Initial imaging.**

Hepatocellular predominant liver chemistry is seen when aminotransferases are elevated much higher than ALP (cholestatic-pattern). Hepatocellular injury causes the release of ALT and AST in serum.

Increase in ALT (mild or moderate to severe) is directly linked to hepatocyte injury. In addition to fatty liver disease, other causes of rising ALT include acute or chronic viral hepatitis, acute Budd-Chiari syndrome, ischemic hepatitis, autoimmune, hemochromatosis, medications/toxins, autoimmune, alpha1-antitrypsin deficiency, and Wilson disease. AST levels are also increased in fatty liver disease and cirrhosis. However, if the aminotransferase rise is predominantly AST, nonhepatic causes (hemolysis, myopathy, thyroid disease, exercise) should also be considered.

Common causes of mild increases in aminotransferases are nonalcoholic fatty liver disease (NAFLD) and alcohol- induced liver disease; uncommon causes include drug-induced liver injury, hepatitis B, hepatitis C, and hereditary hemochromatosis. Rare causes are alpha1-antitrypsin deficiency, autoimmune hepatitis, and Wilson disease.

The 2 most common causes of fatty liver disease are NAFLD and alcohol-induced steatosis/steatohepatitis. Excessive intake of alcohol results in alcohol-induced fatty liver disease. The AST:ALT ratio is generally >2 in alcohol-induced fatty liver disease and <1 in metabolic disease-related fatty liver. Alcohol-induced liver disease is caused by excess alcohol consumption, whereas the nonalcoholic variant is related to insulin resistance and the metabolic syndrome. NAFLD is the most common liver disease in first world countries, with a prevalence of 20% to 30% in the general population; however, this increases to 70% with obesity and 90% with diabetes mellitus.

NAFLD is a spectrum of fat deposition and hepatic inflammation followed by fibrosis due to metabolic insults. Simple hepatic steatosis can be seen in 70% to 75% of cases without cellular insult. Nonalcoholic steatohepatitis (NASH) can be found in 25% to 30% of cases with hepatocyte injury and inflammation due to lipid; these entities, simple hepatic steatosis and NASH, can coexist. Progressive insults with inflammation can result in fibrosis leading to cirrhosis and hepatocellular carcinoma [4,5].

**Variant 1: Abnormal liver function tests. Hepatocellular predominance with mild aminotransferase increase. Initial imaging.**
**A. US Abdomen**

Ultrasound (US) is useful as a first-line investigation tool for mild increase in liver enzymes. US has been used world-wide to screen for both alcohol-induced liver disease and NAFLD. US has the benefit of being noninvasive and is an accurate method to detect steatosis [6,7].

US can be successfully diagnose hepatic lipid content of >33% but can be unreliable with mild fatty infiltration, with an 84.8% sensitivity and a 93.6% specificity with US in moderate and sever hepatic fat deposition (defined as >30% by histology) [8,9].

Both sensitivity and specificity declined to 53.3% to 65% and 77% to 81.2%, respectively, when mild steatosis was included with moderate and severe degrees of steatosis. It is noteworthy that sonographic specificity further deteriorates with confounding factors such as inflammation or fibrosis within the liver parenchyma [8,10,11].

Estimation of hepatic steatosis on conventional US is subjective and challenged by inter- and intraobserver variability. Normal liver shows echogenicity similar to or just higher than normal renal cortex. Fatty infiltration increases the echogenicity of the liver parenchyma. Hepatic steatosis can be graded as mild, moderate, and severe: 1) mild: mild diffuse increase in liver echogenicity and clear definition of the diaphragm and intrahepatic vessel walls; 2) moderate: mild diffuse increase in liver echogenicity and obscuration of the diaphragm and intrahepatic vessel walls; and 3) severe: marked increase in liver echogenicity leading to nonvisualization of diaphragm and intrahepatic vessel walls [12].

Instead of qualitative assessment of liver and kidney parenchyma, quantitative grading can be done to obtain hepatorenal index. Mancini et al and Webb et al have shown an excellent correlation of mild steatosis quantified on hepatorenal index to fat fraction on MR spectroscopy and liver biopsy, with the area under the curve measuring up to 99.2% and 99.6%, respectively. The hepatorenal index is independent of confounding factors including high body mass index, inflammation, or fibrosis [13,14].

**Variant 1: Abnormal liver function tests. Hepatocellular predominance with mild aminotransferase increase. Initial imaging.**
**B. US Abdomen with IV Contrast**

Cocciolillo et al [15] showed hepatic blood flow derangements in the portal vein and liver parenchyma using contrast-enhanced US (CEUS). The percentage of maximal contrast activity, regional blood volume (cubic centimeters) and regional blood flow (cubic centimeters per second) was reduced in NASH and NAFLD compared with controls. CEUS can be added to conventional US and US shear wave elastography; however, there is no evidence in the current literature to support the use of CEUS in this clinical scenario.

**Variant 1: Abnormal liver function tests. Hepatocellular predominance with mild aminotransferase increase. Initial imaging.**
**C. US Duplex Doppler Abdomen**

Duplex Doppler may be added as adjunct to conventional US B-mode images. The normal triphasic flow pattern in right hepatic vein flow may become monophasic following intrahepatic fat deposition or, occasionally, by inflammatory or fibrotic changes [16]. Tarzamni et al [17] found an increase in the arterial resistive index and no change in pulsatility index and portal venous velocity in patients with NAFLD with favorable response to treatment.

