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Performance of a Diagnostic Score in Confirming Acute Cholecystitis Among Patients With Acute Abdominal Pain

MAARET ESKELINEN[1*], JANNICA MEKLIN[1*], KARI SYRJÄNEN[2,3] and MATTI ESKELINEN[1]

[1]*Department of Surgery, Kuopio University Hospital and School of Medicine, University of Eastern Finland, Kuopio, Finland;*
[2]*Molecular Oncology Research Center, Barretos Cancer Hospital, Barretos, Brazil;*
[3]*SMW Consultants, Ltd., Kaarina, Finland*

Abstract. *Background/Aim: Although acute cholecystitis (AC) is quite a frequent clinical cause of acute abdominal pain (AAP), the accuracy of a diagnostic score (DS) in confirming AC is rarely considered. The aim of the study was to conduct a detailed analysis comparing the accuracy of common clinical findings, laboratory tests and DS in AC diagnosis. Patients and Methods: A cohort of 1,333 patients presenting with AAP were included in the study. The clinical history and diagnostic symptoms (n= 21), signs (n=14) and laboratory tests (n=3) were recorded in each patient. Results: The significant independent diagnostic predictors (disclosed by multivariate logistic regression model) were used to construct the DS formulas for AC diagnosis. These formulas were tested at five different cut-off levels to establish the most optimal diagnostic performance for clinically confirmed AC. In the ROC comparison test, there was no statistically significant difference in the AUC values of i) clinical history and symptoms (AUC=0.542), and ii) signs & laboratory tests (AUC=0.580), whereas both were significantly inferior (p=0.0001) to the AUC value of the DS (AUC=0.962). Conclusion: In the diagnosis of clinically confirmed AC, the DS formula is superior to clinical symptoms and signs, justifying the use of DS as an integral part of the diagnostic algorithm of AC in all patients presenting with AAP.*

*These Authors contributed equally to this study.

Correspondence to: Matti Eskelinen, MD, Ph.D., School of Medicine, University of Eastern Finland, P.O. Box 100, FI-70029 KYS, Finland. Tel: +358 17173311, Fax: +358 17172611, GSM: +358 400969444, e-mail: matti.eskelinen@kuh.fi

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Gallstone disease (GSD) is common in the Western population and its prevalence is increasing due to obesity and aging of the population. A third of GSD patients will develop acute cholecystitis (AC) (1, 2). After acute appendicitis, AC is the second most common cause of acute surgical abdomen in the Western countries (1, 2). Over 90% of AC cases result from obstruction of the cystic duct by gallstones. Cystic duct obstruction leads to increased intraluminal pressure inside the gallbladder and triggers an acute inflammatory response.

During the past decades, some attempts have been made to use standardised questionnaires in order to improve the diagnostic accuracy of AC. Chen *et al*. (3) used gallstones condition-specific questionnaire (CSQ) and suggested that it could help doctors in diagnostic decisions. According to common practice, the diagnosis of AC is performed by history taking, physical examination and ultrasonography (US). In unequivocal or difficult cases, computer tomography (CT) or magnetic resonance cholangio-pancreatography (MRCP) could be performed to confirm the diagnosis (4).

Diagnostic score (DS) systems for AC have been suggested by Japanese Society of Gastroenterology (4) and American Association for the Surgery of Trauma (AAST) (5). The AAST grading system has been proposed for use in research as well as in clinical settings. Despite several DS studies in acute abdominal pain (AAP) (6, 7), the diagnostic performance of DS in the diagnosis of AC among AAP patients has not been previously studied.

In our recent studies, we have analysed the diagnostic accuracy of DS in distinguishing acute appendicitis (AA) from nonspecific abdominal pain (NSAP) as well as the potential gender-specificity of DS in confirming AA (6, 7). Prompted by the frequency of AC among AAP patients and the lack of diagnostic performance studies on DS in AC, we designed the present study to assess the relative accuracy of i) a detailed history taking, ii) clinical examination and

Table I. *The clinical history of patients with acute cholecystitis versus other diagnoses of acute abdominal pain.*

Clinical history variable	Positive endpoint	Negative endpoint	TP	FN	FP	TN
1. Location of initial pain	Upper right quadrant of abdomen	Other quadrants of abdomen	101	24	361	847
2. Location of pain at diagnosis	Upper right quadrant of abdomen	Other quadrants of abdomen	70	55	50	1158
3. Duration of pain	>4 h	≤4 h	58	67	329	879
4. Intensity of abdominal pain	Subjectively intolerable pain	Weak or moderate pain	99	26	1,018	190
5. Progression of pain	Subjectively same	Weaker or worse pain than at the onset	56	69	445	763
6. Type of pain	Subjectively steady or colicky pain	Intermittent pain	118	7	1031	177
7. Aggravating factors	Movement, coughing, respiration, food or other	No aggravating factors	30	95	326	882
8. Relieving factors	Vomiting, lying still or other factors	Food, antacids or no relieving factors	77	48	715	493
9. Previous similar pain	No	Yes	54	71	818	376
10. Vertigo	No	Yes	122	3	1,167	37
11. Nausea	Yes	No	39	86	528	680
12. Vomiting	Yes	No	50	75	713	495
13. Appetite	No appetite	Normal appetite	19	106	337	871
14. Previous indigestion	No	Yes	76	49	976	230
15. Jaundice	Yes	No	17	108	16	1,192
16. Bowels	Constipation or diarrhea	Blood, mucus, white or normal stools	26	99	269	939
17. Micturition	Normal	Abnormal	112	13	1,135	73
18. Drugs for abdominal pain	No	Yes	120	5	1,158	49
19. Previous abdominal surgery	Yes	No	42	83	291	916
20. Previous abdominal diseases	No	Yes	94	31	1,004	203
21. Use of alcohol	No	Yes	119	6	1,146	62

laboratory testing, and iii) the DS in detecting clinically confirmed AC among patients with AAP.

