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Research article

External validation of the bedside score for the diagnosis of acute cholecystitis

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ABSTRACT

Objective: Acute cholecystitis usually presents with right upper quadrant (RUQ) abdominal pain. However, there are other conditions with similar findings which make the diagnosis difficult. The objective of this study is to prospectively validate the performance of the bedside score for the diagnosis of cholecystitis in patients presenting to the emergency department (ED) with possible acute cholecystitis.

Study design: We performed a prospective observational study of a convenience sample of patients with RUQ pain admitted to the ED of three academic hospitals. Symptoms (post prandial symptoms), physical signs (RUQ tenderness, murphy's sign) and ultrasound findings (Murphy's sign, gallstone, and gallbladder thickening) were scoring system items. The final diagnosis of cholecystitis was confirmed with a surgical pathology and/or discharge diagnosis of the patient in a 30-day follow-up. The treating physicians' clinical gestalt of acute cholecystitis was also assessed by 5-point Likert scale.

Results: One hundred thirty patients were followed up and were included in the analysis. 42 patients (32 %) had cholecystitis. The bedside clinical score of less than 4 had a sensitivity of 100 % (CI95 %: 91.60 %–100 %), negative predictive value (NPV) of 100 % (CI 95 %: 41.35 %–63 %), and negative likelihood ratio (-LR) of 0. Score of 6 and above had a specificity of 90.91 % (CI 95 %: 82.87 %–95.99 %), positive predictive value (PPV) of 83.67 % (CI 95 %: 72.55 %–90.86 %), and positive likelihood ratio (+LR) of 10.74 (CI95 %: 5.54–20.83). Physicians' clinical gestalt at the scale of 4 and 5 showed a specificity of 95.45 % (CI 95 %: 88.77 %–98.75 %), PPV of 90.91 % (CI 95 %: 79.29 %–96.31 %), and +LR of 20.95 (CI95 %: 8.02–54.71). At the same time at the scale of 1 and 2, the sensitivity was 95.24 % (CI 95 %: 83.84 %–99.42 %), NPV was 97.22 % (CI 95 %: 90.01 %–99.27 %), and the –LR was 0.06 (CI 95 %: 0.02–0.423). The area under the curve of bedside clinical score was not significantly higher than clinical gestalt (97.58 (CI 95 %: 95.31–99.85) vs. 95.37 (CI 95: 99.24–100))(p-value = 0.35)

Conclusion: This study showed while the bedside score would be helpful to rule out and rule in acute cholecystitis, physicians' gestalt had similar diagnostic performance.

1. Introduction

Acute cholecystitis usually presents with right upper quadrant (RUQ) abdominal pain [1,2]. It is estimated that approximately 20 million Americans are affected by acute cholelithiasis, which is about 7 % of men and 11 % of women [1,3]. However, RUQ pain is also

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a symptom of many other diseases such as hepatitis, peptic ulcer disease, liver abscess, pneumonia, and myocardial infarction [4,5]. Therefore, confirming the diagnosis of acute cholecystitis is difficult in many instances [6,7].

For the diagnosis of acute cholecystitis, hepatobiliary scintigraphy has been shown to be superior [8,9], but is rarely used as the initial diagnostic test for suspected cases because of time, cost, and limited availability. Therefore, ultrasonography is the most common initial imaging test in the evaluation of acute cholecystitis. However, the accuracy of ultrasonography alone is controversial [10–15], and its sensitivity ranges from 50 % to 95 % [16,17].

Tokyo 07 guideline (TG07), published in 2007, was the world's first diagnostic criteria for acute cholecystitis [18,19]. In the TG07, local signs (i.e. Murphy's sign, or RUQ mass/pain/tenderness), systemic signs (i.e. fever, elevated C- reactive protein (CRP), or leucocytosis), and imaging findings were used to facilitate the diagnosis [20]. The main problem with the TG07 was that it was difficult to use and vague. In 2013, the TG07 was updated to TG13 considering that definitive diagnosis was not possible in TG07 without positive imaging findings characteristic of acute cholecystitis along with local and systemic signs but in TG13, the probable diagnosis could be made without the presence of this criterion [21]. Moreover, in TG18 same diagnostic criteria as TG13 was suggested without any modification [24].