**Variant 1: Abnormal liver function tests. Hepatocellular predominance with mild aminotransferase increase. Initial imaging.**
**D. US Shear Wave Elastography Abdomen**

US shear wave elastography is increasingly used to assess liver stiffness in chronic liver parenchymal disease. Various US elastography techniques have evolved in recent years that use different shear wave generation and propagation. These include transient elastography, acoustic radiation force impulse elastography, supersonic shear wave, and real-time tissue elastography.

Controlled attenuation parameter is a novel method for the measurement of hepatic steatosis that uses the same radiofrequency data used for quantification of liver stiffness. Shi at al [18] performed a meta-analysis to look at performance of controlled attenuation parameter in detection of severity of steatosis (>S1, >S2, >S3). The sensitivity and specificity were 78% and 79% for S1, 85% and 79% for S2 and, 83% and 79% for S3 steatosis, respectively. Receiver operating characteristic analysis was 85% for >S1, 88% for >S2, and 87% for >S3. According to the meta-analysis, controlled attenuation parameter has a good sensitivity and specificity for detecting hepatic fat content; however, accuracy is limited.

**Variant 1: Abnormal liver function tests. Hepatocellular predominance with mild aminotransferase increase. Initial imaging.**
**E. CT Abdomen and Pelvis Without IV Contrast**

CT abdomen and pelvis without intravenous (IV) contrast is more specific than US in the diagnosis of moderate hepatic steatosis (≥30%), with a 100% specificity and an 82% sensitivity [19,20]. Hepatic parenchymal attenuation of <40 Hounsfield units (HU) correlates with 30% steatosis on unenhanced CT [21]. Progressive decrease in liver attenuation at 64.4 HU, 59.1 HU, 41.9 HU, and 25.0 HU correlates with increasing degrees of fatty infiltration in the liver parenchyma at 0%, 1% to 25%, 26% to 50%, and >50%, respectively. A liver to spleen attenuation difference of >10 HU and attenuation ratio <1 can diagnose moderate to severe steatosis, which may lead to mildly abnormal liver function tests [20,22].

However, CT is not useful as the first modality of choice for the diagnosis of mildly elevated aminotransferases due to mild fatty infiltration for multiple reasons, including failure to detect early steatosis, lack of accuracy, and reliability [20,23,24].

**Variant 1: Abnormal liver function tests. Hepatocellular predominance with mild aminotransferase increase. Initial imaging.**
**F. CT Abdomen and Pelvis With IV Contrast**
Contrast-enhanced CT of the abdomen and pelvis is not useful as the first-line technique to diagnose hepatic steatosis. Unlike unenhanced CT, HU values calculated following contrast injection are variable because of contrast injection timing, location of injection site, protocol differences, length of scan, and the patient's hemodynamic circulation [20,25,26].

**Variant 1: Abnormal liver function tests. Hepatocellular predominance with mild aminotransferase increase. Initial imaging.**
**G. CT Abdomen and Pelvis Without and With IV Contrast**

There is no relevant literature to support the use of CT abdomen and pelvis without and with IV contrast in this clinical scenario.

**Variant 1: Abnormal liver function tests. Hepatocellular predominance with mild**

**aminotransferase increase. Initial imaging.**
**H. MR Elastography Abdomen**

MR elastography is the most useful modality to estimate liver fibrosis. MR elastography is currently being investigated to diagnose NAFLD without liver fibrosis and therefore is not an initial investigation. Chen et al [27] showed higher liver stiffness in patients with steatosis and lobular inflammation than in those with steatosis and lower stiffness when compared with those with parenchymal fibrosis in fatty liver.

**Variant 1: Abnormal liver function tests. Hepatocellular predominance with mild aminotransferase increase. Initial imaging.**
**I. MRI Abdomen Without IV Contrast With MRCP**

MRI has better performance compared with both US and CT in the diagnosis and grading of steatosis by virtue of excellent soft tissue contrast resolution and advanced multiparametric capabilities. Fatty infiltration of ≥5% in the hepatic parenchyma can be diagnosed with a high sensitivity (76.7%-90.0%) and specificity (87.1%-91%) on unenhanced MR techniques without gadolinium administration. MR spectroscopy shows a sensitivity of 80.0% to 91.0% and a specificity of 80.2% to 87.0% in steatosis detection [9-11].

Chemical shift imaging using T1 gradient echo exploits the differences in the resonance frequencies of water and fat proton signals yielding 2-point Dixon T1 in-phase and opposed-phase with fat and iron depiction. However, T2* decay from hepatic iron can erroneously lead to an underestimation of liver fat content by reducing in-phase signal, particularly at longer time to echo [28-31].

