Gender-specific Performance of a Diagnostic Score in Acute Appendicitis

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Abstract. *Background/Aim:* Although a negative appendectomy in female patients with acute abdominal pain (AAP) can be twice as frequent as in male patients, the accuracy of diagnostic scores (DSs) in acute appendicitis (AA) is rarely considered among patients with AAP. The aim was to study the gender-specific performance of a DS in AA. *Patients and Methods:* As an extension of the World Organisation of Gastro-Enterology Research Committee (OMGE) AAP study, 1,333 patients presenting with AAP were included in the study. The clinical history and diagnostic symptoms ($n=22$), signs ($n=14$) and laboratory tests ($n=3$) were recorded in each patient. *Results:* The most significant diagnostic predictors were used to construct DS formulas for AA diagnosis, separately for both genders. The formulas were tested at 6 different cut-off levels to find the best diagnostic performance for AA in females and males. The highest specificities of the DS_{LC-} [DS without leucocyte count (LC)] and DS_{LC+} (DS with LC) scores in detecting AA were 98% (95% CI=97-99%) and 98% (95% CI=96-99%), respectively. In the ROC comparison test, there was no statistically significant difference in the performance of DS_{LC-} and DS_{LC+} in female and male patients. *Conclusion:* Our gender-specific DS reached very high AUC values for AA (0.948-0.956) in both genders, and there was no statistically significant difference in the AUC values of DS_{LC-} and DS_{LC+} between women and men with AAP.

Acute appendicitis (AA) with appendectomy is the most common cause of acute surgical abdomen in the Western countries (1). In a recent meta-analysis, Ferris *et al.* (1) showed that the pooled incidence of the AA with appendectomy was 100/100,000 person years (py) (95% CI=91-100%) in the 2000's in Northern America, and they estimated that the number of AA cases in 2015 was 378,614. In Europe, the pooled incidence ranged from 151/100,000 py in Western Europe to 105/100,000 py in Eastern Europe. The incidence of AA has remained quite stable in most Western countries but in the newly industrialized countries AA is rapidly rising, with the pooled incidence of AA in South Korea being 206/100,000 py, Turkey 160/100,000 py and Chile 202/100,000 py.

We recently designed a diagnostic score (DS) to improve the diagnostic precision in distinguishing AA from non-specific abdominal pain (NSAP) (2). Our experience suggests that DS could assist the clinician in differentiating AA from NSAP and other causes of acute abdominal pain (AAP), although leucocyte count (LC) does not improve the diagnostic performance of a DS in AA (2). Given that the incidence of AA is higher in female patients presenting with AAP than in male patients (3) and to get more insight into the important symptoms, signs and tests related to the clinical diagnosis of AA, we assessed the performance of the DS model i) without leucocyte count (DS_{LC-}) and ii) with leucocyte count (DS_{LC+}), separately in female and male patients with AA.

Patients and Methods

Criteria for inclusion in this study and the diagnostic criteria were those set out by the Research Committee of the World Organization of Gastroenterology (OMGE) (2, 4, 5, 6, 7, 8). There were 636 men (47.7%) and 697 women (52.3%) with mean age ($\pm$ SD) of 38.0 ± 22.1 years (2).

The examination of the clinical symptoms, signs and tests were conducted using a standard technique and the results were graded positive or negative as previously described (2) (Tables I and II). The diagnosis of AA was done by considering all symptoms, signs and results of the laboratory tests together and the diagnostic criteria of AA (2, 4-7).

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Table I. The clinical history of the patients with acute appendicitis versus other diagnosis of acute abdominal pain.

