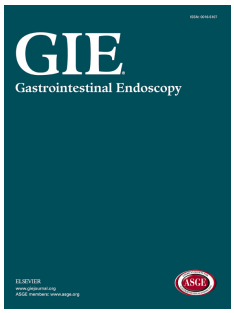

Toward an evidence-based approach for cholangitis diagnosis

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Toward an evidence-based approach for cholangitis diagnosis

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KEYWORDS: Cholangitis; Cholangiopancreatography, endoscopic retrograde; Cholestasis, extrahepatic; Time-to-treatment; Radiography, interventional; Sphincterotomy, transduodenal; Diagnosis; Choledocholithiasis

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BACKGROUND AND AIMS: Despite improvements in imaging and laboratory medicine, consensus criteria for the diagnosis of cholangitis are lacking. Although endoscopic retrograde cholangiopancreatography (ERCP) is an effective treatment for cholangitis, it should be reserved for those patients with a high probability of the diagnosis, given the morbidity associated with the procedure.

METHODS: A comprehensive literature search of PubMed (coverage 1898-present), Web of Science (1900-July 15, 2019), Embase (1943-July 15, 2019), and the Cochrane library (1898-July 15, 2019) was performed to identify studies that reported on diagnostic paradigms and individual diagnostic parameters of cholangitis. This was used to identify domains associated with high probability of cholangitis.

RESULTS: We identified 23 observational studies (N=10,252 patients) that evaluated the performance of individual and combined criteria for the diagnosis of cholangitis. Traditional paradigms including Charcot's criteria and Ranson's criteria have inadequate sensitivity, and complexity has limited the implementation of the contemporary Tokyo Criteria. Furthermore, controlled studies to validate diagnostic criteria for cholangitis are lacking. Existing literature suggests that 4 criteria, summarized by the acronym BILE, identifies those at high risk of cholangitis; Biliary imaging abnormalities or recent intervention; Inflammatory test abnormalities; Liver test elevation; and Exclusion of cholecystitis and acute pancreatitis.

CONCLUSIONS; There is a need for cholangitis diagnostic criteria that are supported by controlled validation studies, consistent with contemporary clinical values, and amenable to implementation. The BILE criteria are straightforward but require prospective study of their diagnostic performance and ability to avert unnecessary ERCP.

INTRODUCTION

Adverse events of gallstone disease, including cholangitis, result in nearly 350,000 hospitalizations each year in the United States.[1] Endoscopic retrograde cholangiopancreatography (ERCP) with decompression is an effective treatment for cholangitis. However, ERCP it is associated with an 8% to 15% risk of post ERCP pancreatitis as well as bleeding and perforation.[2, 3] Classic diagnostic paradigms are insensitive and may be positive in those with cholecystitis and other intra-abdominal processes whereas the implementation of more recent algorithms into clinical practice and research has been limited by high complexity.[4-8] Furthermore, studies of diagnostic criteria among suspected cholangitis patients have primarily included those with confirmed biliary infections and lack patients found to have (noncholangitis) disease processes. The new ASGE guideline in the management of cholangitis offers the latest evidence-based guidance on management of cholangitis.[9]

The guideline panel, however, recognized the need for better diagnostic criteria. Given the risk of serious adverse events, clinicians need simple, reliable, and validated criteria to diagnose patients with cholangitis. Such criteria would ideally identify patients who should proceed directly to ERCP versus those who would benefit from additional noninvasive imaging or other diagnostic tests and consultation, thus minimizing the risk of the adverse events related to ERCP. Therefore, we performed a scoping review of the literature on the diagnostic criteria for cholangitis. Based on our review, we propose an approach to the diagnosis of cholangitis with the purpose of improving care and outcomes in this patient population. Further research is required to validate and refine these criteria based on future evidence.

LITERATURE REVIEW

We performed a scoping review of the topic of cholangitis diagnosis to identify studies that reported the test characteristics of biochemical, radiographic, and clinical features in cholangitis. We searched PubMed (coverage 1898-present), Web of Science (1900-July 15, 2019), Embase (1943-July 15, 2019), and the Cochrane library (1898-July 15, 2019). A combination of subject headings (when available) and key words were used for the concepts of cholangitis, diagnosis, imaging, cholestasis and infection. Cross-referencing (snowballing) of the citations from articles meeting inclusion criterion was performed.