Proton density fat fraction is a quantitative and reproducible method for fat estimation that uses chemical shift while eliminating or reducing the effects of confounding factors, such as T2 decay. Proton density fat fraction is an accurate (area under the receiver operating characteristic curve = 98.9%; 95% confidence interval, 96.8%-100%) and reliable tool for hepatic lipid assessment (grade 1 or higher) across different vendors and magnetic field strengths. Recent investigations suggest that quantitative MR methods may serve as a comparable or even better reference standard for fat quantification to reference standard liver biopsy [32,33].

**Variant 1: Abnormal liver function tests. Hepatocellular predominance with mild aminotransferase increase. Initial imaging.**
**J. MRI Abdomen Without and With IV Contrast With MRCP**

There is no relevant literature to support the use of MRI abdomen without and with IV contrast with MR cholangiopancreatography (MRCP) in this clinical scenario.

**Variant 2: Abnormal liver function tests. Hepatocellular predominance with moderate or severe aminotransferase increase. Initial imaging.**

Breu et al [34], in a large multicenter study, found ischemic hepatitis to be the most common cause for markedly elevated aminotransferase ALT/AST level (5000 IU/L). Ischemic liver injury is a serious condition because it can progress to liver failure and high mortality [35]. Acute viral hepatitis

(hepatitis A and B, hepatitis C), drug-induced liver injury (acetaminophen), and pancreaticobiliary pathologies leading to biliary obstruction and liver injury are other causes of moderate to marked increase in aminotransferases [34].

Chronic liver injury without acute superimposed viral hepatitis does not cause severe derangement of liver function tests. Please note, the ACR Appropriateness Criteria® topic on "Chronic Liver Disease" discusses the recommendation of imaging modalities in diffuse liver fibrosis in detail [36].

**Variant 2: Abnormal liver function tests. Hepatocellular predominance with moderate or severe aminotransferase increase. Initial imaging.**
**A. CT Abdomen and Pelvis Without IV Contrast**

Although intra- and extrahepatic biliary ductal dilatation may be identified on CT abdomen and pelvis without IV contrast, contrast confers added benefit for assessment of ischemic liver injury and possible useful hemodynamic information, such as sequela of portal hypertension or hepatic congestion.

There are advantages to including the pelvis in the CT abdomen and pelvis examination, including detecting pelvic ascites, pelvic collateral vessels in portal hypertension, and possible sources of obstruction (eg, lymphadenopathy).

**Variant 2: Abnormal liver function tests. Hepatocellular predominance with moderate or severe aminotransferase increase. Initial imaging.**
**B. CT abdomen and pelvis without and with IV contrast**

Although the findings of acute hepatitis on CT are not specific for the diagnosis, CT may be useful for evaluating the sequela or complications of hepatitis. CT with IV contrast can also identify ischemic hepatitis.

Acute hepatitis on contrast-enhanced CT demonstrates arterial heterogeneity, periportal hypoattenuation, perihepatic lymphadenopathy (>7 mm), and ascites in decreasing order of prevalence [37]. A thickened gallbladder wall on contrast-enhanced CT (mean 5.2 mm) was an independent predictor of severe hepatitis and prolonged cholestasis [37].

An association of enhanced CT findings with phases of acute hepatitis (prodrome, jaundice, recovery) showed small hepatoduodenal lymphadenopathy, perihepatic fat infiltration, gallbladder wall thickening, contraction, or an undulating inner margin, periportal edema, hepatomegaly, splenomegaly, and pelvic fluid collection in 98.8%, 76.5%, 75.3%, 43.5%, 22.4%, 52.9%, and 56.5% of the patients, respectively [38,39].

Shock liver, leading to ischemic hepatitis, may be secondary to systemic hypoxic or hypotensive causes leading to hypoperfusion of the liver, which may show hypoenhancement of a portion of the liver or entire liver parenchyma. Selective hepatic hypoperfusion due to hepatic arterial of portal venous occlusion could be reversible because of dual blood supply but may result in liver

failure or hepatic infarction [40].

There are advantages to including the pelvis in the CT abdomen and pelvis examination, including detecting pelvic ascites as well as collateral vessels in instances of portal venous hypertension.

**Variant 2: Abnormal liver function tests. Hepatocellular predominance with moderate or severe aminotransferase increase. Initial imaging.**
**C. CT Abdomen and Pelvis Without and With IV Contrast**

CT of the abdomen and pelvis with and without IV contrast is not typically useful for this clinical scenario because there is no benefit from adding unenhanced images.

**Variant 2: Abnormal liver function tests. Hepatocellular predominance with moderate or severe aminotransferase increase. Initial imaging.**
**D. MR Elastography Abdomen**

Currently there is no role for MR elastography to diagnose acute hepatic inflammation from various causes. Superimposed acute inflammation in chronic viral hepatitis does not impact correlation of stiffness with stage of fibrosis [41,42].

**Variant 2: Abnormal liver function tests. Hepatocellular predominance with moderate or severe aminotransferase increase. Initial imaging.**
**E. MRI Abdomen with MRCP**

Although abdominal US is the preferred modality of choice in severely elevated aminotransferase, MRI with IV contrast can be obtained to assess parenchymal inflammation, perfusion, and vascular patency.

Inflamed liver parenchyma shows increased signal intensity on T2-weighted images and decreased signal on T1-weighted images with heterogeneous perfusion, similar to CT. Periportal edema can be appreciated as a hyperintense signal on T2-weighted images. Heterogeneous enhancement of the liver in the arterial phase is seen in acute hepatic inflammation from various causes [43-48].

