



# Does measurement of the hepatic artery velocity improve the sonographic diagnosis of cholangitis?

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## Abstract

**Objective** To determine the frequency of elevated peak systolic proper hepatic artery velocity (HAV) in patients with acute cholangitis and to determine the diagnostic performance of this metric relative to existing criteria.

**Methods** Between 9/2016 and 11/2017, 107 patients clinically suspected to have cholangitis were referred for an abdominal ultrasound. Of these, 56 patients had HAV measurements and were included in the final analysis. Clinical and imaging features, including HAV, HAV resistive index (RI), portal vein velocity (PVV), biliary dilation, and presence of an obstructive etiology were extracted. The diagnostic performance of HAV was compared to the existing available clinical criteria (Charcot's triad and 2018 Tokyo Guidelines). Elevated HAV was defined as HAV > 100 cm/s. Presence of cholangitis was determined by the discharge summary following medical workup and admission or observation.

**Results** 32% had cholangitis while 68% did not. Average HAV for patients with cholangitis was  $152 \pm 54$  cm/s versus  $91 \pm 44$  cm/s for those without ( $p < 0.0001$ ;  $t$  test). The HAV was elevated in 83% of patients with cholangitis. When considered in isolation, an elevated HAV had a high negative predictive value (90%), was more accurate (77%; 95% confidence interval 64–87%) than Charcot's triad (73%; 60–83%), and had similar accuracy compared to 2018 Tokyo Guidelines (79%; 66–88%). Substitution of conventional imaging criteria with elevated HAV in the 2018 Tokyo Guidelines yielded the highest overall accuracy of 84% (72–92%).

**Conclusion** HAV is elevated in the majority of patients with cholangitis. Substitution of an elevated HAV for conventional sonographic criteria is more accurate than existing clinical criteria in identifying patients with cholangitis.

**Keywords** Cholangitis · Hepatic artery velocity · Biliary duct dilation · Ultrasound · Liver · Charcot triad · Tokyo guidelines · Hepatic arterial buffer response

## Introduction

Acute cholangitis is a serious bacterial infection of the biliary tree, which results from a combination of obstruction of bile flow resulting in increased intra-biliary pressure and retrograde migration of the enteric bacteria from the sphincter of Oddi [1–3]. Because the infected bile is under pressure,

this condition rapidly leads to the egress of typically polymicrobial gram-negative rods into the hepatic sinusoids and subsequent sepsis physiology [4, 5]. If untreated, complications can include abscess, portal vein thrombosis, peritonitis, and even death [6, 7]. Thus, prompt diagnosis and treatment of acute cholangitis is critical for this highly morbid and potentially fatal condition.

The underlying cause of obstruction in cholangitis is most commonly due to choledocholithiasis, though other etiologies can include strictures (both benign and malignant) and obstructing neoplasm [8]. Although definitive diagnosis of acute cholangitis requires aspiration of purulent bile [9], e.g., during endoscopic retrograde cholangiopancreatography (ERCP) or percutaneous transhepatic cholangiography (PTC), not all patients with severe cholangitis may have pus in the biliary system [10]. Additionally, cholangitis is more commonly diagnosed clinically given the invasive nature of biliary

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catheterization required to retrieve bile; these procedures are typically reserved for biliary decompression in the critically ill rather than to establish the diagnosis [11, 12]. Blood cultures are only positive in a minority of patients (20–30%), highlighting that this is a diagnosis established clinically [13].

There are two clinical methods of diagnosing acute cholangitis [14]. The first is Charcot's triad, originally described in 1877, which requires the presence of fever, right upper quadrant pain, and jaundice. This triad is still used today and offers high specificity (93%), though at the cost of low sensitivity (36%) [15]. The only other clinical criteria in existence is the 2018 Tokyo Guidelines which requires three clinical features: evidence of an inflammatory response (fever, elevated C-reactive protein, or abnormal white blood cell count), evidence of cholestasis (jaundice, elevated total bilirubin, or elevated liver tests), and imaging evidence of obstruction (bile duct dilation, stricture, or stent) [16].