The primary endpoint, a diagnosis of cholangitis, was based on histologic evidence of duct inflammation, visualization of pus upon decompression procedures, or a consistent response to therapy **(Table 1**). We excluded studies that did not report how the diagnosis of cholangitis was confirmed. The major predictive features were defined as follows: recent biliary intervention included endoscopic, percutaneous, or surgical manipulation of the extrahepatic or intrahepatic bile duct within 30 days, biliary dilation as a common bile duct greater than 6 mm in diameter, fever as a temperature >100.4^{o}F [38ºC], leukophilia as >12x10^{3} cells/mm^{3}, and abnormal liver tests as aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, and total bilirubin greater than the upper limit of normal. Cut-offs were based on the most frequent reference ranges reported in the source data.

The scoping review identified 23 observational studies (N=10,252 patients) that reported the diagnostic performance of clinical features of patient with cholangitis.
Elevated white blood count and fever but not positive blood cultures were strongly associated with cholangitis. Among studies that reported the sensitivity of high white blood cell count

(WBC) or fever, the median (IQR) proportion of cholangitic patients with leukophilia was 73% (40%-84%) and fever was 78.5% (54.5%-96%). Additionally, more than 67% had a history of biliary intervention, and more than 85% had radiographic evidence of biliary dilation. Although the performance of elevated liver (greater than the upper limit of normal) tests varied, overall sensitivity of abnormal liver tests was >72% in all studies and exceeded 90% in 5 studies.

With the exception of one report, the studies were all retrospective cohorts, and only 2 were multicenter (Supplementary Table 1). In addition to problems with study design, most of the reports had deficiencies in the identification and reporting of populations and outcome (Supplementary Table 1).[10] The most significant knowledge gap in the literature was the lack of validation studies of diagnostic criterion in the setting of suspected cholangitis. In the majority of publications, the authors retrospectively reported the sensitivity of various biochemical tests, vital signs, symptoms, and radiographic studies using a sample in which all patients had a confirmed diagnosis of cholangitis[11-13]. However, the absence of patients with suspected cholangitis who did not have cholangitis prevented the assessment of specificity, accuracy, positive predictive value, and negative predictive value. Two recent observational cohorts included “noncholangitis” patients.[6, 14] Nevertheless, in the report by Yokoe et al [6] only 13 of the 74 patients had an alternative diagnosis. Although 609 patients in the series by Kiriyama et al [14] were classified as “noncholangitis” primarily due to lack of inflammatory criteria it appeared that they were actually considered to have cholangitis for the sake of severity classification and mortality assessment.

PROPOSED DIAGNOSTIC CRITERIA

In our opinion, and based on our review of available studies, we believe that the

development of diagnostic criteria for cholangitis should meet the following features:

1) Be supported by the best available evidence
2) Be straightforward and readily available
3) Its application should be consistent with contemporary clinical values.[15, 16]

Finally, such criteria must then be validated in prospective cohorts of patients with suspected, rather than confirmed cholangitis.

Comprehensive literature search indicates that 3 diagnostic domains most strongly correlate the diagnosis of cholangitis: (1) radiographic biliary abnormalities or history of recent bile duct intervention; (2) inflammation as identified by fever or leukocytosis, (3) and abnormal liver biochemistries (Table 1). Nevertheless, abnormalities of all 3 of these tests may be seen with acute pancreatitis and cholecystitis. Although the Atlanta Classification is widely used to diagnose pancreatitis, proposed diagnostic criteria for cholecystitis are less well defined, and with the exception of gallbladder imaging findings, overlap with those of cholangitis.[17-20]

An increasingly strong clinical value is to avoid diagnostic ERCPs, which have limited benefit but significant morbidity and liability.[21] Therefore, the threshold to stratify patients as having a high probability of cholangitis, and recommend that clinicians proceed directly to therapeutic procedures, requires the presence of all 3 criteria as well as exclusion of acute pancreatitis and cholecystitis. Absence of one or more criteria should prompt additional diagnostic evaluation including surgical consultation, imaging, and multidisciplinary discussion.

