Multicenter validation of the American Association for the Surgery of Trauma grading scale for acute cholecystitis

Kevin M. Schuster, MD, MPH, FACS, Rick O'Connor, RN, Michael Cripps, MD, Kali Kuhlenschmidt, MD, Luis Taveras, MD, Haytham M. Kaafarani, MD, Majed El Hechi, MD, Ruchir Puri, MD, MS, FACS, Jennifer Mull, MSN, RN, Thomas J. Schroeppel, MD, MS, Jennifer Rodriquez, Daniel C. Cullinane, MD, Laura M. Cullinane, Toby M. Enniss, MD, FACS, Rachel Sensenig, MD, Brian Zilberman, MD, *and* **Marie Crandall, MD, MPH, FACS**, *New Haven, Connecticut*

CONTINUING MEDICAL EDUCATION CREDIT INFORMATION

Accreditation

The American College of Surgeons is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

AMA PRA Category 1 Credits™

The American College of Surgeons designates this journal-based CME activity for a maximum of 1 *AMA PRA Category 1 Credit*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Of the AMA PRA Category 1 Credit™ listed above, a maximum of 1 credit meets the requirements for self-assessment.

AMERICAN COLLEGE OF SURGEONS
Inspiring Quality: Highest Standards, Better Outcomes
100+years

ACCME ACCREDITED WITH COMMENDATION

AMERICAN COLLEGE OF SURGEONS DIVISION OF EDUCATION

Objectives

After reading the featured articles published in the *Journal of Trauma and Acute Care Surgery*, participants should be able to demonstrate increased understanding of the material specific to the article. Objectives for each article are featured at the beginning of each article and online. Test questions are at the end of the article, with a critique and specific location in the article referencing the question topic.

Disclosure Information

In accordance with the ACCME Accreditation Criteria, the American College of Surgeons must ensure that anyone in a position to control the content of the educational activity (planners and speakers/authors) has disclosed all relevant financial relationships with any commercial interest. For additional information, please visit the ACCME website (see below for definitions).

Commercial Interest: The ACCME defines a "commercial interest" as any entity producing, marketing, re-selling, or distributing health care goods or services used on or consumed by patients. Providers of clinical services directly to patients are NOT included in this definition.

Financial Relationships: Relationships in which the individual benefits by receiving a salary, royalty, intellectual property rights, consulting fee, honoraria, ownership interest (e.g., stocks, stock options or other ownership interest, excluding diversified mutual funds), or other financial benefit. Financial benefits are usually associated with roles such as employment, management position, independent contractor (including contracted research), consulting, speaking and teaching, membership on advisory committees or review panels, board membership, and other activities from which remuneration is received, or expected. ACCME considers relationships of the person involved in the CME activity to include financial relationships of a spouse or partner.

Conflict of Interest: Circumstances create a conflict of interest when an individual has an opportunity to affect CME content about products or services of a commercial interest with which he/she has a financial relationship.

The ACCME also requires that ACS manage any reported conflict and eliminate the potential for bias during the session. Any conflicts noted below have been managed to our satisfaction. The disclosure information is intended to identify any commercial relationships and allow learners to form their own judgments. However, if you perceive a bias during the educational activity, please report it on the evaluation.

AUTHORS/CONTRIBUTORS
Kevin M. Schuster, Rick O'Connor, Michael Cripps, Kali Kuhlenschmidt, Luis Taveras, Haytham M. Kaafarani, Majed El Hechi, Ruchir Puri, Jennifer Mull, Thomas J. Schroeppel, Jennifer Rodriquez, Daniel C. Cullinane, Laura M. Cullinane, Toby M. Enniss, Rachel Sensenig, Brian Zilberman, Marie Crandall - No Disclosures.

PLANNING COMMITTEE / EDITORIAL COMMITTEE	NOTHING TO DISCLOSE	DISCLOSURE		
		COMPANY	ROLE	RECEIVED
Ernest E. Moore, Editor		*Haemonetics*	*PI*	*Shared U.S. Patents*
		Instrumentation Laboratory	*PI*	*Research Support*
		Stago, Humacyte, Prytime	*PI*	*Research Support*
		ThromboTherapeutics	*Co-founder*	*Stock*
Associate Editors David B. Hoyt, Ronald V. Maier, and Steven Shackford	X			
Editorial Staff and Angela Sauaia	X			

Claiming Credit

To claim credit, please visit the AAST website at http://www.aast.org/ and click on the "e-Learning/MOC" tab. You must read the article, successfully complete the post-test and evaluation. Your CME certificate will be available immediately upon receiving a passing score of 75% or higher on the post-test. Post-tests receiving a score of below 75% will require a retake of the test to receive credit.

Credits can only be claimed online

Cost

For AAST members and Journal of Trauma and Acute Care Surgery subscribers there is no charge to participate in this activity. For those who are not a member or subscriber, the cost for each credit is $25.

Questions

If you have any questions, please contact AAST at 800-789-4006. Paper test and evaluations will not be accepted.

BACKGROUND: The American Association for the Surgery of Trauma (AAST) patient assessment committee has created grading systems for emergency general surgery diseases to assist with clinical decision making and risk adjustment during research. Single-institution studies have validated the cholecystitis grading system as associated with patient outcomes. Our aim was to validate the grading system in a multi-institutional fashion and compare it with the Parkland grade and Tokyo Guidelines for acute cholecystitis.

METHODS: Patients presenting with acute cholecystitis to 1 of 8 institutions were enrolled. Discrete data to assign the AAST grade were collected. The Parkland grade was collected prospectively from the operative surgeon from four institutions. Parkland grade, Tokyo Guidelines, AAST grade, and the AAST preoperative grade (clinical and imaging subscales) were compared using linear and logistic regression to the need for surgical "bailout" (subtotal or fenestrated cholecystectomy, or cholecystostomy), conversion to open, surgical complications (bile leak, surgical site infection, bile duct injury), all complications, and operative time.

RESULTS: Of 861 patients, 781 underwent cholecystectomy. Mean (SD) age was 51.1 (18.6), and 62.7% were female. There were six deaths. Median AAST grade was 2 (interquartile range [IQR], 1–2), and median Parkland grade was 3 (interquartile range [IQR], 2–4). Median AAST clinical and imaging grades were 2 (IQR, 2–2) and 1 (IQR, 0–1), respectively. Higher grades were associated with longer operative times, and worse outcomes although few were significant. The Parkland grade outperformed the AAST grade based on area under the receiver operating characteristic curve.

CONCLUSION: The AAST cholecystitis grading schema has modest discriminatory power similar to the Tokyo Guidelines, but generally lower than the Parkland grade, and should be modified before widespread use. (*J Trauma Acute Care Surg.* 2021;90: 87–96. Copyright © 2020 American Association for the Surgery of Trauma.)

LEVEL OF EVIDENCE: Diagnostic study, level IV.