In 2019, Yeh and colleagues developed a practical bedside score (Table 1) for the diagnosis of cholecystitis and tested its accuracy against the TG13 [20]. Their bedside score had an accuracy equivalent to the TG13 without any need for laboratory testing [20]. The present study intended to externally validate the accuracy of this bedside clinical scoring system in patients with RUQ pain suspected of cholecystitis.

2. Methods

2.1. Study design and setting

This was a prospective observational cohort study performed at the emergency departments (EDs) of three tertiary-care, academic hospitals. The annual census of the centers was about 70,000 per year in each hospital and the study was conducted from March 2019 to September 2020. In the EDs, the patients were visited by emergency residents under the supervision of emergency physicians. We carried out this study to validate the performance of the bedside score for the diagnosis of acute cholecystitis.

The study protocol was approved by institutional review board at the centers Iran. Tehran University of Medical Sciences. Registration number 1397.367: (IR.TUMS.IKHC.REC.1397.367).

2.2. Participants

Similar to the original study [20], adult patients (age $\geq$18 years) presenting to the ED with RUQ abdominal pain were considered eligible. We excluded pregnant patients, patients who declined to consent, patients with prior cholecystostomy tube, patients with prior endoscopic retrograde cholangiopancreatography (ERCP) with sphincterotomy, patients with known diagnosis of cholecystitis who were transferred from another hospital, or patients who were directly admitted to the hospital (bypassing the ED).

2.3. Study protocol and measurements

All patients admitted to the EDs during the clinical shifts of one of the researchers (FM) who met the inclusion criteria were enrolled. The researcher was not directly involved in the treatment of the patients. After obtaining informed consent, FM screened the patients for any exclusion criteria.

As mentioned above, the therapeutic and diagnostic processes were performed under the supervision of treating physicians. All patients underwent abdominal sonography by a board-certified radiologist. Afterwards, all data including age, gender, contact detail, and bedside acute cholecystitis score items were extracted and recorded in a data collection sheet.

The treating physicians' clinical gestalt of acute cholecystitis was also assessed by 5-point Likert scale (Definitely (5), Probably (4), Possibly (3), Probably not (2), Definitely not (1)) by the researcher at the time of the ED admission before laboratory or imaging studies.

The final diagnosis was determined using patient follow up within 30 days of the index visit. To reduce miss-rate, if the first call failed, researchers made follow up phone calls in three consecutive days. The surgical pathology results of the patients who underwent cholecystectomy were used to confirm the diagnosis.

Table 1
Bedside acute cholecystitis score.

	Points
Post- prandial symptoms	1
RUQ tenderness	1
Murphy's sign	2
Gallbladder thickening	2
Gall stone	3
Total score	9

3. Outcome

Our primary outcome was the performance of the Yeh et al. [20] score for the diagnosis of cholecystitis. According to the previous publication, a bedside score of less than 4 indicates a low probability of acute cholecystitis and the patients who scored more than 6 have a high probability of acute cholecystitis. The performance of physicians' clinical gestalt for diagnosing cholecystitis was our secondary outcome. The gold standard for the cholecystitis diagnosis was the surgical pathology result of the patient who underwent cholecystectomy. A subgroup of patients who were managed conservatively by the surgical team and discharged with the diagnosis of acute cholecystitis was also followed after 30 days after the ED visit. This is done to ensure that the patient did have other diagnoses. This follow-up was also conducted for patients who were admitted or discharged with other diagnosis.