We propose the BILE diagnostic criteria to identify patients with high probability of cholangitis: **B**iliary abnormalities or intervention, **I**nflammatory marker elevation, **L**iver tests abnormalities, and **E**xclusion of cholecystitis and acute pancreatitis (Table 2). Imaging abnormalities include bile duct dilation greater than 6 mm, strictures, choledocholithiasis and

recent biliary intervention as ERCP, percutaneous biliary drainage, or surgical biliary procedures in the prior 30 days. Inflammatory marker elevation includes fever, T>100.4^{o}F [38^{o}C], leukophilia (WBC >12 x 10^3 cells/mm^3), leukopenia (WBC < 4 x 10^3 cells/mm^3), or bandemia (>10% bands). Liver tests abnormalities are categorized as an elevation above the upper limit of normal of any of the following: total bilirubin; or AST; or ALT; or alkaline phosphatase. A concomitant or alternative diagnosis of acute pancreatitis is defined by the presence of 2 of the following: characteristic upper abdominal pain, amylase or lipase greater than 3 times the upper limit of normal, or consistent imaging findings.[17] Characteristic imaging findings of gallbladder inflammation are used to diagnose cholecystitis as a potential alternative or simultaneous diagnosis.

DISCUSSION

The criterion standard for the diagnosis of cholangitis is the demonstration of inflammation in the bile duct either by surgical or postmortem examination of the ductal structures, or by drainage of pus from the biliary system at time of endoscopic or surgical decompression.[11, 22, 23] Nevertheless, the improvement of cholangitis after systemic antibiotic therapy and other conservative measures may mask these findings. This suggests that a convincing response to these measures should be integrated into this definition.[24, 25] Since the 19th century, Charcot's triad of abdominal pain, fever, and jaundice has been the most widespread system to identify patients with cholangitis.[4] Reynolds et al [5] identified clinical features of severely ill patients requiring emergent surgical decompression. Both clinical investigators operated in a system in which reliable noninvasive imaging studies and biochemical laboratory tests were not readily available. Therefore, several observational studies demonstrated

that the performance of both criteria is highly variable.[6, 13, 26] For example, in a recent systematic review, Rumsey et al [8] reported a median sensitivity of 43.6% (range 7.7%-72%) and specificity of 91% (range 84.6%-95.6%) for Charcot's triad.

In an effort to develop a contemporary tool to identify patients with cholangitis, a group of experts proposed the *Tokyo Criteria* in 2007 (TG7). [7] The 2007 Tokyo criteria for definite cholangitis were defined as either Charcot's triad or a combination of laboratory evidence of inflammation, abnormal liver tests, abnormal imaging, and 2 of 4 history elements: abdominal pain, fever, jaundice, or a history of biliary disease. The more recent versions in 2013 and 2018 (TG13/TG18) eliminated abdominal pain and history of biliary disease because these had suboptimal specificity.[14, 27-30] Specifically, they found that more than a third of patients with cholecystitis were incorrectly diagnosed with cholangitis. However, given complexity, these criteria are not widely used by clinicians .[8] Furthermore, cohort studies used to derive and validate these criteria have almost entirely been from Asian populations in which recurrent pyogenic cholangitis is much more common than in Western populations where cholesterol stone related disease predominates.[31] Nevertheless, we believe that the rigorous effort and accumulated evidence that informed the *Tokyo* Guidelines form the foundation of any future work in this area. Three of the domains of our proposed criteria coincide with Tokyo criteria.

We comprehensively reviewed the existing literature to derive the BILE criteria. Systematic review and meta-analysis was not feasible the given the large number and diverse nature of proposed diagnostic criteria and potentially combinations of these parameters. In this scoping review we aimed to identify and summarize the best evidence on this broad topic. It is our intent is that the BILE criteria serve as starting point for future study. In order to develop meaningful test characteristics, patients with suspected cholangitis, patient subsequently

confirmed to have true cholangitis as well as other forms of pancreaticobiliary and upper abdominal pathology need to be prospectively evaluated. Strengths of the BILE Criteria are that the clinical parameters are readily available and their application is straightforward. In addition to clinical implementation, these features favor validation studies, future revisions, and the emergence of an evidence-based approach to this topic.

The disadvantage of the BILE criteria is the requirement for all 4 criteria to be present to in order to classify patients as high probability for cholangitis, which may prompt additional workup. In contrast to the Tokyo criteria, which provides an algorithm to make a diagnosis of cholangitis with variable levels of confidence depending on having specific combinations of criteria in different diagnostic categories, the primary aim of the BILE criteria is to identify patients who may proceed directly to ERCP. For example, in those with concomitant cholecystitis or pancreatitis, the BILE criteria may prompt a pause for additional evaluation such as for surgical consultation for timing of cholecystectomy or imaging to assess for necrosis. We anticipate that this strategy will reduce the sensitivity of the criteria as those with cholangitis and concomitant pancreatitis or cholecystitis will be excluded. Nevertheless, given the potential morbidity of ERCP, this is a prudent strategy. Stratification of the assessment of this tool by the presence of the first 3 (BIL) versus compete criteria will be informative. Validation studies that address the overall diagnostic performance of the BILE criteria also must consider their ability to minimize unnecessary ERCP, resource utilization and adverse events.