Perihepatic fluid and gallbladder wall edema can be seen on T2-weighted images in acute hepatitis. Hepatic capsular edema may be present in fulminant hepatitis with resultant heterogeneous enhancement on postgadolinium T1-weighted images. Hepatic infarction is seen as nonenhancing wedge-shaped hepatic parenchyma. Vascular cause for ischemic hepatitis can be identified on postcontrast imaging, including MR angiogram [38,49].

Several investigations have shown impaired uptake of liver-specific agents in hepatic dysfunction. Gadolinium ethoxybenzyl-diethylenetriaminepentaacetic acid is a paramagnetic hepatobiliary MR contrast agent, which (due to its OATP1B1/B3-dependent hepatocyte-specific uptake and paramagnetic properties) is used for evaluation of liver function analysis [50-53].

**Variant 2: Abnormal liver function tests. Hepatocellular predominance with moderate or severe aminotransferase increase. Initial imaging.**

**F. US Abdomen**

Abdominal US is the first-line imaging modality for patients with acute severe hepatitis, toxic hepatic injury (drug or alcoholic induced), or ischemic hepatitis seen in shock liver. US is the first-line imaging modality primarily due to its portability. US is used to assess for various etiologies of jaundice (both obstructive and nonobstructive) and the ACR Appropriateness Criteria® topic on "Jaundice" outlines the systematic approach for initial imaging in these patients [54].

Acute hepatic parenchymal inflammation can be seen sonographically as diffuse hepatic hypoechogenicity and increased thickness of portal veins walls. Conspicuity of portal triads "starry sky" on a background of dark edematous liver parenchyma can be seen in acute hepatitis and several other conditions, such as volume overload. Contracted gallbladder with wall thickening and edema is a marker of hepatic dysfunction [55-59].

**Variant 2: Abnormal liver function tests. Hepatocellular predominance with moderate or severe aminotransferase increase. Initial imaging.**
**G. US Abdomen with IV Contrast**

CEUS is not a first-line imaging modality to assess the hepatic parenchyma in acute severe hepatitis or ischemia. Investigations to use as adjunct to check vascular patency in transplant livers has been tried [60], but there is a lack of relevant literature to support the use of CEUS in this clinical scenario.

**Variant 2: Abnormal liver function tests. Hepatocellular predominance with moderate or severe aminotransferase increase. Initial imaging.**
**H. US Duplex Doppler Abdomen**

Duplex Doppler can be added to routine grayscale US to look for vascular patency in patients with suspected ischemic insult.

**Variant 2: Abnormal liver function tests. Hepatocellular predominance with moderate or severe aminotransferase increase. Initial imaging.**
**I. US Shear Wave Elastography Abdomen**

There is no relevant literature to support the use of US shear wave elastography in toxic or ischemic liver injury.

**Variant 3: Abnormal liver function tests. Cholestatic predominance. Elevated alkaline phosphatase with or without elevated gamma-glutamyl transpeptidase. Initial imaging.**

ALP is produced mainly in the liver and is present in the canalicular membrane of the hepatocyte (the biliary epithelium). ALP is also found in bone and in smaller amounts in the intestines, kidneys, and white blood cells. Levels are physiologically higher in childhood, associated with bone growth, and in pregnancy, due to placental production [61]. Elevation of ALP is nonspecific and can occur in a variety of conditions affecting the liver, including cirrhosis, chronic hepatitis, viral hepatitis, congestive heart failure (hepatic congestion), and ischemic cholangiopathy. Pathologically increased levels of ALP may occur in cholestatic liver disease, such as primary biliary cholangitis, primary sclerosing cholangitis, intrahepatic or extrahepatic bile duct obstruction, and drug-induced cholestasis. Pathologically increased levels of ALP may also occur in bone disease, such as Paget's

disease, bony metastases, or fracture.

Measurements of GGT can indicate whether pathologically elevated ALP is of hepatic or nonhepatic origin. GGT is found in the liver and in the kidneys, intestine, prostate, and pancreas; however, GGT is not found in the bone. Concomitantly elevated GGT can help confirm that an elevated ALP originates from the liver and indicates cholestasis. If the liver is suspected to be the source of elevated ALP, together with a review of the patient's clinical history and medications, imaging of the biliary tree may be necessary to determine the etiology of extrahepatic or intrahepatic cholestasis [62].

Choledocholithiasis is the most common cause of extrahepatic biliary obstruction and elevated ALP of liver origin. Additional etiologies of extrahepatic biliary obstruction include malignant obstruction, biliary strictures, and infections (eg, AIDS cholangiopathy, and liver flukes). Isolated elevated ALP of hepatic origin (without other elevated liver function tests) that persists over time suggests a chronic cholestatic process, such as partial bile duct obstruction, primary biliary cholangitis, primary sclerosing cholangitis, or drug-induced cholestasis. Infiltrative liver diseases such as sarcoidosis, amyloidosis, and hepatic metastases, among others, may also lead to intrahepatic cholestasis. ALP may also be elevated nonspecifically in addition to other elevated liver biochemical tests in all types of liver diseases, including hepatitis, cirrhosis, sepsis, and heart failure.