3.1. Statistical analysis

Normally distributed continuous variables were described as mean with standard deviation and categorical variables were presented as numbers (percentage). The categorical variables of included patients were tested for statistical significance using Pearson's chi-squared test or Fisher's exact test when appropriate. For testing of continuous variables, we used the student *t*-test. To calculate the diagnostic test performance, we used an online calculator (available at https://www.medcalc.org/calc/diagnostic_test.php). For sample size calculation, considering the prevalence of cholecystitis in the original study (18 %), 130 patients with and without cholecystitis were needed to achieve the sensitivity and specificity of 90 % and 81 %, respectively. Multivariable logistic regression analysis was used to compare the bedside scores and physicians' clinical gestalt in the optimal cut off value. We used the area under the receiver operating characteristic curve (AUC) for this purpose. The AUC can be interpreted as the proportion of discordant patient-pairs (where one member of the pair had the cholecystitis and the other did not), in which the patient with the cholecystitis had the higher predicted probability. We compared AUCs according to Delong et al. [23] In addition, sensitivity, specificity, positive and negative predictive (PPV and NPV), and positive and negative likelihood ratio (+LR and –LR) values with 95 % CI were reported by creating the two by two contingency tables. We reported the estimates along with the 95 % CI to compare the diagnostic characteristics of the models. For the clinical gestalt, 1 and 2 were considered low risk and used for calculation of sensitivity, NPV, and –LR and 4 and 5 were considered high risk and used for calculation of specificity, PPV, and +LR. Statistical significance was considered as a P-value of less than 0.05. We used SAS® OnDemand for Academics for the analysis.

4. Results

The flow chart of the participants in the study is demonstrated in Fig. 1.

The baseline characteristics of the patients are shown in Table 2. The average age of our patients was 50.26 ± 15.68 (Mean ± SD). Symptoms, physical signs, and ultrasound findings were assessed in both groups of patients (cholecystitis vs. non-cholecystitis group). While RUQ tenderness and postprandial symptoms were higher in patients with no acute cholecystitis, sonographic findings (Murphy's sign, US GB wall thickening > 3 mm, and gallstone) were more prevalent in the cholecystitis group with P value < 0.001.

Bedside clinical score of less than 4 had a sensitivity of 100 % (CI95 %: 91.60 %–100 %), NPV of 100 % (CI 95 %: 41.35 %–63 %), and -LR of 0 (Table 3). In comparison, a score of 6 and above had a specificity of 90.91 % (CI 95 %: 82.87 %–95.99 %), PPV of 83.67 % (CI 95 %: 72.55 %–90.86 %), and +LR of 10.74 (CI95 %: 5.54–20.83). Physicians' clinical gestalt was also assessed. While no patient with the score of 2 and 3 on the Likert's scale had the outcome, 2 (4.9 %) patients with the score of 1 diagnosed with cholecystitis. 11

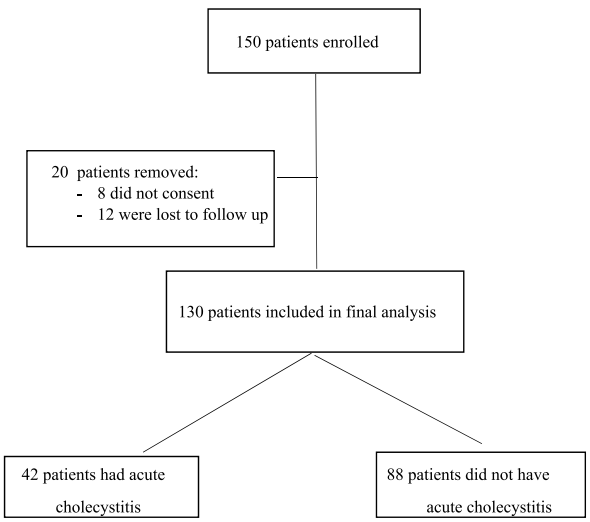

Figure-1. Participants flow diagram.

Table-2
Baseline characteristics of the patients.

Characteristics	All N (%)	Acute Cholecystitis N (%)	No acute cholecystitis N (%)	P value
Number of patients	130	42 (32.3)	88 (67.7)	–
Age (Mean ± SD)	50.25 ± 15.68	49.58 ± 15.62	50.57 ± 15.78	0.74
Sex Male	50 (38.5)	12 (28.6)	68 (77.3)	0.11
Post prandial symptoms	127 (97.7)	42 (33)	85 (67)	0.55[a]
RUQ tenderness	120 (92.3)	42 (35)	78 (65)	0.3[a]
Morphy's sign (US or Clinical)	53 (40.8)	41 (77.3)	12 (22.7)	<0.001[a]
US GB wall thickening > 3 mm	46 (35.4)	39 (84.8)	7 (15.2)	<0.001[a]
US gallstone	76 (58.5)	42 (55.3)	34 (44.7)	<0.001[a]

[a] Fisher's exact test, RUQ = right upper quadrant, US = ultrasound, GB = gallbladder.