Patients and Methods

Criteria for inclusion in this study and diagnostic criteria were those set forth by the Research Committee of the World Organization of Gastroenterology (OMGE) (6-9). Included in the present study were 636 men (47.7%) and 697 women (52.3%) with a mean age (±SD) of 38.0±22.1 years.

The examination of clinical symptoms, signs and relevant laboratory tests were conducted using a standard technique and the results were graded positive or negative as previously described (6, 7, 9) (Tables I and II). The diagnosis of AC was done by considering all symptoms, signs and results of the laboratory tests weighted against the accepted diagnostic criteria of AC (4, 8).

Identifying the DS models. As the first step in constructing the DS, a multivariate logistic (stepwise) regression analysis (SPSS Statistics 26.0.0.1; IBM, NY, USA) was performed to disclose the variables with an independent predictive value. All the variables presented in Tables I and II were included in the analysis as binary data *e.g.* AC=1 and other diagnosis of AAP=0. Using the coefficients of the regression model, a DS was built and its predictive value for AC was studied. The coefficient of the multivariate analysis shows the relative risk (RR=e_, n=β) of a patient with a given symptom or sign to have AC.

The DS formula for AC. The DS formula for AC (Table III), showing the highest diagnostic performance for AC in hierarchical receiver operating characteristic (HSROC) analysis is as follows: DS=0.89 × location of initial pain (positive endpoint=1, negative endpoint=0) + 0.74 × previous similar pain (positive endpoint=1, negative endpoint=0) + 0.75 × vomiting (positive endpoint=1, negative endpoint=0) – 1.01 × micturition (positive endpoint=1, negative endpoint=0) + 2.02 × jaundice (positive endpoint=1, negative endpoint=0) + 2.77 × tenderness (positive endpoint=1, negative endpoint=0) + 2.48 × Murphy's sign (positive endpoint=1, negative endpoint=0) + 2.19 × rectal digital tenderness (positive endpoint=1, negative endpoint=0) – 6.13. The mean (SD) of the DS values for AAP (n=1293) was 2.150 (2.30) (Table III).

Statistical analysis. All other statistical analyses were performed using STATA/SE version 16.1 (StataCorp, College Station, TX, USA). Statistical tests presented were two-sided, and p-value <0.05 was considered statistically significant. Using 2×2 tables, we calculated sensitivity (Se) and specificity (Sp) with 95% confidence intervals (95%CI) for each symptom, sign or laboratory test, and created separate forest plots for showing each set of data, separately for each diagnostic variable. We calculated the summary estimates of Se and Sp, positive likelihood ratio (LR+) and negative likelihood ratio (LR-) and diagnostic odds ratio (DOR), using a random effect bivariate model and fitted the summary HSROC curves, including all diagnostic variables in the DS model, using the AC endpoint.

Using the STATA's prediction tool, we also made posterior predictions [Empirical Bayes (EB) estimates] of the Se and Sp for each diagnostic variable in AC patients, including the different DS cut-offs. Analogous to its use in the meta-analysis, EB estimates give the best estimates of the true Se and Sp for each diagnostic variable, the variable-specific point estimates usually shrinking toward the summary point of the HSROC. We explored the statistical

Table II. *The clinical signs and investigations of patients with acute cholecystitis versus other diagnoses of acute abdominal pain.*

Clinical signs and investigations	Positive endpoint	Negative endpoint	TP	FN	FP	TN
1. Mood	Distressed or anxious	Normal	28	97	199	1,009
2. Colour	Normal, jaundiced	Flushed, pale or cyanosed	117	8	1,087	121
3. Abdominal movement	Normal	Poor/nil	16	108	77	1,131
4. Scar	No	Yes	78	46	908	300
5. Distension	No	Yes	111	13	1125	80
6. Tenderness	Right upper quadrant of abdomen	Other quadrants of abdomen	94	31	60	1,148
7. Mass	No	Yes	105	20	1,094	14
8. Rebound	Yes	No	60	65	571	637
9. Guarding	Yes	No	37	88	589	619
10. Rigidity	Yes	No	82	43	956	251
11. Murphy's positive	Yes	No	77	48	47	1,160
12. Bowel sounds	Normal	Abnormal	110	15	1,034	174
13. Renal tenderness	No	Yes	76	49	896	312
14. Rectal digital tenderness	Normal	Abnormal	121	4	848	357
15. Body temperature	>37.0˚C	≤37.0˚C	74	46	558	554
16. Leucocyte count (LC)	>10000/mm^3	≤10000/mm^3	57	48	559	417
17. Urine	Normal	Haematuria or bacteriuria	110	0	986	72

Table III. *Diagnostic score for acute cholecystitis shown at five different cut-off levels of symptoms, signs and tests. Cut-off levels: DS I=4.0, DS II=4.4, DS III=4.7, DS IV=4.85, DS V=5.0.*

Diagnostic score (DS)	Positive endpoint	Negative endpoint	TP	FN	FP	TN
1. Logistic model DS I	Cholecystitis	Other diagnosis of acute abdominal pain	110	15	82	1,090
2. Logistic model DS II	Cholecystitis	Other diagnosis of acute abdominal pain	109	16	75	1,097
3. Logistic model DS III	Cholecystitis	Other diagnosis of acute abdominal pain	107	18	64	1,108
4. Logistic model DS IV	Cholecystitis	Other diagnosis of acute abdominal pain	106	19	59	1,113
5. Logistic model DS V	Cholecystitis	Other diagnosis of acute abdominal pain	102	23	56	1,116

*Logistic regression analysis formula for DS: 0.89 × location of initial pain (positive endpoint=1, negative endpoint=0) + 0.74 × previous similar pain (positive endpoint=1, negative endpoint=0) + 0.75 × vomiting (positive endpoint=1, negative endpoint=0) – 1.01 × micturition (positive endpoint=1, negative endpoint=0) + 2.02 × jaundice (positive endpoint=1, negative endpoint=0) + 2.77 × tenderness (positive endpoint=1, negative endpoint=0) + 2.48 × Murphy's sign (positive endpoint=1, negative endpoint=0) + 2.19 × rectal digital tenderness (positive endpoint=1, negative endpoint=0) – 6.13.

heterogeneity between diagnostic variables and DS models through visual examination of the forest plots and the HSROC curves.