A scoping review of the literature reveals that a history of biliary intervention, radiographic biliary anomalies, elevated inflammatory markers, and abnormal liver tests have a high sensitivity for the diagnosis of cholangitis. With the aim to minimize unnecessary ERCP,

we propose the BILE criteria, which requires all of these elements. Controlled studies in patients with suspected cholangitis will be needed to test these criteria.

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TABLES:

Table 1: Sensitivity and Specificity of Predictive Models and Clinical Features for Cholangitis

First Author, Journal Year	N	Sens/ Spec Charcot's Triad	Sens Reynolds' Pentad	Sens/ Spec TG7 +	Sens/ Spec TG13-18 ++	Sens Fever chills	Sens High WBC	Sens CRP	Sens History Biliary Disease	Sens Biliary dilation or stricture	Sens Abdominal pain	Sens Any Elevated LFTs	Sens Jaundice	Sens Elevated Bili	Sens Elevated AST	Sens Elevated ALT	Sens Elevated Alk Phos
Haupert, Arch Surg 1966*	15	13	7			100	58				100		62	100	100		
Saharia, Surg Gynecol Obstet 1976	78					100	63				79	≥97	7	91	93	97	92
Welch, Am J Surg 1976*	20	50				85						≥95	65	95			
Boey, Ann Surg, 1980*	99	70	5			50	82	44	75		63	>78		78			74
O Conner, Arch Surg 1982*	65	60	8					20		85							
Thompson, Ann Surg 1982	66	60	4			100			66		59	≥88	66	88	81	74	
Pessa, Ann Surg 1987	44	54	14			95	86				67		86	93	86	85	98
Gigot Ann Surg 1989	412	72	4				79										93
Leung, Lancet 1989	105						90	42				≥86		86			81
Akashi, Dig Endosc, 1990	159	43	4														
Lai, Ann Surg 1990	86	56				66					90		93				
Csendes, Br J Surg 1992*	512	22/91				39	31				92	≥72		65	72		
Chijiiwa, Am J Surg 1995	362					63					96		70				
Rahman, Dig Dis Sci 2005	122	18				41					81	≥85	55	85		82	80
Rossing, Am Surgeon 2007	117	42	3			77	73	74		72	68	≥91	79	87			91
Yokoe, J Hepatobiliary Pancreat Sci 2011	74	12/85		72/39		26 Spec 85					67 Spec 8		69 Spec 39				
Fuji, J Hepatobiliary Pancreat Sci	248	24			94	59					53		41				

2012																	
Tsuyuguchi, J Hepatobiliary Pancreat Sci 2012	215	34					40										
Tomizawa, J GHR 2012	17	24	6														
Kiriyama, J Hepatobiliary Pancreat Sci 2013*	1432	26/96		83/80	92/78												
Sun, J Hepatobiliary Pancreat Sci 2014*	120	51	10	86	81 suspected 36 definite	80	84**		78	91		97					
Kiriyama, J Hepatobiliary Pancreat Sci 2017	6063	21		79/90 suspected 66/73 definite	90 suspected 73 definite	96%	40			90		95**					
Gravito-Soares, Scand J Gastroenterol 2018	183	36	5	#	100/85												

+Tokyo Guidelines 2007, ++ Tokyo Guidelines 2013-2018 *Cholangitis gold standard included demonstrated pus in duct or histologic inflammation, other studies used only record review and evidence of therapeutic response **Included WBC, CRP and other inflammatory markers ##Area under the receiver operating characteristic curve (AUC) 0.92 (95%CI 0.89-0.95) for TG13-18, 0.87 (95%CI 0.89-0.90) for TG7, and 0.68 (95%CI 0.6-0.7) for Charcot's Triad