Clinical history variable	Positive endpoint	Negative endpoint	TP Gender		FN Gender		FP Gender		TN Gender	
			F	M	F	M	F	M	F	M
1. Location of initial pain	Upper quadrant of abdomen	Other quadrants of abdomen	4	2	117	147	94	52	482	435
2. Location of pain at diagnosis	Right lower quadrant of abdomen	Other quadrants of abdomen	94	113	27	36	156	93	420	394
3. Intensity of abdominal pain	Subjectively moderate/intolerable pain	Weak pain	77	102	44	47	381	313	195	174
4. Progression of pain from onset to diagnosis	Subjectively same or worse pain	Weaker pain than at the onset	86	112	35	37	388	302	188	185
5. Type of pain	Subjectively steady pain	Colicky or intermittent pain	109	81	40	40	256	285	231	291
6. Aggravating factors	Movement, coughing, respiration, food or other	No aggravating factors	112	132	9	17	409	324	167	163
7. Relieving factors	No relieving factors	Vomiting, lying still, food, antacids or no relieving factors	24	28	97	121	192	190	384	297
8. Previous similar pain	No	Yes	103	126	16	19	335	308	236	176
9. Vertigo	No	Yes	121	149	0	0	547	472	28	12
10. Nausea	Yes	No	74	80	47	69	345	272	231	215
11. Vomiting	Yes	No	58	71	63	78	230	216	346	271
12. Appetite	No appetite	Normal appetite	100	119	21	30	421	337	155	150
13. Previous indigestion	No	Yes	111	129	10	20	444	368	131	118
14. Jaundice	No	Yes	121	148	0	1	557	476	19	11
15. Bowels	Normal	Constipation, diarrhea, blood, mucus, white or normal stools	102	124	19	25	434	355	142	132
16. Micturition	Normal	Abnormal	115	148	6	1	535	449	41	38
17. Drugs for abdominal pain	No	Yes	120	148	1	1	552	458	24	28
18. Previous abdominal surgery	No	Yes	101	146	20	3	584	368	192	118
19. Previous abdominal diseases	No	Yes	111	138	10	11	463	387	113	99
20. Use of alcohol	No	Yes	121	149	0	0	567	463	9	23

TP, true positive; FN, false negative; FP, false positive; TN, true negative.

Identifying the DS models. In the computation of the diagnostic score (DS), a multivariate logistic (stepwise) regression analysis (SPSS Statistics 26.0.0.1; IBM, NY, USA) was used 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.* AA=1 and other diagnosis of AAP=0. Using the coefficients of the regression model, a DS was built and its predictive value for AA was studied. The coefficient of the multivariate analysis shows the relative risk ($RR=e_{-}$, $n=\beta$) of a patient with a given symptom or sign to have an AA.

The formula without LC (DS_{LC-}) in women. The formula without LC, showing the highest diagnostic performance for AA in HSROC analysis is as follows $DS_{LC-}=2.98 \times \text{tenderness (positive endpoint=1, negative endpoint=0)} + 2.45 \times \text{rigidity (positive endpoint=1, negative endpoint=0)} + 2.08 \times \text{guarding (positive endpoint=1, negative$

$\text{endpoint=0)} + 1.33 \times \text{pain at diagnosis (positive endpoint=1, negative endpoint=0)} + 0.88 \times \text{renal tenderness (positive endpoint=1, negative endpoint=0)} - 7.22$. The mean (SD) of DS_{LC-} values for AA in women ($n=121$) were 0.61 (1.81) and the DS_{LC-} mean (SD) values for all female patients with AAP ($n=697$) were -3.41 (2.84) (Table III).

The formula with LC (DS_{LC+}) in women. The formula with LC, showing the highest diagnostic performance for AA in women is as follows $DS_{LC+}=3.17 \times \text{tenderness (positive endpoint=1, negative endpoint=0)} + 2.39 \times \text{rigidity (positive endpoint=1, negative endpoint=0)} + 2.00 \times \text{guarding (positive endpoint=1, negative endpoint=0)} + 1.63 \times \text{LC} + 1.45 \times \text{pain at diagnosis (positive endpoint=1, negative endpoint=0)} + 0.77 \times \text{renal tenderness (positive endpoint=1, negative endpoint=0)} - 7.80$. The mean (SD) of DS_{LC-} values for AA in women ($n=111$) were 1.32 (1.81) and DS_{LC+} mean (SD) values for all women with AAP ($n=575$) were -3.10 (3.21) (Table IV).

Table II. The clinical signs and tests of patients with acute appendicitis versus other diagnosis of acute abdominal pain.