Results

Diagnostic performance of the symptoms. The pooled overall Se of the diagnostic symptoms in confirming AC was 59% (95%CI=45%-73%) (Figure 1). Se exceeded 59% for 10 diagnostic symptoms, and the best five diagnostic symptoms (vertigo, drugs for abdominal pain, use of alcohol, type of pain and micturition) showed 90-98% Se in the diagnosis of AC (Figure 1). The pooled overall Sp of the diagnostic symptoms for detecting AC was 44% (95%CI=28-61%) (Figure 2). Ten diagnostic symptoms showed Sp higher than 44%, whereas the best five diagnostic symptoms in the diagnosis of AC (jaundice, location of pain at diagnosis, bowels, previous abdominal surgery and duration of pain) showed a Sp varying between 73-99% (Figure 2).

Diagnostic performance of the signs and tests. The pooled overall Se of the diagnostic signs and tests for detecting AC was 68% (95%CI=53-81%) (Figure 3), while seven diagnostic signs and tests had Se exceeding 68%. The five most accurate diagnostic signs and tests (urine, rectal digital tenderness, colour, distension and bowel sounds) showed Se in the range of 88-100% (Figure 3). The pooled overall Sp of the signs and tests was only 41% (95%CI=23-60%) (Figure 4), and eight diagnostic signs and tests showed Sp higher than 41%. The five most accurate diagnostic signs and tests (Murphy's positive, tenderness, abdominal movement, mood and rebound) had Sp of 53-96% (Figure 4).

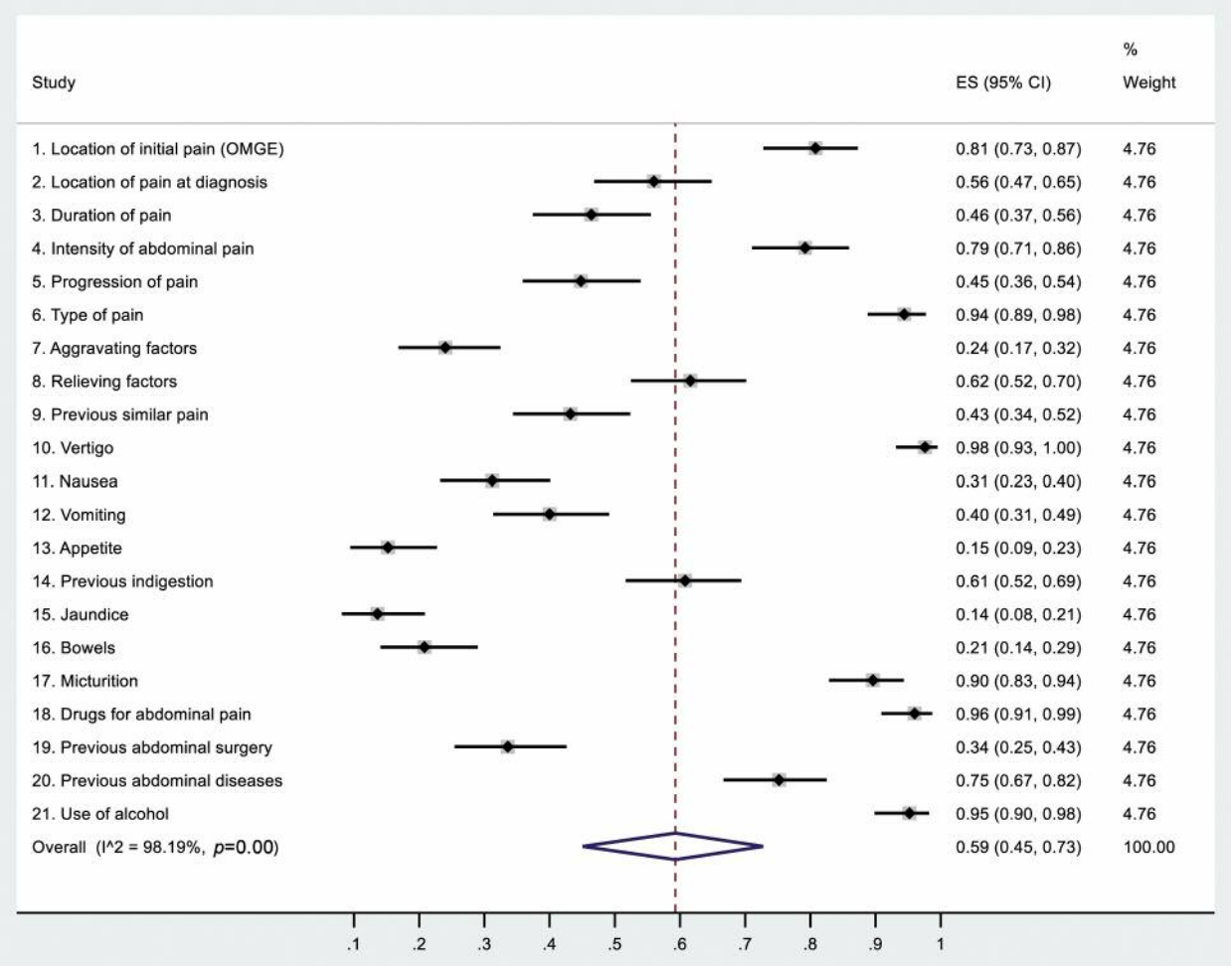

Figure 1. *Pooled sensitivities of the clinical symptoms in acute cholecystitis (random-effects model). ES: Estimated sensitivity; CI: confidence interval.*

Diagnostic performance of the DS formulas. The pooled overall Se of the DS formulas for detecting AC was 86% (95%CI=83-88%). The best three DS models (DS I, DS II and DS III) had Se within a narrow range of 86-88% (Figure 5). The pooled overall Sp of the DS formulas for confirming AC was 94% (95%CI=93-95%), with the best three DS models (DS III, DS IV and DS V) reaching a Sp of 95% (Figure 6).