Table 2: BILE Criteria for High Probability of Cholangitis

Domain	Criterion
Biliary imaging or intervention	Abnormal biliary imaging (ductal dilation, stricture, stones) or recent (prior 30 days) bile duct intervention
Inflammatory	Elevated inflammatory including high WBC (>12 or <4 (10^3cells/mm^3) or bandemia > 10% or Fever (T>100.4^{o}F [38^{o}C], or T<96.8^{o}F [38^{o}C]
Liver Biochemistries	Abnormal liver function tests (greater than upper limit of normal),
Exclusions	Absence of acute pancreatitis[1] or cholecystitis[2]

1) Pancreatitis diagnosis based on 2 of 3: consistent upper abdominal pain, amylase or lipase > 3X upper limit of normal, characteristic pancreas imaging

2) Cholecystitis diagnosis based on characteristic gallbladder imaging

Supplementary Table 1: Quality Assessment[1] of Studies Reporting on the Diagnosis of Cholangitis

First Author, Journal Year	Study Design*	Single or Multiple Center**	Same Primary Outcome for Study and Review ***	Valid Primary Outcome Measures	Diagnostic Criteria Clearly Detailed in Methods	Consecutive Patients Enrolled	<20% Patients not Included in Study	Clear Description of Patient Characteristics	No Evidence that Study is an Outlier
Haupert, Arch Surg 1966*	Retrospective	Single	1	1	0	1	1	0	1
Saharia, Surg Gynecol Obstet 1976	Retrospective	Single	1	1	1	0	0	0	1
Welch, Am J Surg 1976*	Retrospective	Single	0	1	1	0	0	1	1
Boey, Ann Surg, 1980*	Retrospective	Single	1	1	1	0	1	0	1
O Conner, Arch Surg 1982*	Retrospective	Singe	0	1	1	1	1	1	1
Thompson, Ann Surg 1982	Retrospective	Single	0	1	0	0	0	0	1
Pessa, Ann Surg 1987	Retrospective	Single	0	1	1	1	0	0	0
Gigot Ann Surg 1989	Retrospective	Single	0	1	1	1	1	1	1
Leung, Lancet 1989	Retrospective	Single	0	1	1	1	1	1	1
Akashi, Dig Endosc, 1990	Retrospective	Single	0	0	1	1	1	0	0
Lai, Ann Surg 1990	Retrospective	Single	0	1	0	0	0	0	0
Csendes, Br J Surg 1992*	Prospective	Single	1	1	1	1	1	1	1
Chijiiwa, Am J Surg 1995	Retrospective	Single	0	1	1	1	1	1	0
Rahman, Dig Dis Sci 2005	Retrospective	Single	0	1	1	0	0	1	0
Rosing, Am Surgeon 2007	Retrospective	Single	1	1	1	1	1	0	1
Yokoe, J	Retrospective	Single	1	1	1	1	1	1	1

Hepatobiliary Pancreat Sci 2011									
Fuji, J Hepatobiliary Pancreat Sci 2012	Retrospective	Single	1	1	1	1	1	0	1
Tsuyuguchi, J Hepatobiliary Pancreat Sci 2012	Retrospective	Single	1	1	1	1	1	1	1
Tomizawa, J GHR 2012	Retrospective	Single	0	1	1	1	1	0	0
Kiriyama, J Hepatobiliary Pancreat Sci 2013*	Retrospective	Multiple	1	1	1	1	1	1	1
Sun, J Hepatobiliary Pancreat Sci 2014*	Retrospective	Single	1	1	1	1	1	1	0
Kiriyama, J Hepatobiliary Pancreat Sci 2017	Retrospective	Multiple	1	1	1	1	1	1	1
Gravito-Soares, Scand J Gastroenterol 2018	Retrospective	Single	1	1	1	1	1	1	1

*1 point for retrospective, 2 points for prospective **1 point single center study 2 points for multicenter

*** for remainder of categories 1 point for yes, 0 points for no or unclear

[1] Qumseya BJ. Quality assessment for systematic reviews and meta-analyses of cohort studies. Gastrointest Endosc. 2021;93:486-94 e1.

ACRONYMS:

ASGE: American Society of Gastrointestinal Endoscopy

ERCP: endoscopic retrograde cholangiopancreatography

TG7: Tokyo Criteria 2007

TG13: Tokyo Criteria 2013

TG18: Tokyo Criteria 2018

WBC: White blood cell count

BILE Criteria: Biliary abnormalities or intervention

Inflammatory marker elevation

Liver tests abnormalities

Exclusion of cholecystitis and acute pancreatitis.

Placeholder for diversity form; this article was submitted before it was required.