Clinical history variable and investigations	Positive endpoint	Negative endpoint	TP Gender		FN Gender		FP Gender		TN Gender	
			F	M	F	M	F	M	F	M
1. Mood	Normal	Distressed or anxious	103	130	18	19	482	391	94	96
2. Colour	Normal	Jaundiced, flushed, pale or cyanosed	112	133	9	16	506	430	70	57
3. Abdominal movement	Normal	Poor/nil	109	136	12	13	543	451	33	35
4. Scar	No	Yes	101	145	20	4	375	365	201	121
5. Distension	No	Yes	118	146	3	3	532	440	42	45
6. Tenderness	Right lower quadrant of abdomen	Other quadrants of abdomen	113	135	8	14	170	110	406	377
7. Mass	No	Yes	120	149	1	0	551	479	25	8
8. Rebound	Yes	No	111	136	10	13	221	163	355	324
9. Guarding	Yes	No	110	133	11	16	237	227	339	260
10. Rigidity	Yes	No	73	98	48	51	57	66	519	420
11. Murphy's positive	No	Yes	117	142	4	7	499	450	77	36
12. Bowel sounds	Normal	Abnormal	106	130	15	19	510	398	66	89
13. Renal tenderness	No	Yes	90	110	31	39	410	362	166	125
14. Rectal digital tenderness	Abnormal	Normal	70	72	51	77	152	70	424	417
15. Body temperature (Temp)	>37.1°C	≤37.1°C	71	104	48	42	201	150	329	287
16. Leucocyte count (LC)	>10,000/mm ³	≤10,000/mm ³	73	117	38	19	129	146	335	224
17. Urine	Normal	Haematuria or bacteriuria	105	136	1	0	481	374	32	39

TP, True positive; FN, false negative; FP, false positive; TN, true negative.

The formula without LC (DS_{LC-}) in men. The formula without LC, showing the highest diagnostic performance for AA in HSROC analysis is as follows $DS_{LC-}=1.97 \times \text{tenderness (positive endpoint=1, negative endpoint=0)} + 1.88 \times \text{previous abdominal surgery (positive endpoint=1, negative endpoint=0)} + 1.61 \times \text{rebound (positive endpoint=1, negative endpoint=0)} + 1.43 \times \text{rigidity (positive endpoint=1, negative endpoint=0)} + 1.30 \times \text{pain at diagnosis (positive endpoint=1, negative endpoint=0)} + 1.14 \times \text{guarding (positive endpoint=1, negative endpoint=0)} + 1.05 \times \text{body temperature (positive endpoint=1, negative endpoint=0)} - 7.69$. The mean (SD) DS_{LC-} values for AA in males (n=149) were -1.13 (1.74) and DS_{LC-} mean (SD) values for all men with AAP (n=636) were -2.63 (3.05) (Table V).

The formula with LC (DS_{LC+}) in men. The formula with LC, showing the highest diagnostic performance for AA in men is as follows $DS_{LC+}=2.51 \times \text{previous abdominal surgery (positive endpoint=1, negative endpoint=0)} + 2.18 \times \text{LC (positive endpoint=1, negative endpoint=0)} + 1.58 \times \text{pain at diagnosis (positive endpoint=1, negative endpoint=0)} + 1.41 \times \text{tenderness (positive endpoint=1, negative endpoint=0)} + 1.25 \times \text{rigidity (positive endpoint=1, negative endpoint=0)} + 1.04 \times \text{rebound (positive endpoint=1, negative endpoint=0)} + 0.97 \times \text{guarding} + 0.81 \times \text{rectal digital tenderness} + 0.74 \times \text{body temperature} - 8.86$. The mean (SD) DS_{LC-} values for AA in males (n=133) were 1.58 (1.77) and DS_{LC+} mean (SD) values for all male patients with AAP (n=476) were -2.33 (2.21) (Table VI).

Statistical analysis. The 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 2x2 tables, we calculated sensitivity (Se) and specificity (Sp) with 95% confidence intervals

(95% CI) for each symptom, sign or test, and created separate forest plots for showing each set of data, separately for each diagnostic variable. We calculated the summary estimates of sensitivity (Se) and specificity (Sp), positive (LR+) and negative likelihood ratio (LR-) and diagnostic odds ratio (DOR), using a random effect bivariate model and fitted the summary hierarchical receiving operating characteristic (HSROC) curves, including all diagnostic variables in the DS_{LC-} and DS_{LC+} models, using the AA endpoint.