**Variant 3: Abnormal liver function tests. Cholestatic predominance. Elevated alkaline phosphatase with or without elevated gamma-glutamyl transpeptidase. Initial imaging.**
**A. CT Abdomen and Pelvis With IV Contrast**

Although abdominal US is typically the first-line imaging modality for identifying biliary obstruction, contrast-enhanced CT of the abdomen and pelvis may help define the site of obstruction, potential etiology, and coexistent complications [63]. CT is considered less sensitive than MRI with MRCP for the evaluation of the bile ducts; however, CT may provide useful information regarding the etiology of cholestasis.

There are advantages to including the pelvis in the CT abdomen and pelvis examination, including detecting pelvic ascites, pelvic collateral vessels in portal hypertension, and possible sources of obstruction (eg, lymphadenopathy).

**Variant 3: Abnormal liver function tests. Cholestatic predominance. Elevated alkaline phosphatase with or without elevated gamma-glutamyl transpeptidase. Initial imaging.**
**B. CT Abdomen and Pelvis Without and With IV Contrast**

CT of the abdomen and pelvis with and without IV contrast is not typically performed for this clinical scenario because there is no benefit from adding unenhanced images.

**Variant 3: Abnormal liver function tests. Cholestatic predominance. Elevated alkaline phosphatase with or without elevated gamma-glutamyl transpeptidase. Initial imaging.**
**C. CT Abdomen and Pelvis Without IV Contrast**

Although intra- and extrahepatic biliary ductal dilatation may be identified on CT abdomen and

pelvis without IV contrast, contrast confers added benefit for assessment of ischemic liver injury and possible useful hemodynamic information, such as sequela of portal hypertension or hepatic congestion.

There are advantages to including the pelvis in the CT abdomen and pelvis examination, including detecting pelvic ascites, pelvic collateral vessels in portal hypertension, and possible sources of obstruction (eg, lymphadenopathy).

**Variant 3: Abnormal liver function tests. Cholestatic predominance. Elevated alkaline phosphatase with or without elevated gamma-glutamyl transpeptidase. Initial imaging.**
**D. MR Elastography Abdomen**

MR elastography is currently the most accurate imaging modality for the diagnosis and staging of hepatic fibrosis; however, it has a limited to no role in the initial imaging of suspected cholestasis.

**Variant 3: Abnormal liver function tests. Cholestatic predominance. Elevated alkaline phosphatase with or without elevated gamma-glutamyl transpeptidase. Initial imaging.**
**E. MRI Abdomen Without and With IV Contrast With MRCP**

Abdominal US is typically the first-line imaging modality; however, in the setting of persistently elevated ALP and a negative abdominal sonogram, MRI abdomen without and with IV contrast with MRCP may be useful. Sustained elevation of ALP is significantly correlated with choledocholithiasis on MRCP and may be helpful for triaging patients to endoscopic retrograde cholangiopancreatography (ERCP); however, patients who have common bile duct stones demonstrated on US should proceed directly to ERCP [64,65].

If extra- or intrahepatic biliary ductal dilatation is identified on abdominal US, contrast-enhanced MRI with MRCP is the most useful imaging modality for evaluating the etiology of biliary obstruction. Contrast-enhanced MRI with MRCP facilitates noninvasive evaluation of both intra- and extrahepatic bile ducts, as well as the liver parenchyma [66]. Further, contrast-enhanced MRI with MRCP enables triaging of patients to subsequent interventions, such as stenting with ERCP, brushings by endoscopic US, and image-guided or laparoscopic biopsy, as well as serving as a guide for the subsequent approach with these interventions. MRI performed with diffusion sequences and hepatobiliary contrast agents can be advantageous in lesion detection and characterization, although a decreased uptake of hepatobiliary agents by hepatocytes might decrease diagnostic accuracy, especially in patients with reduced liver function [51].

**Variant 3: Abnormal liver function tests. Cholestatic predominance. Elevated alkaline phosphatase with or without elevated gamma-glutamyl transpeptidase. Initial imaging.**
**F. MRI Abdomen Without IV Contrast With MRCP**

Although less sensitive than contrast-enhanced MRI, a noncontrast MRI (including MRCP) may be useful for identifying biliary obstruction as a source of cholestasis. Contrast administration improves the sensitivity for detection of acute cholangitis, hepatic metastases, and the detection of primary sclerosing cholangitis. Furthermore, excretion of hepatobiliary contrast and opacification of the biliary ducts and gallbladder provide additional information regarding the site and etiology

of obstruction, as well as liver function [67-69].

**Variant 3: Abnormal liver function tests. Cholestatic predominance. Elevated alkaline phosphatase with or without elevated gamma-glutamyl transpeptidase. Initial imaging. G. US Abdomen**

Patients with elevated ALP suspected to be liver in origin and no alternative etiology should undergo transabdominal US to assess for dilated intra- or extrahepatic ducts and gallstones as the possible cause. Gallstone disease is prevalent with approximately 10% of adults having cholelithiasis and approximately 500,000 cholecystectomy operations performed annually [70]. Approximately 18% of adults undergoing cholecystectomy have choledocholithiasis [71,72]. Although abdominal US has a low sensitivity for detection of choledocholithiasis, in part related to frequent overlying bowel gas, it has high specificity [65]. When biliary obstruction is identified on abdominal US, frequently dynamic contrast-enhanced CT, MRI, or CEUS is required for further evaluation of the cause and possibly procedure planning. The absence of gallstones or choledocholithiasis suggests a nongallstone etiology and a normal caliber of the extrahepatic bile duct suggests intrahepatic cholestasis [71-73].