HSROC analyses and empirical Bayes (EB) estimates. STATA (metandiplot algorithm) was used to draw the HSROC curves and EB estimates to visualise the comparison of the pooled overall diagnostic performance of the different symptoms, signs, tests and the DS formulas in the diagnosis of AC (Figures 7, 8 and 9). Based on comparisons of the HSROC AUC values, i) the common clinical findings, as well as ii) signs and tests, were significantly inferior to iii) the AUC values reached by the DS formulas as follows: between Figure 7 (AUC=0.542, 95%CI=0.520-0.562) and Figure 8 (AUC=0.580, 95%CI=0.540-0.621) p=0.611 (ROC comparison test); between Figure 7 (see above) and Figure 9 (AUC=0.962, 95%CI=0.950-0.974), p=0.0001; between Figure 8 and Figure 9, the difference is also highly significant (p=0.0001).

Discussion

Although, gallstones are the most common cause of AC, the clinical picture of AC may vary within a patient population. AC occurs as a result of cystic duct obstruction and gall bladder mucosa damage by mechanical mural irritation by gallstones, which leads to the release of phospholipases from the mucosa cells (1, 2). Phospholipases catalyse the production of lysolecithin, which irritates the gallbladder epithelium and leads to oedema and epithelial vascular insufficiency (1, 2).

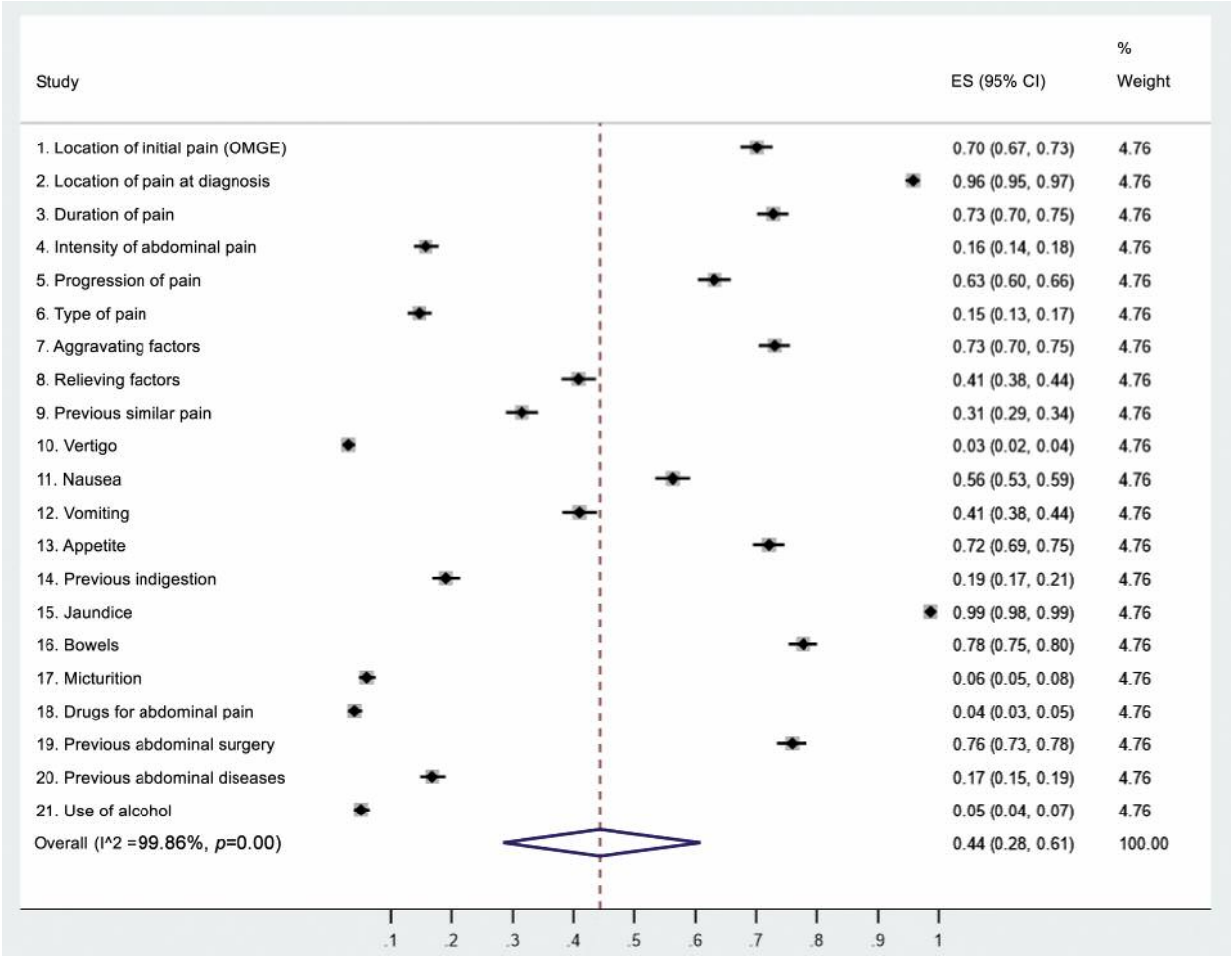

Figure 2. *Pooled specificities of the clinical symptoms in acute cholecystitis (random-effects model). ES: Estimated specificity; CI: confidence interval.*

The diagnosis of AC is traditionally made on the basis of common clinical findings, supported by signs and lab tests and confirmed with an US. Clinical findings of AC include right upper quadrant pain and tenderness, Murphy's sign, nausea, vomiting, fever and poor appetite. The differential diagnosis of AC among AAP patients can be difficult and may include several different diseases (6, 7, 9-11). There is no specific laboratory test for the diagnosis of AC, but the high leucocyte count might support the AC diagnosis, albeit the Se and Sp are not particularly high as confirmed in the present series; 54% and 43%, respectively.