KEY WORDS: Cholecystitis; grading scales; outcomes.

The burden of emergency general surgical operations in the United States is significant, with a cost of more than US $20 billion in calendar year 2010.[1,2] Of these, gallbladder-related disease is the second most common by volume but the single most costly.[3] Emergency cholecystectomy accounts for more than 300,000 cases or about one third of emergency general surgery operative cases annually, with costs of approximately US $12,000 per hospitalization in 2010.[3] Although the complications of cholecystectomy are generally minor, several studies have documented occurrence of complications between 20% and 70% of cases.[4–6] Mortality for acute cholecystitis has been reported to range from 0.5% to 20%.[4–7] Outcomes pertaining to need for posthospitalization care, long-term complications, quality of life, and gastrointestinal quality of life have been reported but only in small studies.[8,9]

Given the wide range of reported outcomes for acute cholecystitis and the associated high costs, nationally, the ability to predict outcomes of the disease becomes important. Although early cholecystectomy is now the most common treatment for acute cholecystitis, there exists wide variation in practice patterns, likely because surgeons are choosing not to operate early when they judge disease to be severe.[10–12] A risk stratification for acute cholecystitis should therefore inform and improve operative and nonoperative decision making. In addition to clinical decision making, risk stratification will also improve research efforts by more accurately assigning expected outcome, improving risk adjustment in quality registries, and potentially leading to differential reimbursement for managing more severe disease.

Several grading systems for acute cholecystitis have been developed through expert consensus. The first clinical grading system for acute cholecystitis that has gained widespread acceptance are the Tokyo Guidelines, which were originally published in 2007 and updated in 2013 and 2018 with minimal change.[7,13,14] These guidelines introduced diagnostic criteria based on symptoms and imaging findings and further graded severity based on laboratory, imaging, and physiologic measures.[13] In 2016, the Patient Assessment Committee of the American Association for the Surgery of Trauma (AAST) developed grading systems for 16 emergency general surgery conditions including acute cholecystitis.[15] Unlike the Tokyo Guidelines, the grading system was based almost entirely on anatomic structural pathology of the gallbladder as assessed by imaging, operative findings, and pathology, rather than patient physiology. The AAST grading system is designed to predict overall patient outcome possibly working through the latent variable of surgical difficulty of cholecystectomy. Three scoring systems, the G10, Fresno, and Parkland, which use operative findings to predict surgical difficulty and patient outcomes, have recently been developed.[16–18] The Fresno grade has not been prospectively validated and is similar to Parkland based mostly on operative impression.[18] The other two scoring systems have been prospectively validated as predictors of operative outcomes as measured by conversion to open and/or overall patient outcomes.[19,20] A significant limitation of the G10 system, however, is that it lacks simplicity when compared with Parkland. Single-institution studies have compared the AAST system to the Parkland grading system and Tokyo Guidelines. These studies have demonstrated Parkland to be

Submitted: June 30, 2020, Revised: July 22, 2020, Accepted: July 23, 2020, Published online: September 15, 2020.

From the Department of Surgery (K.M.S., R.O.), Yale School of Medicine, New Haven, CT; Department of Surgery (M. Cripps, K.K., L.T.), University of Texas Southwestern School of Medicine, Dallas, TX; Department of Surgery (H.M.K., M.E.), Massachusetts General Hospital, Boston, MA; Department of Surgery (R.P., M. Crandall, J.M.), College of Medicine — Jacksonville, University of Florida, Jacksonville, FL; Department of Surgery (T.J.S., J.R.), UC Health, Colorado Springs, CO; Department of Surgery (D.C.C., L.M.C.), Marshfield Clinic, Marshfield, WI; Department of Surgery (T.M.E.), School of Medicine, University of Utah, Salt Lake City, UT; and Department of Surgery (R.S., B.Z.), Cooper Medical School of Rowan University, Camden, NJ.

This study was presented at the 79th Annual Meeting of the American Association for the Surgery of Trauma, September 8–18, 2020, virtually.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text, and links to the digital files are provided in the HTML text of this article on the journal's Web site (www.jtrauma.com).

Address for reprints: Kevin M. Schuster, MD, MPH, FACS, Department of Surgery, Yale School of Medicine, 330 Cedar St, BB310, PO Box 208062, New Haven, CT 06520-8062; email: kevin.schuster@yale.edu.

DOI: 10.1097/TA.0000000000002901

TABLE 1. Patient Characteristics Comparing Those That Underwent Cholecystectomy and Those That Did Not