**Variant 3: Abnormal liver function tests. Cholestatic predominance. Elevated alkaline phosphatase with or without elevated gamma-glutamyl transpeptidase. Initial imaging. H. US Abdomen with IV Contrast**

For initial imaging, there is currently no role for CEUS in the evaluation of cholestasis. CEUS has been assessed for the evaluation of liver fibrosis, which may nonspecifically elevate ALP, and is used in the characterization of potentially obstructing hepatic lesions. Similar to CT and MRI perfusion techniques, CEUS uses contrast media transit characteristics to make deductions about liver hemodynamics that relate to the presence and severity of liver fibrosis and for the characterization of hepatic lesions.

**Variant 3: Abnormal liver function tests. Cholestatic predominance. Elevated alkaline phosphatase with or without elevated gamma-glutamyl transpeptidase. Initial imaging. I. US Duplex Doppler Abdomen**

There is debate regarding the diagnostic value of adding Doppler US to the US abdomen examination for initial imaging. Doppler US can demonstrate hemodynamic alterations related to infection (such as elevated velocity in the main hepatic artery in acute cholecystitis) or indicative of portal hypertension as seen in fibrosis or infiltrative liver diseases. The diagnostic value of Doppler US of the portal vein for the evaluation of liver function is still controversial [74].

**Variant 3: Abnormal liver function tests. Cholestatic predominance. Elevated alkaline phosphatase with or without elevated gamma-glutamyl transpeptidase. Initial imaging. J. US Shear Wave Elastography Abdomen**

There is no relevant literature to support the use of US shear wave elastography in the evaluation of cholestasis. US shear wave elastography is used to assess for evaluation of liver fibrosis, which may nonspecifically elevate ALP; however, it has a limited to no role in the initial imaging of suspected cholestasis.

**Variant 4: Abnormal liver functions tests. Hyperbilirubinemia. Acute or subacute cholestasis.**

**Conjugated or unconjugated. Initial imaging.**

Hyperbilirubinemia is defined by a serum bilirubin >2.5 to 3 mg/dL. Metabolism of red blood cells results in the breakdown of heme rings, forming bilirubin. Metabolism of bilirubin can be divided into the prehepatic, intrahepatic, and posthepatic phases.

- *Prehepatic*: Excessive bilirubin reaching the liver may overwhelm the conjugation process, thereby leading to a predominance of unconjugated hyperbilirubinemia. This can be seen from hemolysis or absorption of a large hematoma and related to increased heme production in hemolytic anemias (such as sickle cell disease, thalassemia, hereditary spherocytosis, glucose-6-phosphate dehydrogenase deficiency) [75].

- *Intrahepatic*: A predominance of unconjugated hyperbilirubinemia results from errors in enzyme metabolism in the hepatocytes. Gilbert syndrome, affecting 5% of the American population, is a benign hereditary disorder that reduces the enzyme glucuronosyltransferase's activity, leading to a transient increase in unconjugated bilirubin levels that does not require further management [76]. An abnormality in the excretion of bile causes increased levels of conjugated bilirubin. Hepatic inflammation can disrupt the transport of conjugated bilirubin in acute hepatitis (hepatitis, A, B, C, D, E, Epstein-Barr virus infection), alcohol-induced liver disease, and autoimmune hepatitis. Primary biliary cholangitis, primary sclerosing cholangitis, and medication-induced liver injury can also result in cholestasis with elevated conjugated bilirubin. Common drugs can result in abnormal liver function tests with hyperbilirubinemia, including acetaminophen, penicillin, oral contraceptives, estrogenic or anabolic steroids, and chlorpromazine (Thorazine) [77,78].

- *Posthepatic*: Conjugated hyperbilirubinemia can occur because of obstruction of the biliary tract from intrinsic or extrinsic obstruction. Obstructive biliopathy with cholestasis can result from cholelithiasis, acute calculus cholecystitis, choledocholithiasis, and cholangitis, increasing direct bilirubin. Cholangiocarcinoma or gallbladder cancer can also present with biliary obstruction. These are all intrinsic causes. Extrinsic causes external to the biliary system include pancreatitis or pancreatic tumor causing a biliary obstruction or a diffuse malignancy, such as lymphoma. Isolated unconjugated (indirect) hyperbilirubinemia is seen in hemolysis. Please refer to the ACR Appropriateness Criteria® topics on "Chronic Liver Disease" [36] and "Jaundice" [54]. Conjugated or direct bilirubin is increased conditions affecting liver parenchyma (cirrhosis) or the biliary system. Conditions resulting in increased ALP and conjugated bilirubin due to obstructive biliopathy are discussed above.