Using the STATA's predict tool, we also made posterior predictions [Empirical Bayes (EB) estimates] of the Se and Sp in each variables in both female and male AA patients in DS_{LC-} and DS_{LC+} . Analogous to its use in meta-analysis, EB estimates here 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 heterogeneity between diagnostic variables and DS models through visual examination of the forest plots and the HSROC curves. To study the potential bias, we used the Cook's distance to check for the particularly influential variables, together with a scatter plot of the standardised (level 2) residuals to find out the variables that are distinct outliers.

Results

Diagnostic performance of the symptoms. The pooled overall gender-specific (F vs. M) Se of the diagnostic symptoms for detecting AA was 80% (95% CI=67%-90%) and 81% (95% CI=82-94%), respectively (Figures 1 and 2). In women Se was higher than 80% for 12 diagnostic symptoms, while in men Se was higher than 81% for 11 diagnostic symptoms.

Table III. Diagnostic score of female patients (n=697) without leucocyte count (DS_{LC-}) shown at six different cut-off levels of symptoms, signs and test.

Diagnostic score (DS)	Positive endpoint	Negative endpoint	TP	FN	FP	TN
1. Logistic model without leucocyte count DS_{LC-} I	Appendicitis	Other diagnosis of acute abdominal pain	114	7	147	429
2. Logistic model without leucocyte count DS_{LC-} II	Appendicitis	Other diagnosis of acute abdominal pain	108	13	69	507
3. Logistic model without leucocyte count DS_{LC-} III	Appendicitis	Other diagnosis of acute abdominal pain	103	18	50	526
4. Logistic model without leucocyte count DS_{LC-} IV	Appendicitis	Other diagnosis of acute abdominal pain	99	22	39	537
5. Logistic model without leucocyte count DS_{LC-} V	Appendicitis	Other diagnosis of acute abdominal pain	97	24	36	540
6. Logistic model without leucocyte count DS_{LC-} VI	Appendicitis	Other diagnosis of acute abdominal pain	99	7	39	429

TP, True positive; FN, false negative; FP, false positive; TN, true negative. Cut-off levels: DS I=-2.03, DS II=-1.4, DS III=-0.90, DS IV=-0.49, DS V=0.03, VI=-2.03--0.49 (follow-up patients n=123).

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

The five best diagnostic symptoms in women (vertigo, jaundice, micturition, drugs for abdominal pain and use of alcohol) showed 95-99% Se, whereas in men (vertigo, jaundice, micturition, drugs for abdominal pain and use of alcohol) showed 99-100% Se in diagnosis of AA (Figure 2). The pooled overall Sp of the diagnostic symptoms for detecting AA was 30% (95% CI=19%-42%) and 31% (95%

CI=20-43%) for women and men, respectively (Figures 3 and 4). In women 9 diagnostic symptoms showed Sp higher than 30%, while in men Sp exceeded 31% for 10 diagnostic symptoms. The five best diagnostic symptoms in diagnosis of AA among women (location of initial pain, location of pain at diagnosis, type of pain, relieving factors, vomiting) showed 60-84% Sp while those (location of initial pain,

Table IV. Diagnostic score of female patients (n=575) with leucocyte count (DS_{LC+}) shown as six different cut-off levels of symptoms, signs and test.

Diagnostic score (DS)	Positive endpoint	Negative endpoint	TP	FN	FP	TN
1. Logistic model with leucocyte count DS_{LC+} VII	Appendicitis	Other diagnosis of acute abdominal pain	107	4	192	272
2. Logistic model with leucocyte count DS_{LC+} VIII	Appendicitis	Other diagnosis of acute abdominal pain	104	7	105	359
3. Logistic model with leucocyte count DS_{LC+} IX	Appendicitis	Other diagnosis of acute abdominal pain	101	10	62	402
4. Logistic model with leucocyte count DS_{LC+} X	Appendicitis	Other diagnosis of acute abdominal pain	97	14	35	429
5. Logistic model with leucocyte count DS_{LC+} XI	Appendicitis	Other diagnosis of acute abdominal pain	85	26	20	444
6. Logistic model with leucocyte count DS_{LC+} XII	Appendicitis	Other diagnosis of acute abdominal pain	97	7	35	359

TP, True positive; FN, false negative; FP, false positive; TN, true negative. Cut-off levels: DS I=-3.2, DS II=-2.33, DS III=-0.80, DS IV=-0.41, DS V=0.10, VI=-2.33--0.41 (follow-up patients n=77).