Of the imaging modalities available, the 2018 Tokyo Guidelines recommend ultrasound as the first line of study given its availability and cost effectiveness [16]. However, one of the three criteria, bile duct dilation, is a subjective assessment with no universally agreed upon cutoff for what constitutes a normal bile duct caliber. Moreover, bile duct caliber may be enlarged in the absence of pathology in elderly patients and in patients following cholecystectomy [17, 18]. To complicate matters, the common bile duct diameter may not dilate in the setting of acute, intermittent, or partial obstruction.

On the other hand, the hepatic artery velocity (HAV) is an objective sonographic finding that can be accurately measured due to recent advances in resolution and color Doppler sensitivity. Hepatic artery flow is increased in animal studies when portal venous inflow is decreased, which is thought to reflect a compensatory response known as the hepatic arterial buffer response [19–21]. More recently, we observed that the HAV is elevated in the setting of a structural hepatobiliary abnormality or obstruction, including cholangitis and cholecystitis [22, 23]. We hypothesize that HAV elevates in these conditions through a combination of the hepatic arterial buffer response compensating for increased vascular resistance to portal venous inflow as well as the inflammation of the biliary tree which is primarily supplied by the hepatic artery [24]. The purpose of our study was to determine how frequently HAV is elevated in patients with acute cholangitis and to determine the diagnostic performance of this metric compared to existing criteria in diagnosis of acute cholangitis.

## Materials and methods

### Patients

This retrospective study was approved by our institutional review board (IRB) and was compliant with the Health

Insurance Portability and Accountability Act (HIPAA). The IRB waived the need for informed consent due to the retrospective nature of the study. After querying the electronic database at our hospital, we evaluated all patients without a history of orthotopic liver transplant or cirrhosis who underwent abdominal ultrasound with HAV measurements from 9/2016 to 11/2017 with an indication specifically to evaluate for cholangitis. As only a minority of patients underwent percutaneous transhepatic cholangiography (PTC) or endoscopic retrograde cholangiopancreatography (ERCP), the presence of acute cholangitis was determined by the clinician's assessment in the discharge summary following clinical workup and a period of observation or admission. This assessment included a review of emergency department notes, inpatient notes, procedures, biochemical tests, microbiology tests, and imaging data.

### Definitions and criteria

Clinical data, including patient symptoms, physical exam findings, and laboratory values, were extracted from the electronic medical record. Charcot's triad was defined as the presence of fever, right upper quadrant pain, and jaundice. The 2018 Tokyo Guidelines diagnostic criteria were defined as the presence of systemic inflammation (either by laboratory data or fever/chills), cholestasis (either laboratory data or jaundice), and a positive imaging study (either biliary dilation or identification of an obstructive etiology) (16). An elevated proper hepatic artery velocity was defined as HAV > 100 cm per second (cm/s) after angle correction. Extrahepatic duct dilation was defined as a common bile duct diameter measuring > 7 mm. We used the original ultrasound report impression to define the intrahepatic biliary duct dilation and to preserve the subjective nature of interpretation, as there is currently no commonly accepted numeric threshold. Table 1 summarizes the diagnostic criteria, including specific numerical thresholds for fever and laboratory values.