Although several different DS systems are available for AAP diagnosis (6, 7), some guidelines suggest DS to improve the diagnosis of AAP (6, 7), and international guidelines cautiously recommend a DS-supported severity grading to improve the clinical management of AC (4, 5). A debate continues on the shortcomings of the specific DS models in sorting out AAP patients. Although AC is a common cause of AAP, the accuracy of DS in the diagnosis of AC has not been critically evaluated. To cast further light on this issue, the present study was designed to conduct a detailed analysis on the relative accuracy of i) the common clinical findings, ii) signs and tests, as compared with iii) the DS, to establish whether the DS could improve the diagnostic accuracy of AC.

Previous studies with a design similar to ours are scanty. Vera *et al*. (5) included 350 patients with AC in a retrospective cohort study and investigated concordance between the AAST grade and outcome of AC patients. Higher scores of AAST were independently associated with some clinical outcomes in AC patients, however, no significant differences in clinical outcome were shown between the AAST grade 1 and 2 AC patients. Authors concluded that current AAST scoring needs validation with larger patient cohorts (5). Yacoub *et al*. (12) attempted to identify preoperative predictors of AC patients

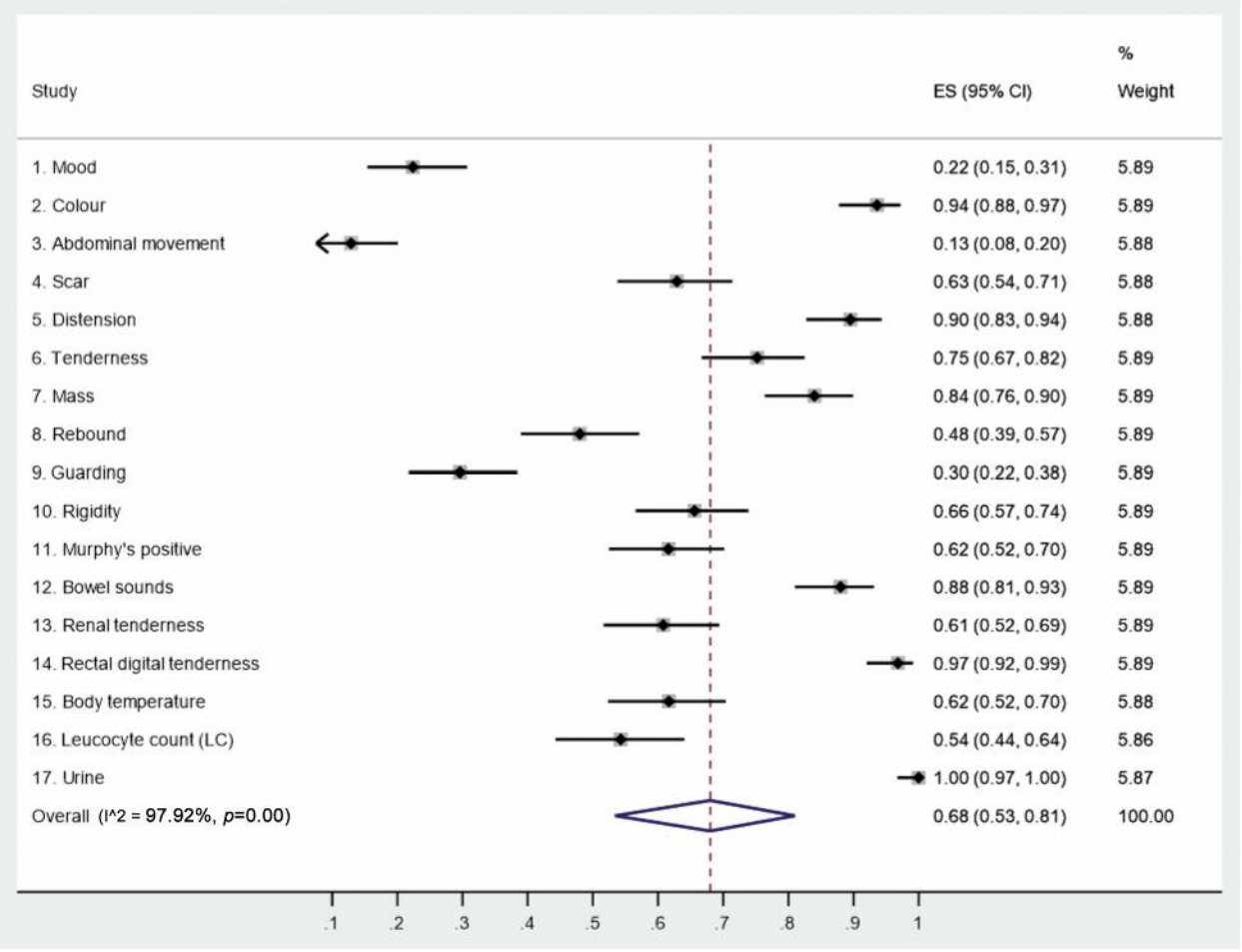

Figure 3. *Pooled sensitivities of the clinical signs and tests in acute cholecystitis (random-effects model). ES: Estimated sensitivity; CI: confidence interval.*

and to develop a DS for AC patients. They calculated retrospectively a DS for 245 patients based on 5 independent variables. After regression analysis, the five independent variables were; gender (male), leucocyte count (>13 000/mm^3), heart rate (>90 bpm), gallbladder wall thickness in US (>4.5 mm) and age (>45 years). Authors concluded that DS could help in the severity grading of AC patients, but they failed to demonstrate any AUC values based on ROC analysis. Ambe *et al*. (13) investigated a retrospective cohort of patients undergoing laparoscopic cholecystectomy and tried to grade the severity of AC with a DS. According to these authors, a DS has a potential to select AC patients with severe disease, but they concluded that their DS system needs to be validated prospectively (13). Finally, Gouveia *et al*. (14) evaluated the diagnostic performance of a DS in AC patients with common bile duct stones (CBDS), examining 40 patients with a clinical or US suspicion of CBDS. These data indicated that the American Society for Gastrointestinal Endoscopy (ASGE) score was not useful for diagnosing CBDS patients with AC and they suggested that the ASGE score should not be used in patients with CBDS (14).