Patient Demographics	Cholecystectomy	Nonoperative Management
n	781	80
Age, mean (SD), y	48.9 (17.8)	73.0 (15.0)
Sex, female, %	506 (64.8)	34 (42.5)
Race		
Asian	7 (0.9)	0 (0.0)
Black	79 (10.1)	15 (18.8)
Native American	1 (0.1)	1 (1.2)
White	582 (74.5)	60 (75.0)
Other/unknown	112 (14.3)	4 (5.0)
Ethnicity		
Latino	275 (35.2)	8 (10.0)
Not Latino	499 (63.9)	71 (88.8)
Unknown	7 (0.9)	1 (1.2)
Admitted from		
Extended care facility	7 (0.9)	14 (17.5)
Home	740 (94.8)	56 (70.0)
Other acute care hospital	33 (4.2)	10 (12.5)
Rehabilitation facility	1 (0.1)	0 (0.0)
Comorbidities and clinical risk factors		
Hypertension	254 (32.5)	59 (73.8)
CHF	19 (2.4)	15 (18.8)
CAD	50 (6.4)	27 (33.8)
HIV/AIDS	1 (0.1)	1 (1.2)
Smoking	6 (7.5)	69 (8.8)
COPD	29 (3.7)	12 (15.0)
Ascites	1 (1.2)	1 (0.1)
Acute kidney injury	11 (1.4)	7 (8.8)
Dialysis	2 (0.3)	1 (1.2)
Disseminated cancer	10 (1.3)	12 (15.0)
Chronic wound	2 (0.3)	8 (10.0)
Immunosuppression	18 (2.3)	17 (21.2)
Weight loss	13 (1.7)	1 (1.2)
Bleeding disorder	31 (4.0)	24 (30.0)
SIRS/sepsis		
None	646 (82.7)	46 (57.5)
SIRS	85 (10.9)	19 (23.8)
Sepsis	47 (6.0)	7 (8.8)
Septic shock	3 (0.4)	8 (10.0)
Dyspnea		
None	724 (92.7)	62 (77.5)
With exertion	53 (6.8)	12 (15.0)
At rest	4 (0.5)	6 (7.5)
Functional status		
Independent	731 (93.6)	44 (55.0)
Partially dependent	28 (3.6)	23 (28.7)
Dependent	13 (1.7)	13 (16.2)
Unknown	0 (0.0)	9 (1.2)
Vasopressors	46 (5.9)	6 (7.5)
Intubated	2 (0.3)	1 (1.2)
Altered mental status	12 (1.5)	9 (11.2)
BMI, mean (SD), kg/m^2	31.6 (8.4)	31.4 (8.8)
WBC, mean (SD), per mm^3	11.9 (6.3)	13.5 (6.4)
Hematocrit, mean (SD), %	41.0 (5.6)	35.6 (7.5)
Platelets, mean (SD), $\times 10^9$/L	269 (79)	240 (109)
Creatinine, mean (SD), mg/dL	0.87 (0.55)	1.32 (0.89)
Total bilirubin, median (IQR), mg/dL	0.6 (0.4–1.2)	1.0 (0.5–1.6)
Albumin, g/dL	4.2 (0.5)	3.5 (0.6)
Duration of pain, median (IQR), d	2 (1–4)	2 (1–3)
Preoperative grading		
AAST preoperative grade		$p < 0.001$*
I	9 (1.2)	1 (1.3)
II	729 (93.8)	63 (78.8)
III	18 (2.3)	9 (11.3)
IV	19 (2.4)	4 (5.0)
V	2 (0.3)	3 (3.8)
Tokyo Guidelines		$p < 0.001$*
0	242 (31.0)	13 (16.3)
I	147 (18.8)	14 (17.5)
II	290 (37.1)	24 (30.0)
III	102 (13.1)	29 (36.3)
Outcomes		
New dialysis	0 (0.0)	2 (2.5)
Acute kidney injury	6 (0.8)	6 (7.5)
Urinary tract infection	5 (0.6)	3 (3.8)
CVA	2 (0.3)	0 (0.0)
Myocardial infarction/cardiac arrest	2 (0.3)	1 (0.1)
Pneumonia	2 (0.3)	0 (0.0)
Venous thromboembolism	3 (0.3)	1 (1.2)
Persistent/postoperative sepsis		
None	737 (95.7)	67 (83.8)
SIRS	21 (2.7)	3 (3.8)
Sepsis	10 (1.3)	4 (5.0)
Septic shock	2 (0.3)	6 (7.5)
Discharge disposition		
Home	761 (97.4)	40 (50.0)
Transferred to another acute care hospital	0 (0.0)	2 (2.5)
Rehabilitation	17 (2.2)	32 (40.0)
Nursing home	1 (0.1)	0 (0.0)
Death	3 (0.3)	3 (3.8)
Length of stay, median (IQR), d	2 (2–4)	6 (3–10)

Data are reported as n (%) unless otherwise noted.
*p Value associated with Wilcoxon signed rank.
CAD, coronary after disease; CHF, congestive heart failure; HIV, human immunodeficiency virus; COPD, chronic obstructive pulmonary disease; SIRS, systemic inflammatory response syndrome; BMI, body mass index; WBC, white blood cell; CVA, cerebral vascular accident; IQR, interquartile range).

superior to AAST with respect to complications and AAST to be better calibrated than Tokyo.[4,21] The AAST and Parkland grading scales are available as a Supplemental Digital Content (Supplementary Table 1, http://links.lww.com/TA/B786).

Given the retrospective nature of prior comparisons, which complicates accurate capture of several characteristics of the grading system, and the single-institution comparison of the Parkland grade, a multi-institution prospective evaluation was needed to compare the predictive capacity of these grading systems and potentially identify opportunities for further refinement. Prediction

of patient outcomes and prediction of surgical difficulty are both important for surgeons and should be considered when assessing a cholecystitis scoring system. We therefore hypothesized that, under prospective conditions, the AAST system, which includes both preoperative and intraoperative variables would outperform the Tokyo Guidelines and Parkland grade.

PATIENTS AND METHODS

Data Collection

Prospective data collection was carried out at eight institutions practicing an acute care surgery model. All are American College of Surgeons Committee on Trauma–verified trauma centers and represented geographically diverse regions of the United States. All adult patients, 18 years or older, who were admitted to the hospital and prospectively identified as having a diagnosis of acute cholecystitis were included. The diagnosis of acute cholecystitis was assigned by an attending surgeon at the time of admission. The only exclusion was the concomitant presence of pancreatitis. This approach was taken because Tokyo diagnostic criteria for acute cholecystitis are not entirely sensitive and specific.[22] The elements of the various scoring systems, where possible, were abstracted objectively from the patient charts. The criteria for the three grading systems being compared are reported elsewhere.[7,15,17] To avoid the potential for bias in assigning grades of disease, the data were collected at a granular level with the grades calculated on the entire data set. Individual laboratory values, discrete imaging, and operative and pathologic findings were collected such that a grade could be assigned, using each of the grading systems. The exception to this was the Parkland grade, which was assigned by the operative surgeon within 24 hours of surgery at four institutions and by operative note review at the remaining four institutions. This translated to 62.5% of patients having prospective capture of the Parkland grade. Outcome variables were defined based on interpretation of the National Surgical Quality Improvement Project (NSQIP) postoperative occurrence variables. Specific surgical outcome variables were considered separately from NSQIP variables and included bile leak, operative time, use of a bailout procedure, or conversion to open. All data were entered into the AAST data collection system (World Advancement of Technology for EMS and Rescue, Inc., San Diego, CA). All data were then transferred to the primary institution for analysis.

Data Analysis

The data were analyzed to characterize the patient cohort with respect to demographics, surgical outcomes, other nonsurgical complications, and mortality. Frequency plots for each of the levels of the grading systems were created to assess the distribution of grades across the systems. Outcomes were compared between those patients who that underwent operative and nonoperative management. The AAST system was also broken down into a final grade and a preoperative grade, which consisted of the clinical and radiologic subscales. This was done because it is important to predict outcomes for nonoperatively managed patients and predict outcomes before surgery to inform the decision for surgery. Patients who did not meet the criteria for cholecystitis by Tokyo Guidelines were classified as Tokyo grade zero. Patients with only gallstones by imaging were classified as grade zero on the AAST imaging subscale to understand the number of patients in this group. A pathologic finding of chronic cholecystitis was classified as AAST pathologic grade zero. When patients met none of the criteria for operative grading on the AAST subscale, these patients were also assigned an AAST operative grade zero. These patients all had an AAST clinical grade of two, and therefore, assigning zeros did not impact overall scoring. The patients were compared based on AAST preoperative grade and Tokyo Guidelines to determine association with choice of operative versus nonoperative treatment. Grades across patient groups were compared with the Wilcoxon rank sum test.