### Image acquisition and analysis

A sonographer certified by the American Registry for Diagnostic Medical Sonography performed each ultrasound examination which was then immediately reviewed by a board-certified radiologist with abdominal imaging expertise. Grayscale and color Doppler views of the liver, gallbladder and biliary tree, proper hepatic artery, portal vein, and hepatic veins were obtained using 2.5–5.5 MHz curved array or vector transducers using either GE Logiq E9 (GE Healthcare, Waukesha, WI) or ACUSON S2000 (Siemens Medical Solutions, Mountain View, CA) ultrasound machines. Spectral Doppler evaluation of the extrahepatic proper HAV was most commonly evaluated via the right

**Table 1** Summary of clinical criteria for the diagnosis of cholangitis

	Criteria	Threshold
Charcot's triad	<ul style="list-style-type: none"> <li>• Fever</li> <li>• Right upper quadrant pain</li> <li>• Jaundice</li> </ul>	<ul style="list-style-type: none"> <li>• Temperature (T) &gt; 38 degrees Celsius (C)</li> <li>• Documentation in EMR</li> <li>• Documentation in EMR</li> </ul>
2018 Tokyo Guidelines	Evidence of inflammatory response <ul style="list-style-type: none"> <li>• Fever OR</li> <li>• WBC abnormality</li> </ul> Evidence of cholestasis <ul style="list-style-type: none"> <li>• Jaundice OR</li> <li>• Abnormal liver tests &gt; 1.5 upper limits of normal</li> </ul> Imaging <ul style="list-style-type: none"> <li>• Biliary duct dilation OR</li> <li>• Etiology of obstruction (stone, stent, stricture)</li> </ul>	<ul style="list-style-type: none"> <li>• T &gt; 38 C OR</li> <li>• WBC &lt; 4 or &gt; 10 (<math>\times 10^3</math> cells/mL)</li> <li>• Documentation in EMR or TBili &gt; 2 (mg/dl) OR</li> <li>• AP &gt; 195 U/l, AST &gt; 60 U/l, ALT &gt; 90 U/l</li> <li>• Documentation in original ultrasound report</li> </ul>
Elevated HAV	<ul style="list-style-type: none"> <li>• HAV &gt; 2 standard deviations above mean</li> </ul>	<ul style="list-style-type: none"> <li>• HAV &gt; 100 cm/s</li> </ul>

TBili total bilirubin, AP alkaline phosphatase, ALT alanine transaminase, AST aspartate transaminase

lateral intercostal approach at the porta hepatis. The HAV was measured in cm/s with angle correction, using a Doppler angle of < 60 degrees.

The following features were extracted from the ultrasound report in a blinded fashion: peak systolic HAV, HAV resistive index (RI), portal vein velocity (PVV), presence of biliary duct dilation, and presence of an obstructing etiology (specifically, stent, stricture, or stone as specified in the 2018 Tokyo Guidelines). The original ultrasound report was reviewed without modification of the interpretation to preserve the impact of this imaging data.

## Data and statistical analysis

Continuous variables were reported as mean  $\pm$  standard deviation. Categorical and continuous variables were compared using the Fisher's exact test and Student *t* test, respectively. Two-sided  $p < 0.05$  was used to determine whether differences were significant. Statistical analysis was performed using GraphPad Prism Windows Version 6.07 (GraphPad Software, La Jolla, CA).

## Results

A total of 107 patients underwent abdominal ultrasound for clinically suspected cholangitis during the study period. 51 patients were excluded because they did not have HAV measurements or a complete clinical workup (e.g., patient left against medical advice, deceased prior to further diagnostic testing, or transferred to another hospital). A total of 56 patients were included in the final analysis. 18 (32%) patients had cholangitis while 38 (68%) did not. There was no statistically significant difference in

patient age. However, patients with cholangitis tended to be male, had a history of gastrointestinal or genitourinary malignancy, and tended to have a higher total bilirubin at presentation (Table 2). There were no statistically significant differences in other baseline laboratory values, including white blood cell count, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, and proportion of patients with hepatic metastases if they had a history of a malignancy.