and 33 patients were stratified to 4 and 5, respectively. Of these population, 3 (27.3 %) and 1 (3 %) had the outcome, respectively. The scale of 4 and 5, it showed a specificity of 95.45 % (CI 95 %: 88.77 %–98.75 %), PPV of 90.91 % (CI 95 %: 79.29 %–96.31 %), and +LR of 20.95 (CI95 %: 8.02–54.71). At the same time at the scale of 1 and 2, the sensitivity was 95.24 % (CI 95 %: 83.84 %–99.42 %), NPV was 97.22 % (CI 95 %: 90.01 %–99.27 %), and the –LR was 0.06 (CI 95 %: 0.02–0.423) (Table 3).

As mentioned above, we generated a Receiver Operating Characteristic curve to compare the overall diagnostic performance of physician clinical gestalt and bedside clinical score system in acute cholecystitis. The AUC of bedside clinical score was higher than clinical gestalt (97.58 (CI 95 %: 95.31–99.85) vs. 95.37 (CI 95: 99.24–100)). However, the difference did not reach statistical significance. (p-value = 0.35) (Fig. 2)

5. Discussion

In this study, the external validity of the clinical scoring system in the diagnosis of acute cholecystitis in patients with RUQ pain was evaluated. We considered clinical signs and imaging findings to obtain the overall accuracy of this bedside scoring system which was 93.08 %. Patients with a score <4 had a sensitivity of 100 % and a score of ≥6 had a specificity of 90.91 %. Findings also revealed that physician clinical gestalt would perform similarly.

In this study, the incidence of acute cholecystitis was 32.2 % among our patients which was higher in comparison to the Yeh et al. cohort study (18 %) [20]. A possible explanation for this finding was the characteristics of the centers; our study took place in three tertiary-care academic hospitals which were among the largest medical centers in the country.

Laboratory findings were considered as diagnostic criteria for acute cholecystitis in both Tokyo guidelines (TG07 and TG13), however, these findings have no place in this new scoring system created by Yeh and his colleagues [20]. Probably the Yeh et al. [20] scoring system helps with a decrease in length of stay in hospital, less medical costs, and fewer adverse effects for the patients presenting to the ED with RUQ pain by using ultrasound and without requiring laboratory testing [24].

In our study, the bedside clinical score of ≥6 had 90.91 % specificity for acute cholecystitis; however, in another external validation by Graglia et al. [25], a score of ≥7 with 95.7 % specificity was considered for ruling in the patients with the same scoring system. Additionally, Graglia et al. have mentioned [21] a low bedside score of <2 with 100 % sensitivity for ruling out the patients with the complaint of right upper abdominal pain. While previous external validation study by Yeh et al. [20], proposed results that were the same as ours, considering the cut off of <4 with a NPV of 98 % (100 % NPV in our study) for ruling out the patients with RUQ pain. Therefore, this bedside score might be valuable in ruling out acute cholecystitis.

We also measured the +LR for different scores of this bedside score. This index for score of 6 and above was 10.74 (95 % CI

Table-3
Indicators related to clinical rule according to Scale score and Physician clinical gestalt.

Scale score/ Physician gestalt		Sensitivity (95 % CI)	Specificity)95 % CI(	Positive Predictive Value)95 % CI(	Negative Predictive Value)95 % CI(	Positive Likelihood Ratio)95 % CI(	Negative Likelihood Ratio)95 % CI(	Accuracy)95 %CI(
bedside clinical score	<4	100.00 % (91.60–100)	52.27 %)41.35–63 (	50.00 %)44.56–55.44 (	100.00 %	2.1 %)1.68–2.61 (	0.00	67.7)58.93–75.63 (
	4–5	100.00 % (91.60–100)	52.27 % (41.35–63)	50.00 % (44.56–55.44)	100.00 %	2.10 (1.68–2.61)	0.00	
	≥6	97.62 %)87.43–99.94 (	90.91 %)82.87–95.99 (	83.67 %)72.55–90.86 (	98.77 %)92.01–99.82 (	10.74)5.54–20.83 (	0.03)0.00–0.18 (	93.08)87.26–96.79 (
Clinical Gestalt		95.24 % (83.84–99.42)*	95.45 % (88.77–98.75)†	90.91 % (79.29–96.31) †	97.22 % (90.01–99.27)*	20.95 (8.02–54.71) †	0.06 (0.02–0.23)*	–

CI= Confidence Interval, *: for the 1 and 2 on the scale of 0–5, †: for the 4 and 5 on the scale of 0–5.