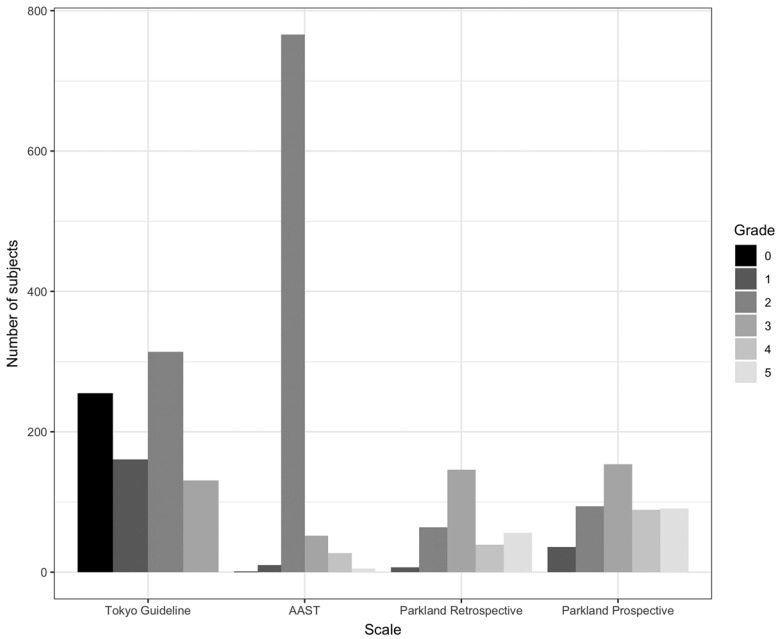

Figure 1. Distribution of patients across the assessed acute cholecystitis grading scales.

We assessed the performance of each of the grading systems with respect to higher grades being associated with higher frequencies of poor outcomes. Several postoperative or post admission complications were grouped, including new-onset pneumonia, sepsis or septic shock, 48 hours or more of new mechanical ventilation, acute kidney injury, new dialysis, urinary tract infection, stroke, cardiac arrest, myocardial infarction, venous thromboembolism, and surgical site infection. Surgical bailout was the use of any one or more of the following techniques: subtotal cholecystectomy, fenestrated cholecystectomy, or placement of a surgical cholecystostomy tube without cholecystectomy or partial cholecystectomy. The surgical outcomes of bile leak or conversion from laparoscopic to open cholecystectomy were considered separately. Initial assessment was with the Cochran Armitage one-sided test for trend with increasing grade for each system compared with outcomes. Logistic regression was used to generate receiver operating characteristic (ROC) curves and calculate an area under the curve (AUC). These AUC values were then compared across the various grading systems using the method of Delong.[23] Linear regression was used to compare grade with operative time. Fit of the nonnested linear models were then compared using the methods of Davidson and Mackinnon.[24] All statistical analyses were performed with R: a language and environment for statistical computing version 4.0.0 (R Foundation for Statistical Computing, Vienna, Austria) with the following packages installed: lmtest, pROC, ggplot2, arsenal, DescTools, and dplyr.

RESULTS

Demographics and Overall Outcomes

Among the 8 centers, 861 patients were enrolled. The mean age of patients was 51.1, and 62.7% were female. Of the enrolled patients, 781 (90.7%) underwent cholecystectomy with 88 undergoing preoperative endoscopic retrograde cholangiopancreatography (ERCP) and 135 undergoing intraoperative cholangiogram. Forty-two of the cases required conversion to open, 26 required a bailout procedure, and 12 required an unplanned return to the operating room. There was one common bile duct injury. The remaining 80 patients were managed nonoperatively. There were 79 patients who experienced a complication, and there were 6 deaths. For the entire cohort, the median hospital length of stay was 3 days with interquartile range of 2 to 4.

Patients who were managed without surgery were older, more commonly male, and less likely to be admitted from home, when compared with those patients who received surgical intervention (Table 1). In general, comorbid conditions were more common in the nonoperatively managed patients as were measures of worse acute clinical illness. Duration of pain was similar. With respect to the grading schema that would have been available preoperatively, both the AAST and Tokyo captured the increased degree of illness with higher median grades based on both systems in the nonoperative patients (Table 1). There were more complications in the nonoperative group, and hospital length of stay was longer.

Characterization of Grading Systems

There were notable differences in the distribution of severity when comparing the three grading systems (Fig. 1). There were 255 patients (29.6%) who did not meet the diagnostic criteria for acute cholecystitis based on Tokyo Guidelines definitions and were assigned a grade of zero. The remaining patients were distributed across grades I to III. Patients were distributed across the Parkland grades similarly, whether these data were collected prospectively or retrospectively from the operative reports. When examining the distribution of grades for the AAST grade, 766 patients (89.0%) were a grade II. Examination of the subgrades in the AAST system demonstrates that the majority of patients were graded on the clinical scale as II (95.5%) (Fig. 2). This is due to the fact that clinical grade I and grade II have identical definitions. By adding the radiologic, operative, and pathologic grades, 56 patients were upgraded. Although 371 patients are depicted as grade 0 by imaging, these are the patients where the only imaging finding was gallstones without signs of

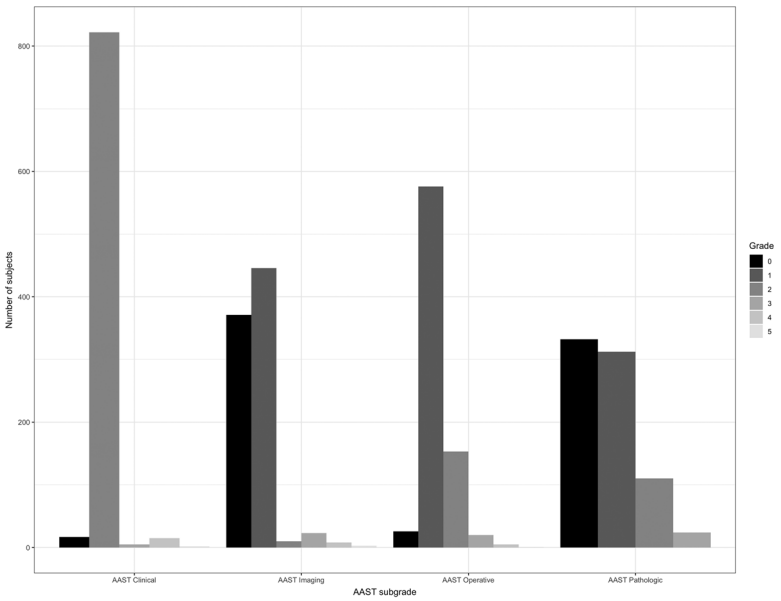

Figure 2. Distribution of patients across the AAST subscales.