Figure 2. Pooled sensitivities of the clinical symptoms in acute appendicitis (random-effects model) in men. ES: Estimated specificity; CI: Confidence interval.

location of pain at diagnosis, type of pain, relieving factors, vomiting) in men showed Sp of 51-89% (Figure 4).

Diagnostic performance of the signs and tests. The pooled overall Se of the diagnostic signs and tests for detecting AA was 86% (95% CI=79%-92%) and 88% (95% CI=82-94%), for women and men, respectively (Figures 5 and 6). In

women 10 diagnostic signs and tests had Se exceeding 86%, while in men Se was higher than 88% for 10 diagnostic signs and tests. In diagnosis of AA the five best diagnostic signs and tests in women (distension, tenderness, mass, Murphy's sign, urine) showed 93-99% Se whereas those (scar, distension, mass, Murphy's sign, urine) in men showed 95-99% Se (Figure 6). The pooled overall Sp of the signs and

Table V. Diagnostic score of male patients (n=636) without leucocyte count (DS_{LC-}) shown as six different cut-off levels of symptoms, signs and test.

Diagnostic score (DS)	Positive endpoint	Negative endpoint	TP	FN	FP	TN
1. Logistic model without leucocyte count DS_{LC-} I	Appendicitis	Other diagnosis of acute abdominal pain	142	4	174	261
2. Logistic model without leucocyte count DS_{LC-} II	Appendicitis	Other diagnosis of acute abdominal pain	140	6	144	291
3. Logistic model without leucocyte count DS_{LC-} III	Appendicitis	Other diagnosis of acute abdominal pain	139	7	101	334
4. Logistic model without leucocyte count DS_{LC-} IV	Appendicitis	Other diagnosis of acute abdominal pain	131	15	66	369
5. Logistic model without leucocyte count DS_{LC-} V	Appendicitis	Other diagnosis of acute abdominal pain	125	21	40	395
6. Logistic model without leucocyte count DS_{LC-} VI	Appendicitis	Other diagnosis of acute abdominal pain	125	7	40	334

TP, True positive; FN, false negative; FP, false positive; TN, true negative. Cut-off levels: DS I=-3.1, DS II=-2.6, DS III=-2.0, DS IV=-1.4, DS V=-0.48, VI=-2.00--0.48 (follow-up patients n=75).

Figure 3. Pooled specificities of the clinical symptoms in acute appendicitis (random-effects model) in women. ES: Estimated specificity; CI: Confidence interval.

tests was 34% (95% CI=20%-50%) and 34% (95% CI=20-51%) for women and men, respectively (Figures 7 and 8). In women 8 diagnostic signs and tests showed Sp higher than 34%, whereas in men Sp was 34% for 7 diagnostic signs and tests. The seven best diagnostic signs and tests in women showed 59-90% Sp whereas those in men showed 53-86% Sp in diagnosis of AA (Figure 8).

Diagnostic performance of the DS without leucocytes (DS_{LC-}) in women. The most important predictors of AA in women without LC (n=697) were tenderness, rigidity, guarding, location of pain at diagnosis, and renal tenderness. The significant predictors were used to construct the DS_{LC-} formula for AA diagnosis. In practice, the use of the DS formula is relatively simple as shown by the following;

Table VI. Diagnostic score of male patients ($n=476$) with leucocyte count (DS_{LC+}) shown as six different cut-off levels of symptoms, signs and test.