**Variant 4: Abnormal liver functions tests. Hyperbilirubinemia. Acute or subacute cholestasis. Conjugated or unconjugated. Initial imaging.**
**A. US Abdomen**

US is the most useful imaging modality to evaluate conjugated hyperbilirubinemia due to liver parenchymal cause (alcoholic or viral hepatitis and cirrhosis) or biliary obstruction. US shows a positive predictive value of 98% and a sensitivity in the range of 65% to 95% for the diagnosis of liver parenchymal disease. Biliary obstruction can be demonstrated on US with a wide range of sensitivity (32%-100%) and specificity (71%-97%); however, the cause for distal obstruction may be obscured by overlying bowel gas [54].

**Variant 4: Abnormal liver functions tests. Hyperbilirubinemia. Acute or subacute cholestasis. Conjugated or unconjugated. Initial imaging.**

**B. US Abdomen with IV Contrast**

There is no relevant literature to support the use of CEUS in this clinical scenario.

**Variant 4: Abnormal liver functions tests. Hyperbilirubinemia. Acute or subacute cholestasis. Conjugated or unconjugated. Initial imaging.**
**C. US Duplex Doppler Abdomen**

US duplex Doppler abdomen is not useful for this clinical scenario.

**Variant 4: Abnormal liver functions tests. Hyperbilirubinemia. Acute or subacute cholestasis. Conjugated or unconjugated. Initial imaging.**
**D. US Shear Wave Elastography Abdomen**

US shear wave elastography is not useful as the first-line imaging modality to assess hyperbilirubinemia. Liver fibrosis can be demonstrated using elastography techniques with improved accuracy in higher stages of fibrosis (area under the curve, 0.88 and 0.91 for S2 and S4 fibrosis, respectively) [18]. There is no evidence to support use of US shear wave elastography in biliary obstruction.

**Variant 4: Abnormal liver functions tests. Hyperbilirubinemia. Acute or subacute cholestasis. Conjugated or unconjugated. Initial imaging.**
**E. CT Abdomen and Pelvis With IV Contrast**

CT abdomen with IV contrast can be used to look for morphologic changes of chronic liver parenchymal disease and its complications. CT can help identify the site of obstruction and the potential etiologies. MRI with MRCP is superior to evaluate the biliary system. Malignant biliary strictures can be identified with a high sensitivity (95%), specificity (93.35%), and accuracy (88.5%) on CT [79].

CT abdomen with IV contrast is very accurate for diagnosis and staging of pancreaticobiliary malignancies, which can present with hyperbilirubinemia. Tumor resectability and surgical planning for both pancreatic and biliary cancers can be done using CT. There are advantages to including the pelvis in the CT abdomen and pelvis examination, including detecting lymphadenopathy and pelvic ascites.

**Variant 4: Abnormal liver functions tests. Hyperbilirubinemia. Acute or subacute cholestasis. Conjugated or unconjugated. Initial imaging.**
**F. CT Abdomen and Pelvis Without and With IV Contrast**

CT of the abdomen and pelvis with and without IV contrast is not typically useful for this clinical scenario because there is no benefit from adding unenhanced images.

**Variant 4: Abnormal liver functions tests. Hyperbilirubinemia. Acute or subacute cholestasis. Conjugated or unconjugated. Initial imaging.**
**G. CT Abdomen and Pelvis Without IV Contrast**

Unenhanced CT has limited utility in assessing biliary obstruction (including etiologies) and liver fibrosis.

**Variant 4: Abnormal liver functions tests. Hyperbilirubinemia. Acute or subacute cholestasis. Conjugated or unconjugated. Initial imaging.**
**H. MRI Abdomen with MRCP**

As discussed in Variant 3 above, MRI with MRCP is the most useful for evaluating the etiology of biliary obstruction. Contrast is helpful to look for cholangitis and assess malignant etiologies of biliary obstruction.

MRI has comparable and slightly better accuracy than CT in the diagnosis, local staging, and surgical planning of pancreaticobiliary malignancies that may present with malignant biliary obstruction. MRI and CT have demonstrated accuracies of 90.7% and 85.1%, respectively, for the detection of bilateral secondary biliary confluence obstruction. See also the ACR Appropriateness Criteria® topics on "Jaundice" [54] and "Staging of Pancreatic Ductal Adenocarcinoma" [80].

**Variant 4: Abnormal liver functions tests. Hyperbilirubinemia. Acute or subacute cholestasis. Conjugated or unconjugated. Initial imaging.**
**I. MR Elastography Abdomen**

MR elastography is currently the most useful imaging modality for the diagnosis and staging of hepatic fibrosis; however, it has a limited to no role in the initial imaging of acute or subacute cholestasis [81].

**Summary of Recommendations**

- **Variant 1**: US abdomen and US duplex Doppler abdomen are usually appropriate as the initial imaging for patients with abnormal liver functions tests with hepatocellular predominance with mild aminotransferase increase. These procedures are complementary (ie, more than one procedure is ordered as a set or simultaneously where each procedure provides unique clinical information to effectively manage the patient's care).