Of interest was to compare the diagnostic performance of the symptoms, signs and tests among the AC patients to those of the AA patients, reported in our recent study (7), to see whether the diagnostic accuracy of common clinical findings differs in AA and AC patients. Indeed, this seems to be the case in that the pooled Se of the diagnostic symptoms in detecting AA (80%; 95%CI=67-90%) was substantially higher than that in detecting AC; (59%; 95%CI=45-73%). However, the pooled overall Sp of the diagnostic symptoms in the diagnosis of AA was lower than that in detecting AC; 30% (95%CI=19-42%) and 44% (95%CI=28-61%), respectively. Similarly, the pooled overall Se of the diagnostic signs and tests in the diagnosis of AA was significantly higher than that for AC; 86% (95%CI=79-92%) and 68% (95%CI=53-81%), respectively. As anticipated,

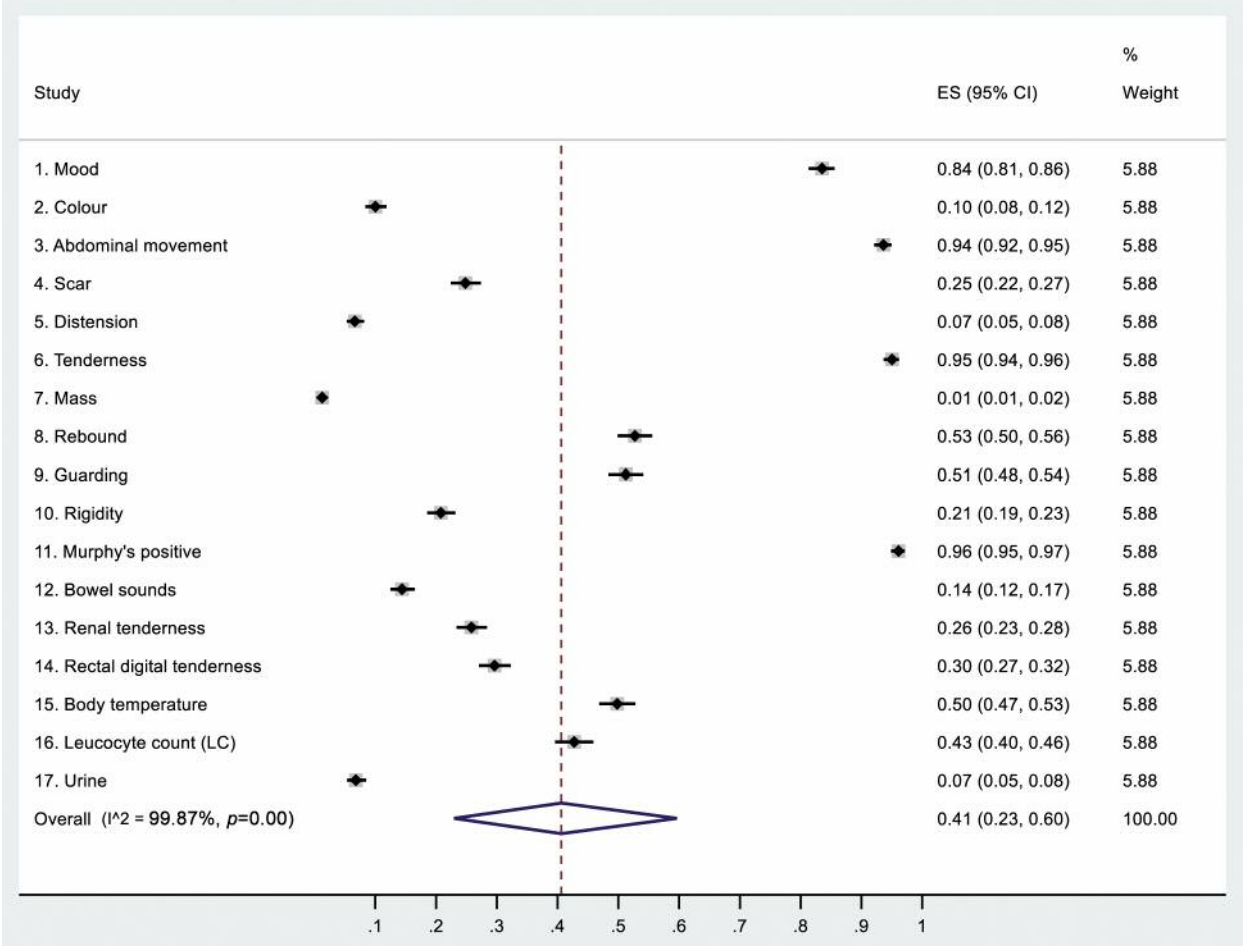

Figure 4. *Pooled specificities of the clinical signs and tests in acute cholecystitis (random-effects model). ES: Estimated specificity; CI: confidence interval.*

however, the pooled overall Sp of the diagnostic signs and tests for AA was lower than that in detecting AC; 34% (95%CI=20-50%) *versus* 41% (95%CI=23-60%).