TABLE 2. Patient Outcomes Relative to Each of the Grading Scales

	AAST Preoperative	AAST Final	Tokyo Guidelines	Parkland Retrospective	Parkland Prospective
Complication (n = 79)	0–0	0–1 (0)	0–21 (8.2)	1–1 (14.3)	1–0
	1–0	1–10 (0)	1–9 (5.6)	2–8 (12.5)	2–3 (3.2)
	2–67 (8.5)	2–61 (8.0)	2–29 (9.2)	3–12 (8.2)	3–4 (2.6)
	3–7 (25.9)	3–12 (23.1)	3–20 (15.3)	4–5 (12.8)	4–12 (13.5)
	4–5 (21.7)	4–6 (22.2)		5–4 (7.1)	5–12 (13.2)
	5–0	5–5 (0)			
	$p = 0.007$	$p < 0.001$	$p = 0.035$	$p = 0.458$	$p < 0.001$
Death (n = 6)	0–0	0–0	0–0	1–0	1–0
	1–0	1–0	1–1 (0.6)	2–1 (1.6)	2–0
	2–4 (0.5)	2–4 (0.5)	2–1 (0.3)	3–1 (0.7)	3–1 (0.6)
	3–0	3–0	3–4 (3.1)	4–0	4–0
	4–2 (8.7)	4–2 (7.4)		5–0	5–0
	5–0	5–0			
	$p = 0.041$	$p = 0.003$	$p = 0.007$	$p = 0.824$	$p = 0.733$
Bile leak (n = 18), n (%)	0–0	0–0	0–7 (2.9)	1–1 (1.4)	1–0
	1–0	1–0	1–1 (0.7)	2–0	2–0
	2–16 (2.2)	2–12 (1.7)	2 = 9 (3.1)	3–2 (1.4)	3–1 (0.6)
	3–2 (11.1)	3–5 (11.6)	3–1 (1.0)	4–2 (5.1)	4–5 (5.6)
	4–0	4–1 (4.3)		5–2 (3.6)	5–5 (5.5)
	5–0	5–0			
	$p = 0.580$	$p = 0.007$	$p = 0.660$	$p = 0.192$	$p = 0.007$
Mean operating room time, min	0–70.2	0–40	0–103	1–115	1–90.9
	1–111	1–86	1–123	2–88.2	2–78.3
	2–114	2–113	2–117	3–109	3–108
	3–159	3–146	3–127	4–144	4–165
	4–133	4–141		5–126	5–137
	5–121	5–121			
Bailout procedure (n = 26)	0–0	0–0	0–4 (1.6)	1–0	1–0
	1–0	1–0	1–3 (1.9)	2–0	2–0
	2–22 (2.8)	2–18 (2.3)	2–14 (4.5)	3–1 (0.7)	3–4 (2.6)
	3–2 (7.4)	3–4 (7.7)	3–5 (3.8)	4–1 (2.6)	4–8 (9.0)
	4–1 (4.3)	4–3 (11.1)		5–1 (1.8)	5–11 (12.1)
	5–1 (20.0)	5–1 (20.0)			
	$p = 0.018$	$p < 0.001$	$p = 0.027$	$p = 0.028$	$p < 0.001$
Laparoscopic procedure converted to open (n = 42)	0–0	0–0	0–8 (3.3)	1–0	1–0
	1–1 (11.1)	1–0	1–4 (2.7)	2–0	2–0
	2–38 (5.3)	2–31 (4.5)	2–20 (7.1)	3–5 (3.5)	3–0
	3–1 (6.7)	3–7 (18.4)	3–10 (10.4)	4–6 (16.7)	4–9 (10.1)
	4–1 (5.9)	4–3 (14.3)		5–8 (16.0)	5–14 (15.6)
	5–1 (50.0)	5–1 (50.0)			
	$p < 0.001$	$p < 0.001$	$p = 0.002$	$p < 0.001$	$p < 0.001$

All data are reported as n (%) unless otherwise noted. *p* Values are based on Cochran-Armitage test for trend (one sided, increasing).

cholecystitis. These patients are plotted here to demonstrate the high frequency of these patients. Following the scoring system strictly, there would have been 817 (94.9%) graded as grade I. Similar patterns were present on the operative and pathologic grades with 755 (96.7%) and 754 (96.9%) being grade II or lower (Fig. 2). On the pathologic grade, 332 (42.7%) did not rise to the level of grade I.

Comparing Grading Systems

All three grading systems demonstrated correlation between increasing occurrence of complications and higher grade of disease severity (Table 2). Mortality correlated with higher grade in both the AAST system and Tokyo Guidelines, but the few deaths in operated patients prevented demonstration of any trends with respect to the Parkland grade. There was an association between bile leak and operative grading criteria but not for preoperatively derived grades. Each of the scoring systems demonstrated statistically significant trends toward more bailout procedures and more conversions to open with higher grades of disease. When comparing scoring systems based on their predictive capacity, the AUCs for the complete AAST grade and the preoperative grade were similar across most outcomes and when compared with Tokyo. The Tokyo Guidelines did outperform AAST with respect to discharge home (Table 3). The Parkland

TABLE 3. Accuracy of Each of the Evaluated Grading System for Operated Patients as Measured by Area Under the Receiver Operating Characteristic Curve or for Linear Regression R^2

Outcome Measure	AAST	AAST Preoperative	Tokyo Guidelines	Parkland Prospective	Parkland Retrospective	Compare AAST and Tokyo (p Value)	Compare AAST and Parkland (p Value)
Complications	0.599	0.568	0.568	0.720	0.570	1.000	0.005
Mortality	0.679	0.645	0.794	0.835	0.731	0.286	0.059
Bile leak	0.632	0.537	0.524	0.781	0.752	0.875	<0.001
Abbreviated procedure	0.579	0.561	0.622	0.769	0.730	0.540	0.002
Conversion to Open	0.603	0.511	0.628	0.844	0.772	0.612	<0.001
OR time (R^2)	0.009	0.003	0.005	0.063	0.095	0.516	<0.001
Discharge home	0.573	0.571	0.657	0.675	0.632	0.047	0.309

Areas under the curve for AAST are reported for the entire data set; however, for comparison with Parkland prospective, only those subjects with prospective Parkland grades were included.
OR, operative.

grade also outperformed the AAST grade with respect to all outcomes except mortality and discharge home (Table 3). Representative ROC curves provide a graphical impression of the differences between scores (Supplemental Digital Content, Supplementary Fig. 1, http://links.lww.com/TA/B787). Because many of the patients did not meet the Tokyo Guidelines criteria for a diagnosis of acute cholecystitis, we validated their inclusion in the study by examining their prospectively acquired Parkland grade and AAST pathologic grade. Twenty of 169 patients had a normal gallbladder intraoperatively and on the AAST pathologic grade. Half of the patients had findings of acute cholecystitis, and the remaining patients had chronic cholecystitis (Table 4).

DISCUSSION

Grading systems for acute surgical disease processes are a benefit to patient communication and surgical decision making if they accurately predict outcomes and operative difficulty. Accurate grades also allow for grouping of patients and assessing response to treatment during research, and potentially informing payment decisions. The AAST created grades for multiple acute surgical diseases using a Delphi method and expert consensus.[15] Our study represents the first prospective multicenter validation of an AAST grading system with comparison with both the Tokyo Guidelines and the Parkland grade. Although data were collected prospectively, not all centers collected the Parkland grade directly from the surgeon and chose to abstract it from the operative note, thereby allowing us to assess this method for obtaining the Parkland grade. Using these data, strengths and weaknesses of each of the grading systems were simultaneously compared.