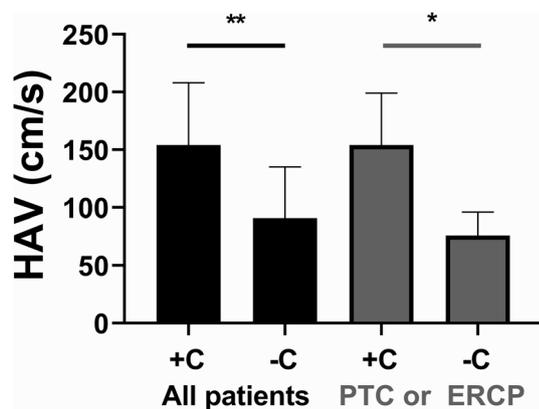
The peak systolic HAV in patients with cholangitis was statistically significantly higher than those without cholangitis ( $152 \pm 54$  cm/s vs.  $91 \pm 44$  cm/s;  $p < 0.0001$ ; Fig. 1). In a subgroup analysis of patients with diagnosis confirmed with ERCP or PTC, HAV was statistically significantly higher in patients with cholangitis ( $154 \pm 45$  cm/s) than those without ( $76 \pm 20$ ;  $p = 0.02$ ; Fig. 1). There were no statistically significant differences in HAV resistive indices (cholangitis  $0.66 \pm 0.12$  vs. without cholangitis  $0.71 \pm 0.08$ ;  $p = 0.11$ ) and portal vein velocities ( $29 \pm 10$  cm/s vs.  $35 \pm 22$  cm/s;  $p = 0.16$ ). The threshold of 100 cm/s was used for an elevated HAV because this represents approximately 2 standard deviations above the mean [22]. Using this threshold, the presence of elevated HAV was statistically correlated with cholangitis ( $p = 0.0001$ ). An example of a patient with an elevated HAV in the setting of cholangitis is shown in Fig. 2.

There was no statistically significant difference between the average caliber of the common bile ducts in patients with cholangitis ( $8.6 \pm 3.4$  mm) and those without ( $7.0 \pm 3.7$ ;  $p = 0.12$ ). However, the presence of biliary duct dilation, stricture, stone, or stent was also statistically correlated with cholangitis ( $p = 0.003$ ). Among patients without cholangitis, 16/38 (42%) patients had intrahepatic biliary duct dilation reported, but only 4 of these patients had an elevated HAV. Additionally, 14/38 (21%) of these patients without

**Table 2** Patient baseline demographics and laboratory values

	All patients	No cholangitis	Cholangitis	<i>p</i> value
Number of patients	56	38	18	
Age	65 ± 16	63 ± 15	68 ± 16	0.259
Male:female	29:27 (1.1:1)	15:23 (0.65:1)	14:4 (3.5:1)	0.01*
History of malignancy	28 (50%)	14 (37%)	14 (78%)	0.009*
History of hepatic metastases	19 (34%)	12 (32%)	7 (39%)	0.76
ERCP or PTC	12 (21%)	3 (8%)	9 (50%)	0.0008*
In-house mortality or transition to comfort care	7 (13%)	3 (8%)	4 (22%)	0.19
White blood cell count (× 10 <sup>3</sup> cells/ml)	13 ± 8	13 ± 8	13 ± 8	1
Aspartate aminotransferase (U/l)	297 ± 609	300 ± 709	290 ± 323	0.95
Alanine aminotransferase (U/l)	244 ± 370	233 ± 402	266 ± 303	0.76
Alkaline phosphatase (U/l)	428 ± 546	359 ± 599	574 ± 389	0.17
Total bilirubin (mg/dl)	3.2 ± 5.0	1.8 ± 2.4	6.1 ± 7.5	0.002*
Alternative diagnoses		Sepsis (non-hepatobiliary): 13 (34%) Nonspecific pain: 7 (18%) Biliary colic, cholecystitis, or chole- docholithiasis: 6 (16%) Disease progression with hepatic metastases: 5 (13%) Hepatitis: 4 (11%) Other: 3 (8%)		

\*Denotes statistical significance ( $p < 0.05$ )



**Fig. 1** Graph of HAV in patients with cholangitis (+C) versus no cholangitis (-C) for all patients in the cohort (left) and a subgroup analysis inclusive of only patients who underwent PTC or ERCP (right). \*\* $p = 0.0001$ ; \* $p = 0.02$

cholangitis had a common bile duct measuring > 7 mm, but only 4 of these patients had an elevated HAV.