When the same comparisons were calculated for the diagnostic accuracy of the DS formulas between AA and AC patients, the trend was similar. Indeed, the pooled Se of the DS formulas was higher in detecting AA than AC: 91% (95%CI=87-95%) and 86% (95%CI=83-88%), respectively. Because Se and Sp behave reciprocally, it was not unexpected to find that the pooled overall Sp of the DS was lower for AA than for AC; 84% (95%CI=75-92%) and 94% (95%CI=93-95%), respectively.

AUC values based on the SROC comparison test showed that diagnostic performance of the clinical signs and tests is slightly better than that of the clinical symptoms, although the difference was not significant. However, the AUC value based on the DS formula is superior to AUC values based on symptoms and signs. A reader might consider that a lack of US is a possible limitation of the present study. However, even with US and inflammatory markers it may be impossible to reach a higher diagnostic accuracy than the 96% AUC (Se/Sp balance) for the DS in AC diagnosis found in this study. Although we could not perform comparisons to previous clinical studies, because the only DS study on AC patients is still unclosed and not analysed (15), the present study is the first to provide data that the DS could be used for the clinical diagnosis of AC among patients presenting with AAP. One of the major advantages of our DS is that this formula does not need US or LC analyses to reach a high diagnostic accuracy in AC.

Conclusion

Taken together, our novel DS formula, constructed by including the significant independent predictors disclosed by a multivariate analysis, reached very high diagnostic

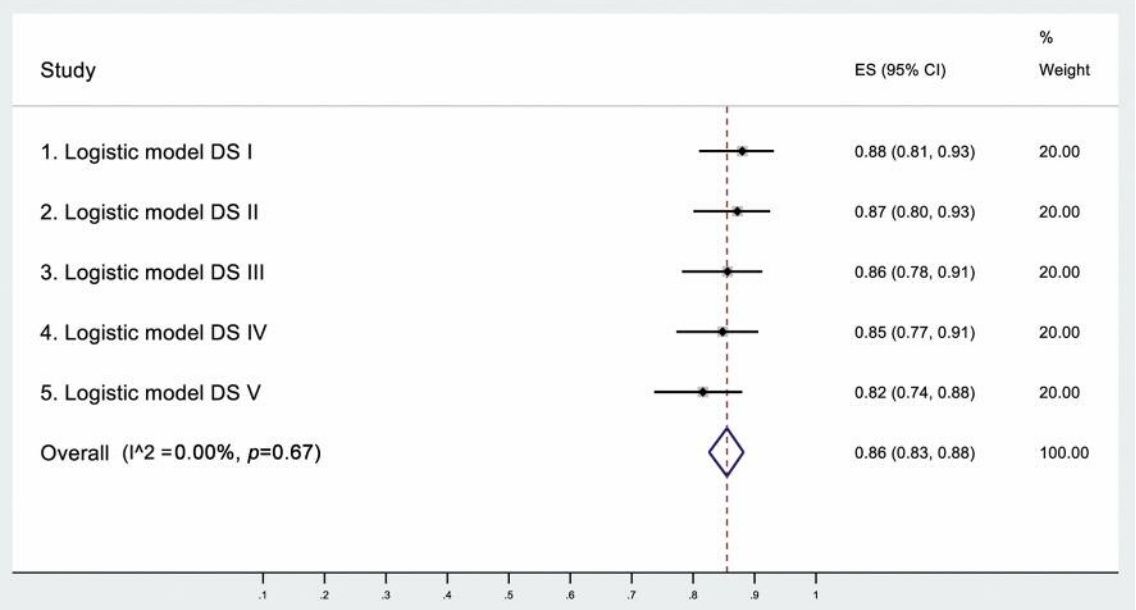

Figure 5. *Sensitivities of diagnostic scores at five different cut-off levels (DS I-V).*

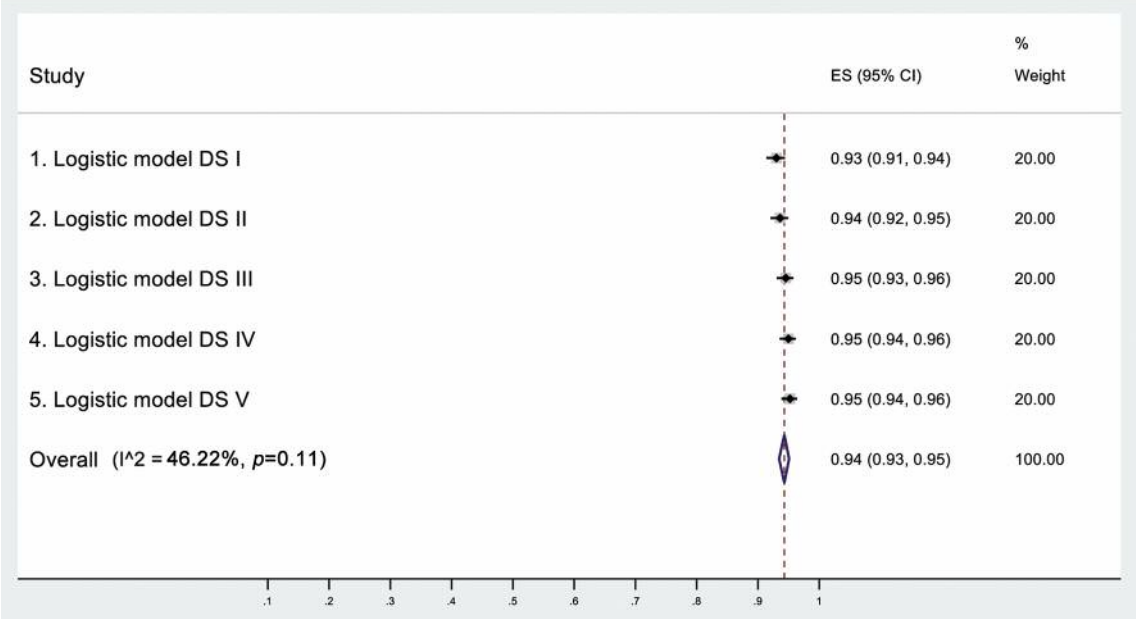

Figure 6. *Specificities of diagnostic scores at five different cut-off levels (DS I-V).*

accuracy (Se/Sp balance; AUC=0.962) in AC among AAP patients. As compared with the diagnostic performance of the clinical findings, signs and tests (ROC comparison test), the DS proved to be far superior to both these conventional diagnostic tools in the diagnosis of AC in patients with AAP.