TABLE 4. Prospectively Acquired Parkland Grade and AAST Pathologic Grade in Tokyo Grade 0 Patients

Grade	Parkland, n	AAST Pathologic, n
0		121
I	20	99
II	39	20
III	62	2
IV	28	
V	20	

As expected, patients with greater degrees of comorbid conditions and greater severity of physiologic illness were less likely to undergo operation for acute cholecystitis. These nonoperatively managed patients had more complications, longer lengths of stay, and a different patterns of hospital discharge. A higher mean Tokyo grade in the nonoperative patients was demonstrated as expected given the physiologic parameters that make up the Tokyo grade. The preoperative AAST grade (clinical and imaging characteristics) by contrast has few physiologic variables, yet higher grades were also associated with nonoperative management. It is not clear which of these factors led surgeons to choose nonoperative management; however, it suggests that anatomic and physiologic findings are interrelated and support the anatomic basis for AAST grading. All of the grading systems, despite being developed by expert consensus, demonstrate that at higher grades patients more commonly develop medical complications and bile leaks, and require bailout procedures or conversion to an open operation. Surprisingly, there were no clear correlations between operative times and grade. This may have been due to the involvement of trainees during the surgical procedures in all of these academic institutions.

The Parkland grade had clear advantages with respect to the AAST grade across most outcomes, while the Tokyo and AAST performed similarly. This is consistent with Madni et al.[21] who demonstrated superiority of the Parkland grade but discordant with Hernandez et al.[4] who demonstrated AAST superiority to the Tokyo Guidelines. Because our data were collected prospectively in a granular format with grades objectively calculated rather than subjectively assigned, we believe this method to be more consistent with potential future application of the grades either by nonsurgeons or an automated algorithm. Therefore, our findings regarding grading system performance should inform decisions regarding which system to use in these applications. The operative portion of the grade will remain subjective; however, application of Parkland or similar semiobjective operative grade has the potential to be the most powerful predictive index for future risk adjustment when applied to research or physician reimbursement. Therefore, systems that prompt surgeons to apply a grade in the immediate perioperative period require further exploration and may need to be included in the AAST system. This will be necessary because we also identified poorer performance of the Parkland grade when it was abstracted retrospectively from the operative reports.

Several potential weaknesses of all grading systems were identified by our data. For the Parkland grade, although it performed well, it is not applicable to patients who are managed without surgery. The AAST grades performed less well than the Parkland, which is not surprising given the skewed the distribution of grades toward lower severity. The AAST grades were poorly distributed with almost 90% of patients having a final grade of II. When breaking this down into subscales, it can be seen that clinical grade is almost always a grade II and more than 90% of patients have an imaging grade of I or less. The operative and pathologic subscales add some range to the AAST grades. This translates into slightly higher AUC for some of the outcome measures comparing preoperative and final AAST grades. Future work optimizing the AAST grades should consider using clinical and imaging findings that predict worse outcomes to improve the range of grades assigned under these subscales. The addition of more physiologic markers similar to the Tokyo Guidelines is another potential solution. However, the additional benefit gleaned is uncertain given the similar performance of the Tokyo Guidelines to the AAST grade. This also violates the underlying philosophy of the AAST system as purely anatomic, although leukocytosis is incorporated into the AAST grade. Alternatively, a parallel EGS physiology grade such as the Emergency Surgery Score or the American College of Surgeons NSQIP risk calculator could be used to augment the AAST anatomic grade.[25,26] As a starting point, perforation should be moved to grade IV or V. Adjusting the imaging criteria to obtain a more equal distribution should then be strongly considered given the clustering of patients at the lower grades. This would likely lead to a significantly improved scoring system for patients who do not undergo operation. It would also assist in situations where a surgeon is weighing the risks and benefits of operation and operative criteria would be unknown. Using a surgeon-assigned grade based on operative findings would likely improve the final grade. Whether this means simply replacing the AAST operative grade with the Parkland grade, adding additional characteristics to the AAST operative grade or some other approach is uncertain. Another important implication of our findings was the failure of the Tokyo Guidelines to identify all patients with cholecystitis including those with clinically severe disease based on Parkland grade and the AAST pathology subscale. This also suggests weaknesses in either the pathologic evaluation of specimens or the actual AAST pathologic subscale. Further investigation will be necessary before potential modification of this subscale. Developing an improved definition of acute cholecystitis based on the AAST grade is another opportunity to improve benchmarking of this common disease.

Limitations

There are several limitations to our study. Most importantly, there are no specific statistical methods for comparing grading systems as such, we used measures that are most available. These methods do give strong evidence of the Parkland system being superior to AAST. In addition, significant outcomes such as death and major medical complication are not common in cholecystitis, especially among the most common cases that are lower grade. This also makes drawing strong conclusions regarding grading system performance for these outcomes difficult. Our use of surgeon assignment of a diagnosis of cholecystitis could also be criticized given the common use of the Tokyo definition of cholecystitis in the literature.[4,27] We did however find that, despite failing to meet Tokyo Guidelines for diagnosis of acute cholecystitis, the vast majority of these patients had intraoperative findings of cholecystitis and half had pathologic findings of acute cholecystitis with 5% demonstrating severe disease with abscess or necrosis. The method of data collection could also be criticized because we did not rely on surgeons or others to assign the grades and address interrater reliability. We did however collect the data at a very granular level. The majority of the data necessary to create these grades is available at this granular level and will likely be collected autonomously in the future eliminating any subjectivity introduced by having humans assign the grades. This may have contributed to the overall lower AUCs for the grading systems we identified compared with Hernandez et al.[4] The very granular data collection does however introduce greater potential for errors of transcription.

Finally, a formal power analysis was not performed to determine a sample size, although differences among AUCs for each of the scoring systems were identified. The reasons for a lack of power analysis were multiple, primarily because many of the outcomes measured had no prior ROC curves derived for reference; in addition, the ROC curves previously derived had variable AUCs.[4,20] Using the methods of Hajian-Tilaki[28] and considering our data, we would have been able detect differences in AUC as small as 0.05 for most comparisons and all differences less than 0.1.

CONCLUSIONS

All scoring systems we examined had predictive ability with respect to outcomes, although the Parkland grade performed better than AAST grade across a range of important outcomes. The ASST grade and Tokyo Guidelines performed equally, but neither performed well. Grading of acute cholecystitis has multiple applications, and improvements to the AAST grade would increase its applicability.