Of the individual clinical criteria used to diagnose cholangitis, the presence of fever or abnormal white blood cell count ( $p = 0.045$ ) and the presence of jaundice or abnormal liver tests ( $p = 0.005$ ) were statistically correlated with cholangitis (Table 3). There was no statistically significant difference in the presence of right upper quadrant pain ( $p = 0.57$ ).

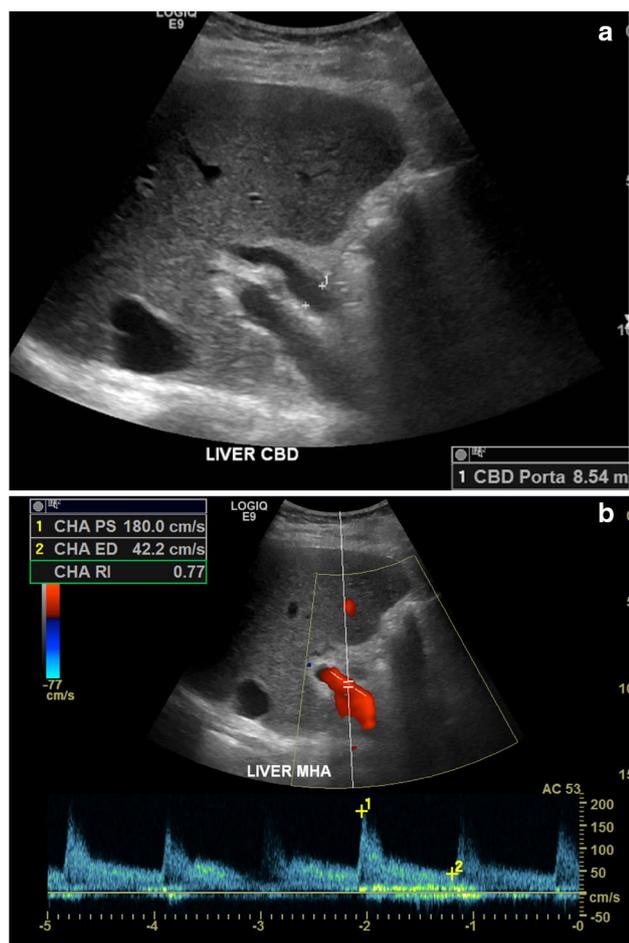
Diagnostic performance of Charcot's triad, 2018 Tokyo Guidelines, conventional imaging criteria alone, elevated

HAV alone, and modified 2018 Tokyo Guidelines are summarized in Table 4. Charcot's triad had the highest specificity (95%) but the lowest sensitivity (28%). When considered in isolation, an elevated HAV had similar accuracy (77%; 95% confidence interval 64–87%) to Charcot's triad (73%; 60–83%) and 2018 Tokyo Guidelines (79%; 66–88%). Additionally, substitution of conventional imaging criteria with elevated HAV in the 2018 Tokyo Guidelines yielded the highest overall accuracy of 84% (72–92%).

## Discussion

Our study showed that the HAV is elevated in the majority of patients with acute cholangitis and substitution of conventional imaging criteria with an elevated HAV yielded the highest overall accuracy (Modified Tokyo Criteria). The greatest advantage of HAV as a sonographic criterion is that it is an objective imaging finding and can help distinguish among patients with pre-existing biliary duct dilation, thereby decreasing false positive cases. Moreover, the high negative predictive value of HAV (90%) for acute cholangitis may help clinicians consider alternative causes of sepsis during the initial workup.