- **Variant 2**: US abdomen, US duplex Doppler abdomen, and CT abdomen and pelvis with IV contrast are usually appropriate as the initial imaging for patients with abnormal liver functions tests with hepatocellular predominance with moderate or severe aminotransferase increase. These procedures are complementary (ie, more than one procedure is ordered as a set or simultaneously where each procedure provides unique clinical information to effectively manage the patient's care).

- **Variant 3**: US abdomen, MRI abdomen without and with IV contrast, and CT abdomen and pelvis with IV contrast are usually appropriate as the initial imaging of patients with abnormal liver function tests that show cholestatic predominance and elevated ALP with or without elevated gamma-glutamyl transpeptidase. These procedures are complementary (ie, more than one procedure is ordered as a set or simultaneously where each procedure provides unique clinical information to effectively manage the patient's care).

- **Variant 4**: US abdomen or MRI abdomen without and with IV contrast with MRCP or MRI abdomen without IV contrast with MRCP or CT abdomen and pelvis with IV contrast is usually appropriate as the initial imaging of patients with abnormal liver function tests with

hyperbilirubinemia or acute or subacute cholestasis and can be conjugated or unconjugated. These procedures are equivalent alternatives (ie, only one procedure will be ordered to provide the clinical information to effectively manage the patient's care).

**Supporting Documents**

The evidence table, literature search, and appendix for this topic are available at https://acsearch.acr.org/list. The appendix includes the strength of evidence assessment and the final rating round tabulations for each recommendation.

For additional information on the Appropriateness Criteria methodology and other supporting documents, please go to the ACR website at https://www.acr.org/Clinical-Resources/Clinical-Tools-and-Reference/Appropriateness-Criteria.

**Appropriateness Category Names and Definitions**

| Appropriateness Category Name | Appropriateness Rating | Appropriateness Category Definition |
|---|---|---|
| Usually Appropriate | 7, 8, or 9 | The imaging procedure or treatment is indicated in the specified clinical scenarios at a favorable risk-benefit ratio for patients. |
| May Be Appropriate | 4, 5, or 6 | The imaging procedure or treatment may be indicated in the specified clinical scenarios as an alternative to imaging procedures or treatments with a more favorable risk-benefit ratio, or the risk-benefit ratio for patients is equivocal. |
| May Be Appropriate (Disagreement) | 5 | The individual ratings are too dispersed from the panel median. The different label provides transparency regarding the panel's recommendation. "May be appropriate" is the rating category and a rating of 5 is assigned. |
| Usually Not Appropriate | 1, 2, or 3 | The imaging procedure or treatment is unlikely to be indicated in the specified clinical scenarios, or the risk-benefit ratio for patients is likely to be unfavorable. |

**Relative Radiation Level Information**

Potential adverse health effects associated with radiation exposure are an important factor to consider when selecting the appropriate imaging procedure. Because there is a wide range of radiation exposures associated with different diagnostic procedures, a relative radiation level (RRL) indication has been included for each imaging examination. The RRLs are based on effective dose, which is a radiation dose quantity that is used to estimate population total radiation risk associated with an imaging procedure. Patients in the pediatric age group are at inherently higher risk from exposure, because of both organ sensitivity and longer life expectancy (relevant to the long latency that appears to accompany radiation exposure). For these reasons, the RRL dose estimate ranges for pediatric examinations are lower as compared with those specified for adults (see Table below). Additional information regarding radiation dose assessment for imaging examinations can be found in the ACR Appropriateness Criteria® Radiation Dose Assessment Introduction document [82].

| **Relative Radiation Level Designations** | | |
|---|---|---|
| **Relative Radiation Level*** | **Adult Effective Dose Estimate Range** | **Pediatric Effective Dose Estimate Range** |
| O | 0 mSv | 0 mSv |
| ☢ | <0.1 mSv | <0.03 mSv |
| ☢☢ | 0.1-1 mSv | 0.03-0.3 mSv |
| ☢☢☢ | 1-10 mSv | 0.3-3 mSv |
| ☢☢☢☢ | 10-30 mSv | 3-10 mSv |
| ☢☢☢☢☢ | 30-100 mSv | 10-30 mSv |
| *RRL assignments for some of the examinations cannot be made, because the actual patient doses in these procedures vary as a function of a number of factors (eg, region of the body exposed to ionizing radiation, the imaging guidance that is used). The RRLs for these examinations are designated as "Varies." | | |

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**Disclaimer**

The ACR Committee on Appropriateness Criteria and its expert panels have developed criteria for determining appropriate imaging examinations for diagnosis and treatment of specified medical condition(s). These criteria are intended to guide radiologists, radiation oncologists and referring physicians in making decisions regarding radiologic imaging and treatment. Generally, the complexity and severity of a patient's clinical condition should dictate the selection of appropriate

imaging procedures or treatments. Only those examinations generally used for evaluation of the patient's condition are ranked. Other imaging studies necessary to evaluate other co-existent diseases or other medical consequences of this condition are not considered in this document. The availability of equipment or personnel may influence the selection of appropriate imaging procedures or treatments. Imaging techniques classified as investigational by the FDA have not been considered in developing these criteria; however, study of new equipment and applications should be encouraged. The ultimate decision regarding the appropriateness of any specific radiologic examination or treatment must be made by the referring physician and radiologist in light of all the circumstances presented in an individual examination