AUTHORSHIP

K.M.S. contributed in the study conception, study design, data acquisition, data interpretation, article drafting, and final revisions. R.O. contributed in the data acquisition, data interpretation, article drafting, and final revisions. M. Cripps contributed in the study conception, study design, data acquisition, and final revisions. K.K. contributed in the data acquisition, final revisions. L.T. contributed in the data acquisition and final revisions. H.M.K. contributed in the study conception, study design, data acquisition, and final revisions. M.E.H. contributed in the data acquisition and final revisions. R.P. contributed in the data acquisition and final revisions. J.M. contributed in the data acquisition and final revisions. T.J.S. contributed in the data acquisition and final revisions. J.R. contributed in the data acquisition and final revisions. D.C.C. contributed in the data acquisition and final revisions. L.M.C. contributed in the data acquisition and final revisions. T.M.E. contributed in the data acquisition and final revisions. R.S. contributed in the data acquisition and final revisions. B.Z. contributed in the data acquisition and final revisions. M. Crandall contributed in the study conception, study design, data acquisition, data interpretation, and final revisions.

DISCLOSURE

For all authors, no conflicts of interest are declared. The only funding for this study was from the AAST for the use of the multi-institutional data collection system.

REFERENCES

1. Scott JW, Olufajo OA, Brat GA, Rose JA, Zogg CK, Haider AH, Salim A, Havens JM. Use of national burden to define operative emergency general surgery. *JAMA Surg*. 2016;151(6):e160480.
2. Ogola GO, Gale SC, Haider A, Shafi S. The financial burden of emergency general surgery: national estimates 2010 to 2060. *J Trauma Acute Care Surg*. 2015;79:444–448.
3. Ogola GO, Shafi S. Cost of specific emergency general surgery diseases and factors associated with high-cost patients. *J Trauma Acute Care Surg*. 2016; 80:265–271.
4. Hernandez M, Murphy B, Aho JM, Haddad NN, Saleem H, Zeb M, Morris DS, Jenkins DH, Zielinski M. Validation of the AAST EGS acute cholecystitis grade and comparison with the Tokyo guidelines. *Surgery*. 2018;163:739–746.
5. Vera K, Pei KY, Schuster KM, Davis KA. Validation of a new American Association for the Surgery of Trauma (AAST) anatomic severity grading system for acute cholecystitis. *J Trauma Acute Care Surg*. 2018;84:650–654.
6. Rice CP, Vaishnavi KB, Chao C, Jupiter D, Schaeffer AB, Jenson WR, Griffin LW, Mileski WJ. Operative complications and economic outcomes of cholecystectomy for acute cholecystitis. *World J Gastroenterol*. 2019; 25:6916–6927.
7. Yokoe M, Hata J, Takada T, et al. Tokyo Guidelines 2018: diagnostic criteria and severity grading of acute cholecystitis (with videos). *J Hepatobiliary Pancreat Sci*. 2018;25(1):41–54.
8. Lien HH, Huang CC, Wang PC, Huang CS, Chen YH, Lin TL, Tsai MC. Changes in quality-of-life following laparoscopic cholecystectomy in adult patients with cholelithiasis. *J Gastrointest Surg*. 2010;14:126–130.
9. Wanjura V, Lundström P, Osterberg J, Rasmussen I, Karlson BM, Sandblom G. Gastrointestinal quality-of-life after cholecystectomy: indication predicts gastrointestinal symptoms and abdominal pain. *World J Surg*. 2014;38:3075–3081.
10. de Mestral C, Rotstein OD, Laupacis A, Hoch JS, Zagorski B, Alali AS, Nathens AB. Comparative operative outcomes of early and delayed cholecystectomy for acute cholecystitis: a population-based propensity score analysis. *Ann Surg*. 2014;259:10–15.
11. Gurusamy K, Samraj K, Gluud C, Wilson E, Davidson BR. Meta-analysis of randomized controlled trials on the safety and effectiveness of early versus delayed laparoscopic cholecystectomy for acute cholecystitis. *Br J Surg*. 2010;97:141–150.
12. Schuster K, Davis K, Hernandez M, Holena D, Salim A, Crandall M. American Association for the Surgery of Trauma emergency general surgery guidelines gap analysis. *J Trauma Acute Care Surg*. 2019;86:909–915.
13. Hirota M, Takada T, Kawarada Y, et al. Diagnostic criteria and severity assessment of acute cholecystitis: Tokyo Guidelines. *J Hepatobiliary Pancreat Surg*. 2007;14:78–82.
14. Yokoe M, Takada T, Strasberg SM, et al, Tokyo Guidelines Revision Committee. TG13 diagnostic criteria and severity grading of acute cholecystitis (with videos). *J Hepatobiliary Pancreat Sci*. 2013;20(1):35–46.
15. Tominaga GT, Staudenmayer KL, Shafi S, et al. The American Association for the Surgery of Trauma grading scale for 16 emergency general surgery conditions: disease-specific criteria characterizing anatomic severity grading. *J Trauma Acute Care Surg*. 2016;81:593–602.
16. Sugrue M, Sahebally SM, Ansaloni L, Zielinski MD. Grading operative findings at laparoscopic cholecystectomy — a new scoring system. *World J Emerg Surg*. 2015;10:14.
17. Madni TD, Leshikar DE, Minshall CT, et al. The Parkland grading scale for cholecystitis. *Am J Surg*. 2018;215:625–630.
18. Siada S, Jeffcoach D, Dirks RC, Wolfe MM, Kwok AM, Sue LP, Davis JW. A predictive grading scale for acute cholecystitis. *Trauma Surg Acute Care Open*. 2019;4:e000324.
19. Sugrue M, Coccolini F, Bucholc M, Johnston A, Contributors from WSES. Intra-operative gallbladder scoring predicts conversion of laparoscopic to open cholecystectomy: a WSES prospective collaborative study. *World J Emerg Surg*. 2019;14:12.
20. Madni TD, Nakonezny PA, Barrios E, et al. Prospective validation of the Parkland grading scale for cholecystitis. *Am J Surg*. 2019;217:90–97.
21. Madni TD, Nakonezny PA, Imran JB, et al. A comparison of cholecystitis grading scales. *J Trauma Acute Care Surg*. 2019;86:471–478.
22. Yokoe M, Takada T, Strasberg SM, et al. New diagnostic criteria and severity assessment of acute cholecystitis in revised Tokyo Guidelines. *J Hepatobiliary Pancreat Sci*. 2012;19:578–585.
23. Zhang Y, Tang N. Confidence intervals of the difference between areas under two ROC curves in matched-pair experiments. *Stat Med*. 2020;39(20): 2621–2638.
24. Davidson R, Mackinnon JG. *Estimation and Inference in Econometrics*. New York, NY: Oxford University; 1993.
25. Nandan AR, Bohnen JD, Sangji NF, et al. The Emergency Surgery Score (ESS) accurately predicts the occurrence of postoperative complications in emergency surgery patients. *J Trauma Acute Care Surg*. 2017;83:84–89.
26. Havens JM, Columbus AB, Seshadri AJ, Brown CVR, Tominaga GT, Mowery NT, Crandall M. Risk stratification tools in emergency general surgery. *Trauma Surg Acute Care Open*. 2018;3:e000160.
27. Joseph B, Jehan F, Dacey M, Kulvatunyou N, Khan M, Zeeshan M, Gries L, O'Keeffe T, Riall TS. Evaluating the relevance of the 2013 Tokyo Guidelines for the diagnosis and management of cholecystitis. *J Am Coll Surg*. 2018; 227:38–43.e1.
28. Hajian-Tilaki K. Sample size estimation in diagnostic test studies of biomedical informatics. *J Biomed Inform*. 2014;48:193–204.