To our knowledge, this is the first study to identify an alternative imaging criterion to biliary duct dilation in the diagnosis of acute bacterial cholangitis. This is important because assessment of bile duct dilation is potentially



**Fig. 2** 58-year-old woman with acute cholangitis. Patient status was post-remote cholecystectomy and presented with sepsis physiology and elevated liver tests. A right upper quadrant ultrasound showed that the distal common bile duct measured up to 8.5 mm (a), which in some instances may be considered borderline in the size following cholecystectomy. However, patient's HAV was elevated to 180 cm/s (b). Patient was treated with intravenous antibiotics and subsequently underwent an ERCP which showed an obstructing common bile duct stone as etiology of cholangitis

subjective. Although the most commonly accepted “normal” size of the common bile duct is < 5–7 mm, it is unclear whether and to what degree advancing age or cholecystectomy state may affect the common bile duct diameter [25–28]. Indeed, what is considered normal in the literature is quite variable [25, 29, 30], with one study showing that a normal duct may be as large as 8.5 mm and others showing that the bile duct may be as large as 10 mm in asymptomatic patients following cholecystectomy [17, 18, 31]. Thus one of the three main criteria of the Tokyo Guidelines, “biliary dilatation or evidence of an etiology on imaging,” is somewhat nebulous. Indeed, in one large international multi-institutional study testing the 2013 Tokyo Criteria, the definition of “biliary dilatation” was not clearly defined [31].

Other sonographic findings that have been described in acute cholangitis but not specified in the 2018 Tokyo Guidelines include bile duct wall thickening and debris within the biliary tree [32]. However, we were unable to find any recent studies in the literature to evaluate the diagnostic performance of these criteria in acute cholangitis. Moreover, in our cohort, these findings, while are highly suggestive of acute cholangitis, were rarely reported. It is unclear how sensitive or specific bile duct thickening or visible debris is in the diagnosis of acute cholangitis, but future studies may be warranted to determine the clinical utility of these additional sonographic findings.

We hypothesize that the hepatic artery velocity is elevated in acute cholangitis due to several factors. First, the inflammation and increased biliary ductal pressures associated with acute cholangitis likely leads to increased pressures and portal venous resistance in the hepatic sinusoids. Second, in the setting of inflammation, the normally quiescent stellate cells located in the Space of Disse activate, contract, and proliferate, further adding to increased resistance in the hepatic sinusoids. Because portal flow is passive, increased pressure and resistance in the hepatic sinusoids causes an overall decrease in portal venous flow. This in turn, likely induces the hepatic arterial buffer response to increase hepatic arterial inflow to compensate for diminished portal venous inflow [20]. Third, cholangitis is an acute bacterial infection which leads to an acute inflammatory response [5].

**Table 3** Individual criteria correlated with the presence of acute cholangitis

	No cholangitis	Cholangitis	<i>p</i> value
Fever or WBC < 4 or > 10 (Tokyo A criteria for systemic inflammation)	30 (79%)	18 (100%)	0.045*
Jaundice or total bilirubin > 2 OR abnormal liver tests (Tokyo B criteria for cholestasis)	25 (66%)	18 (100%)	0.005*
Biliary dilation or evidence of etiology (stricture, stone, stent) (Tokyo C criteria for imaging)	17 (45%)	16 (89%)	0.003*
Right upper quadrant pain	19 (50%)	7 (39%)	0.57
Elevated HAV	10 (26%)	15 (83%)	0.0001*
Average common bile duct diameter	7.0 ± 3.7 mm	8.6 ± 3.4 mm	0.13

\*Denotes statistical significance ( $p < 0.05$ )