Diagnostic score (DS)	Positive endpoint	Negative endpoint	TP	FN	FP	TN
1. Logistic model with leucocyte count DS_{LC+} VII	Appendicitis	Other diagnosis of acute abdominal pain	130	3	111	232
2. Logistic model with leucocyte count DS_{LC+} VIII	Appendicitis	Other diagnosis of acute abdominal pain	128	5	90	253
3. Logistic model with leucocyte count DS_{LC+} IX	Appendicitis	Other diagnosis of acute abdominal pain	125	8	69	274
4. Logistic model with leucocyte count DS_{LC+} X	Appendicitis	Other diagnosis of acute abdominal pain	118	15	40	303
5. Logistic model with leucocyte count DS_{LC+} XI	Appendicitis	Other diagnosis of acute abdominal pain	109	24	20	323
6. Logistic model with leucocyte count DS_{LC+} XII	Appendicitis	Other diagnosis of acute abdominal pain	109	8	20	274

TP, True positive; FN, false negative; FP, false positive; TN, true negative. Cut-off levels: DS I=-2.8, DS II=-2.3, DS III=-1.74, DS IV=-0.9, DS V=-0.14, VI=-1.74- -0.14 (follow-up patients $n=65$).

Figure 4. Pooled specificities of the clinical symptoms in acute appendicitis (random-effects model) in men. ES: Estimated specificity; CI: Confidence interval.

“ DS_{LC-} =a female patient is admitted to the emergency room with abdominal pain; at diagnosis the pain was localized at RLQ (1 point $\times$ 1.33); clinical examination showed RLQ tenderness (1 point $\times$ 2.98), rigidity (1 point $\times$ 2.45), guarding (1 point $\times$ 2.08) and the renal tenderness test was positive (1 point $\times$ 0.88)”. The best diagnostic performance level for DS_{LC-} formula in females (Se=93%, Sp=92%) in AA

diagnosis was reached when the patients with a DS_{LC-} value between -2.03 and -0.49 were considered as “grey area” patients=follow-up required before the decision to operate ($n=123$). The formula was tested at six different cut-off levels to disclose the best diagnostic performance in women (Figures 9 and 10). The pooled overall Se and Sp of these six DS_{LC-} formulas were 88% (95% CI=83-92%) and 89%

Figure 5. Pooled sensitivities of the clinical signs and tests in acute appendicitis (random-effects model) in women. ES: Estimated sensitivity; CI: Confidence interval.

(95% CI=84-94%), respectively (Figures 9 and 10). Three of these formulas showed Se >88% and four formulas had Sp >89%. At the best diagnostic DS_{LC-} formula in women (formula DS VI, Figure 9 and 10) showed Se of 93% (95% CI=87-97%) and Sp of 92% (95% CI=89-94%).

Diagnostic performance of the DS with leucocytes in women (DS_{LC+}). Similar as for the DS_{LC-} formulas, the significant independent predictors were used to build up the six different DS_{LC+} formulas. The pooled overall Se and Sp of these six DS_{LC+} models in women was 90% (95% CI=85-95%) and 85% (95% CI=74-94%), respectively (Figures 11 and 12). Four formulas showed Se >90% and four formulas Sp over 85%. The DS_{LC+} formula (formula DS XII, Figures 11 and 12) showed Se of 93% (95% CI=87-97%) and Sp of 91% (95% CI=88-94%) (Figures 11 and 12).

Diagnostic performance of the DS without leucocytes (DS_{LC-}) in men. The most important predictors of AA in male patients without LC (n=636) were location of pain at diagnosis, previous abdominal surgery, tenderness, rebound, rigidity, guarding and body temperature (DS_{LC-} formula is shown in

patients and methods chapter). In male patients DS_{LC-} formula model reached Se of 95% with Sp of 89% when the male patients with DS value between -2.00 and -0.48 were considered as “grey area” patients=follow-up required before the decision to operate (n=75). The DS_{LC-} formula was tested at six different cut-off levels to find the best diagnostic performance for AA in men (Figures 13 and 14). The pooled overall Se and Sp of these six DS_{LC-} formulas were 94% (95% CI=90-96%) and 79% (95% CI=68-88%), respectively (Figures 13 and 14). Four of these formulas showed Se >94% and three formulas had Sp >79%. At the best diagnostic DS_{LC-} in men (formula DS XI, Figures 13 and 14) showed Se of 95% (95% CI=89-98%) and Sp of 89% (95% CI=86-92%).