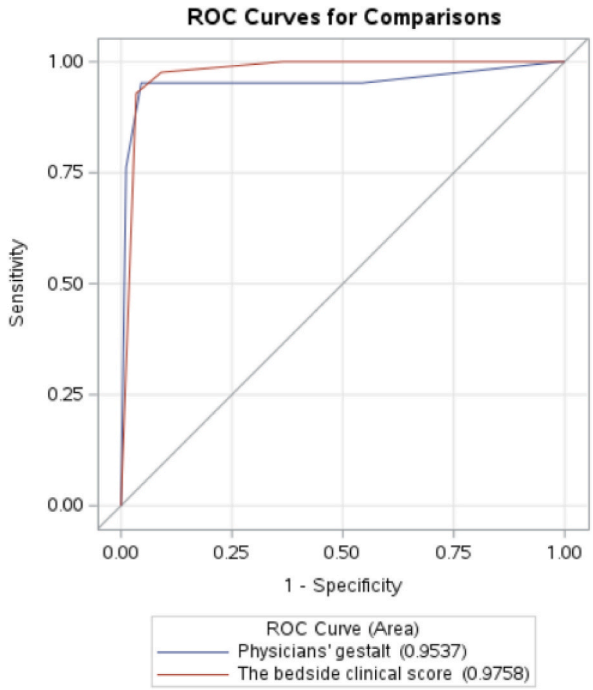

Figure-2. Receiver operating characteristics of gestalt and bedside clinical score.

5.54–20.83). Although the CI lower bound was below ten, it can be considered as a good tool for ruling in acute cholecystitis. However, Graglia et al. mentioned a +LR of 10.40 (95 % CI 4.09–26.40) for score of the 7 and above [21].

Moreover, in our study physicians' gestalt of acute cholecystitis was also measured by using 5-point Likert scale for the first time. The physicians' gestalt was not assessed in previous studies by Yeh et al. [20] and Graglia et al. [21] and was not even mentioned in previous TG-7, TG13 and TG-18 guidelines [20,22]. The specificity of 95.45 % and sensitivity of 95.24 % were obtained. Although the specificity of physicians' gestalt was high in comparison to our bedside scoring system (score $\geq$6), the AUC of bedside clinical score was higher. Eventually, the difference did not reach statistical significance.

In TG-13 guidelines [20], radiologic imaging findings (e.g. US, CT scan, or even MRI) were all used for making the diagnosis of cholecystitis. These imaging modalities might be sophisticated, time-consuming, or have radiation exposure. Even ultrasonography findings compatible with the diagnosis are operator-dependent and sometimes yield conflicting findings for diagnosis. In contrast, the rule incorporates three ultrasound findings gallstones, gallbladder thickening, Murphy's sign) which makes it easier to apply and less prone to detection differences by technicians. Furthermore, it can be conducted at the bedside. Using point-of-care ultrasound (POCUS) enables us to make an immediate decision as shown in Glaria et al. study [25].

Therefore, according to the results of this study and the previous validation study [25] the bedside scoring system would be more practical and convenient in comparison to TG-13 for ruling in/out acute cholecystitis.

6. Limitations

There are some limitations to this study. Firstly, although all the patients in the researcher's shift were approached, there is a risk of sampling bias due to convenience sampling. Secondly, the interrater reliability of the rule was not assessed as all the patients were evaluated by one researcher. Finally, although we followed patients with conservative or delayed surgical treatment for acute cholecystitis for 30 days, they had different clinical management.

7. Conclusion

While the bedside score would be helpful to rule out and rule in acute cholecystitis, physicians' gestalt had similar diagnostic performance.

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N/A.

CRediT authorship contribution statement

Fatemeh Mahmoudzadeh: Writing – original draft, Visualization. **Atousa Akhgar:** Writing – review & editing, Visualization, Project administration. **Hadi Mirfazaelian:** Writing – review & editing, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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