DISCUSSION

ERIC A. TOSCHLOG, M.D. (Greenville, North Carolina): Thank you, Dr. Henry, members and guests. As always I would like to thank the American Association for the Surgery of Trauma for the opportunity to review what I think is a really excellent study. I would also like to thank Dr. Schuster and the authors for a timely and very well-written manuscript.

Dr. Schuster and colleagues at Yale have continued their very important work both assessing and attempting to validate scoring systems for acute cholecystitis. I have five questions. Seems like a lot but I promise they are concise.

First, with respect to the methodology, why did half of the centers identify operative findings at the time of surgery with the remainder abstracting findings from the operative reports? Did this subjectivity affect your analysis in any way?

Second, I think we can agree that a critical flaw in the AAST scoring system is the use of perforation as a diagnostic criteria in Grades III through V.

Your study as well as numerous other studies assessing the AAST scoring system notes a preponderance of patients as Grade II with really less than 10 percent of patients in most of the studies scattered within Grades I, III, IV, and V so in your manuscript you suggested moving perforation to Grade IV. I would suggest that perforation, even if included in a grading system, should be a Grade V and I would ask you to comment.

My third question relates to a very excellent presentation we heard earlier in this meeting noting the complications associated with the discharge of symptomatic cholelithiasis patients from the emergency department.

In the study by (indistinguishable) and colleagues at Fresno 20 percent of Grade I patients actually had SIRS and in any study there is a paucity of Tokyo Grade 0 patients.

At East Carolina we admit all of these patients and operate on them at 24 hours and I cannot recall a normal gall bladder at the time of surgery or normal pathology reports in this population.

So with your knowledge of the scoring systems, do we really think that symptomatic cholelithiasis exists? I, in fact, do not. And I think most of these patients or all of them have at least Grade I acute cholecystitis and some worse.

My fourth question relates to the fact that there may be limitations in all of these scoring systems. All the scoring systems, including the German, the Italian scoring systems have significant predictive limitations.

So do you think this is related to the fact that any variable within these scoring systems, from Murphy's sign to ultrasound findings, studied individually have either poor sensitivity or specificity and in some cases both?

Fifth is either the easiest or the hardest question so what is in or what should be in the Yale Scoring System for Acute Cholecystitis?

Again, I would like to thank the AAST for the privilege of reviewing this study and Dr. Schuster and colleagues for a really, really well-written manuscript. Thank you.

KEVIN M. SCHUSTER, M.D., M.P.H. (New Haven, Connecticut): Thank you, Dr. Henry and thank you Dr. Toschlog for reviewing our manuscript and mitigating some of the Zoom challenges by sending the questions in advance.

And let me – in atypical research fashion provide some transparency. The plan was initially to collect the Parkland Grade prospectively, which is how it was designed to be collected. Unfortunately, several of the centers didn't have the resources and chose to abstract the data from the operative reports.

This was actually somewhat serendipitous in that we were able to determine a somewhat lower predictive power when we took this approach and abstracted it from the operative reports retrospectively.

The other caveat is that the other centers may have used the prospective Parkland grade to inform the AAST grade which may have given the AAST grade an advantage and so it's hard to sort all of that out from the data but it's certainly a potential limitation.

About reclassifying perforation. Moving perforation to a IV or V would likely lead to a significant improvement in the scoring system. Clearly, we need to dig further into the data to determine the best way to adjust the scoring system, whether it's a IV or a V. It certainly needs to be moved up. That's the one thing that is absolutely clear.

And, as you also pointed out in one of your other questions, the individual findings of stand-alone measures will never be adequate, which is why I think the concept of the AAST grading scale is important in that it combines multiple measures simultaneously and hopefully we can improve upon it and make the best scoring system possible.

I think the best approach probably is to identify all the variables that are potentially collinear and eliminate those and then take the remaining variables to further refine the AAST scale.

I think we generally agree with respect to the existence of symptomatic cholelithiasis. I think the patients I see in the office who have intermittent right upper quadrant pain that has been recurring for a number of years and you take out their gall bladder and they feel better, I think those patients do have symptomatic cholelithiasis; but I think you are referring to a different group of patients whose pain is severe enough to present to the emergency department. And I agree, these patients likely have early acute cholecystitis.

Our approach, although not quite the same, is relatively similar in that we usually, if the patient can tolerate a diet, we will not admit them but will schedule them for surgery two or three days later to try and mitigate some of the costs of hospital admission and some of the challenges that it puts on the operating room to get a patient into the operating room urgently rather than electively within the next week. Although the approach is slightly different, I think overall the outcome is the same.

And then you asked about the Yale Scoring System. Hopefully further debate will follow the meeting and we will be able to use the data we collected to build upon the AAST grade.

Whether that means using the Parkland or similar system for the OR grade, moving perforation up, further modifications to the radiologic grade certainly needs to be thought about significantly, as you saw in the presentation.

Additionally each of the sub-portions of the AAST grade have poor predictive power alone and group the patients into a single grade for the most part so we need to spread those out and get better distributions. I think the best scenario is that we complete this through the Patient Assessment Committee of the AAST and further refine the scoring system.

In concluding I would like to, again, thank the AAST for the privilege of presenting and Dr. Toschlog for discussing the manuscript.

SHARON HENRY, M.D. (Baltimore, Maryland): Great. Great answers, Dr. Schuster. Thanks for that, being concise. I was wondering what do you think is missing or is there something missing from the AAST score? Or is it about reshuffling the components in a different way?

KEVIN M. SCHUSTER, M.D., M.P.H. (New Haven, Connecticut): So having looked at all these data we have that we collected – we collected a ton of granular data and that reflects on my coauthors from all the centers having done an immense amount of work to get all of that granular data.

And I can tell you from looking at all of that data, as Dr. Toschlog pointed out, each individual measurement does not add a whole lot.

I could be missing something but I can't come up with anything that we didn't collect with a potential for helping to predict the outcomes of these patients.

Therefore, I think it's going to be a matter of, unfortunately, reshuffling the deck a little bit and finding the things that, aren't collinear and including all of them in the system without, hopefully, making it too onerous for people to actually apply.