**Table 4** Diagnostic performance of clinical criteria used to diagnose cholangitis with 95% confidence intervals

	Charcot's triad	HAV alone	Tokyo criteria	Modified Tokyo criteria
Sensitivity	28% (10–53%)	83% (59–96%)	89% (65–99%)	83% (56–96%)
Specificity	95% (82–99%)	74% (57–87%)	74% (57–87%)	84% (69–94%)
Positive likelihood ratio	5.3 (1.1–25)	3.4 (1.8–87)	3.4 (1.9–5.9)	5.3 (2.5–11)
Negative likelihood ratio	0.76 (0.6–1)	0.2 (0.08–5.6)	0.15 (0.04–0.56)	0.2 (0.07–0.56)
Positive predictive value	71% (35–92%)	60% (46–73%)	62% (48–74%)	71% (54–84%)
Negative predictive value	73% (67–79%)	90% (77–96%)	93% (79–98%)	91% (79–97%)
Accuracy	73% (60–83%)	77% (64–87%)	79% (66–88%)	84% (72–92%)

We hypothesize that this incites hyperemia and vasodilatation of the peribiliary plexus which is primarily vascularized by the hepatic artery. Thus, biliary ductal inflammation likely leads to an overall additional increase in hepatic arterial inflow. Future studies would be warranted to definitively identify the reasons for increased hepatic arterial velocities. We did not observe any statistically significant differences in resistive indices of the hepatic artery between the two groups, likely because the diastolic velocity increased by the same amount among patients with cholangitis.

Our study had several limitations. First, we had a relatively small sample size. This limitation was due to the fact that we only recently started incorporating standardized measurements of the HAV into our abdominal ultrasound protocol. Because visualization of the hepatic artery is critical to making the measurement, advances in ultrasound imaging and technology is instrumental in facilitating this measurement in all patients. In addition, acute cholangitis is a relatively uncommon condition which again limited the number of patients in our study. Future larger multicenter studies would be warranted to validate our findings. Second, we found that the average HAV in patients without cholangitis was higher than that of normal controls. This may be due to the fact that some alternative pathologies with overlapping initial presentations may also elevate the HAV, such as acute cholecystitis or hepatic abscess. In practice, these other diagnoses are readily distinguished from acute cholangitis based on imaging. Nonetheless, because these patients may have a similar initial clinical presentation, they were included in our study group, which may have artifactually lowered the diagnostic accuracy of HAV in our study. Of note, other entities that are known to increase HAV such as end stage cirrhosis, sinusoidal obstruction syndrome, or alcoholic hepatitis [33–36] were not alternative diagnoses in our study group. Third, although a greater percentage of patients with cholangitis had a history of a malignancy (in part because malignant strictures are a common cause of biliary obstruction), the proportion of patients with hepatic metastases were approximately equal in both groups. The latter is worth noting because diffuse liver metastases is a

known cause of an elevated hepatic artery velocity [23]. Fourth, we did not normalize each individual patient's hepatic artery velocity to aortic velocity to exclude the possibility of a hyperdynamic state contributing to the hepatic artery velocity. Future studies may be warranted to determine if, or to what degree, aortic velocities might affect the hepatic artery velocities. Finally, we relied upon the clinical impression as the standard of reference for determining if patients had cholangitis, as only a minority (21%) of our patients underwent definitive testing with PTC or ERCP. However, this may increase the applicability of our results as establishing a diagnosis of cholangitis on clinical grounds is more reflective of actual practices. Additionally, in a subgroup analysis that included only patients who underwent definitive testing, HAV was still statistically significantly higher in patients with cholangitis compared to those without.

In light of the relative paucity of investigative research on the topic of diagnosis of acute cholangitis, our study fills a large void in the literature of this potentially highly lethal, yet treatable condition.

## Conclusion

Hepatic artery velocity is elevated in the majority of patients with acute cholangitis. When considered in isolation, an elevated HAV > 100 cm/s has a high negative predictive value, is more accurate than Charcot's triad, and achieves similar accuracy to the 2018 Tokyo Guidelines in identifying patients with cholangitis. Substitution of hepatic artery velocity for conventional imaging criteria in these guidelines yielded the highest overall accuracy. HAV can be thus used as an alternative and more objective criteria to assess for cholangitis.

## Compliance with ethical standards

**Conflict of interest** Aya Kamaya, Book royalties, Elsevier. The other authors declare that they have no conflict of interest.

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