Conflicts of Interest

The Authors have no conflicts of interest or financial ties to disclose. The Authors alone are responsible for the content and writing of this article.

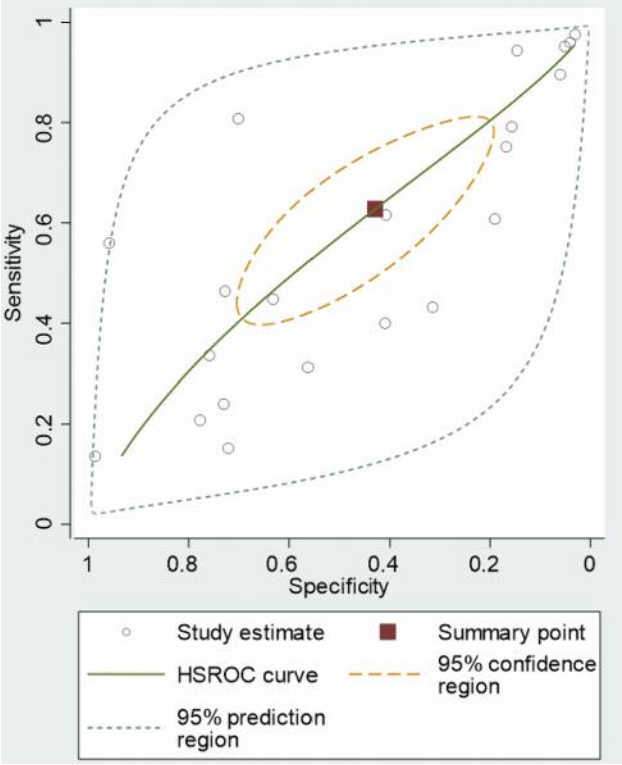

Figure 7. *Hierarchical summary receiver operating characteristic (HSROC) curve of the symptoms.*

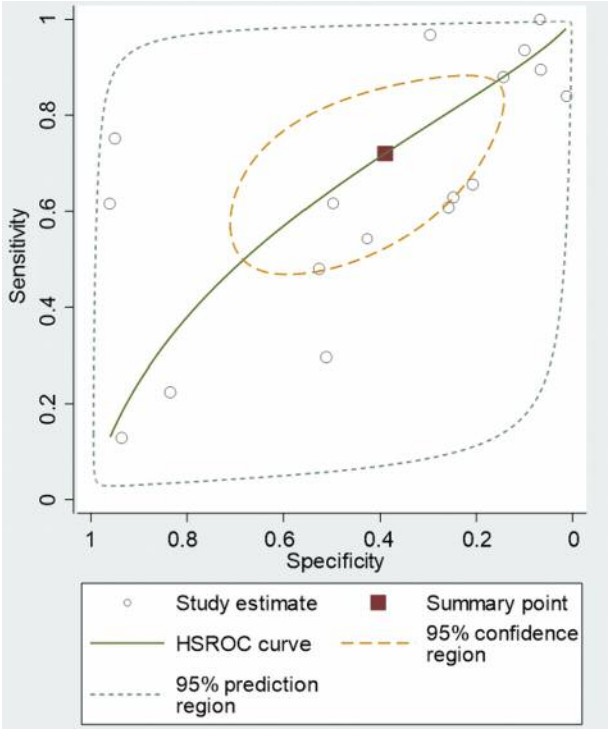

Figure 8. *Hierarchical summary receiver operating characteristic (HSROC) curve of the signs and tests.*

Authors' Contributions

All Authors have met all of the following four criteria: 1. Substantial contributions to the conception or design of the work or the acquisition, analysis, or interpretation of data for the work, 2. Drafting the work or revising it critically for important intellectual content, 3. Final approval of the version to be published, 4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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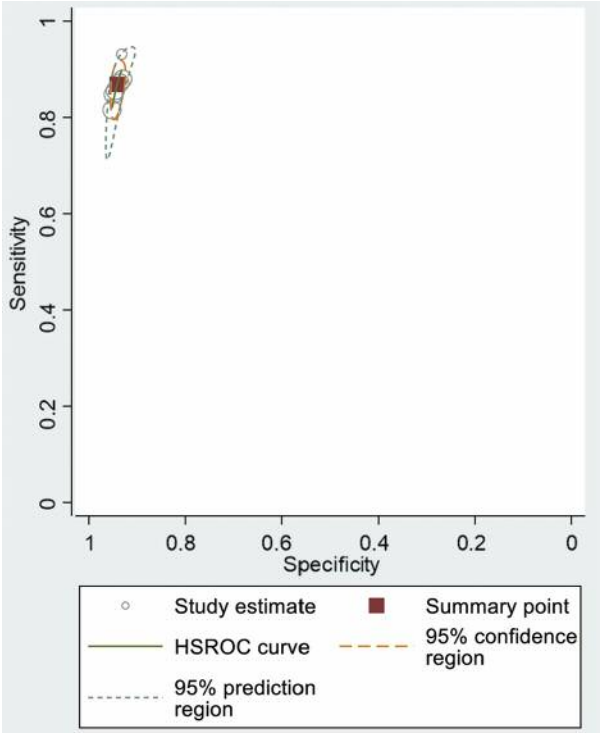

Figure 9. *Hierarchical summary receiver operating characteristic (HSROC) curve of the five DS.*

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