Diagnostic performance of the DS with leucocytes in men (DS_{LC+}). The pooled overall Se and Sp of the six DS_{LC+} formulas in men was 93% (95% CI=88-96%) and 84% (95% CI=74-92%), respectively (Figures 15 and 16). Four formulas showed Se >93% and three formulas had Sp >84%. The best diagnostic DS_{LC+} formula in men (formula DS XII, Figures 15 and 16) showed Se of 93% (95% CI=87-97%) and Sp of 93% (95% CI=90-96%) (Figures 15 and 16).

Figure 6. Pooled sensitivities of the clinical signs and tests in acute appendicitis (random-effects model) in men. ES: Estimated sensitivity; CI: Confidence interval.

HSROC analyses and empirical Bayes (EB) estimates in both genders. 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 DS formulas in detecting AA in women (Figures 17 and 18) and men (Figures 19 and 20). In the HSROC analysis in women, there is no statistically significant difference between the DS_{LC-} and DS_{LC+} formulas, with $AUC=0.949$ (95% $CI=0.921-0.968$) and $AUC=0.953$ (95% $CI=0.923-0.969$) ($p=0.631$, ROC comparison test). The same is true with the HSROC analysis in men, with no difference between the DS_{LC-} and DS_{LC+} formulas, with $AUC=0.948$ (95% $CI=0.920-0.964$) and $AUC=0.956$ (95% $CI=0.930-0.969$) ($p=0.321$, ROC comparison test).

Discussion

We studied patients presenting with AAP as a part of the survey by the OMGE Committee (4-8) and estimated the diagnostic accuracy of a combined history-taking, clinical examination and laboratory testing in verified AA (5), NSAP (5), acute small bowel obstruction (7) and in acute renal

stone disease (8). Although there are several different DS systems designed for AAP diagnosis (5, 9-15) and the international guidelines recommend routine diagnostic scoring to improve the diagnosis of AA (16, 17), a debate continues on the shortcomings of the specific DS models in women and men with AAP. Thus, it was appropriate to compare the performance of our gender-specific DS models in both genders, using DSs with and without LC.

Comparison of the symptoms, signs and laboratory tests in women vs. men. There was no gender-specific difference in the clinical symptoms, since the five diagnostic symptoms with highest diagnostic accuracy were identical in women and men (vertigo, jaundice, micturition, drugs for abdominal pain and use of alcohol), showing 95-100% Se in diagnosis of AA. The same applies to gender-specific difference in Sp, the five most relevant symptoms being identical in both genders (location of initial pain, location of pain at diagnosis, type of pain, relieving factors and vomiting) presenting with 51-89% Sp in diagnosis of AA.

Similarly, there was no significant difference in signs and laboratory test results between women and men with confirmed

Figure 7. Pooled specificities of the clinical signs and tests in acute appendicitis (random-effects model) in women. ES: Estimated sensitivity; CI: Confidence interval.

AA in their pooled Se, because the five best diagnostic signs and tests were very similar in both genders; women (distension, tenderness, mass, Murphy's sign, urine) and men (scar, distension, mass, Murphy's sign, urine) showing 93-99% Se in diagnosis of AA. Also, the pooled Sp of the signs and tests in AA detection was equal in both genders.

Female DS_{LC-} and DS_{LC+} . Of interest was to assess, whether the addition of LC would give any added value to our DSs, herein performed by comparing the diagnostic accuracy of DS_{LC-} and DS_{LC+} scores. The present analysis suggests that female patients with DS_{LC-} below -2.03 should not be operated while women with DS_{LC-} falling between -2.03 and -0.49 should be followed-up before the final decision. According to our data, only the AAP-women with the DS_{LC-} values exceeding -0.49 should be operated without delay. In women whose LC was calculable ($n=575$) the important predictors of AA were the same as in women without LC, but LC is added to DS_{LC+} formula ($LC \geq 10,000 \mu l$) (see the methods for formula details). In women, the highest diagnostic accuracy for DS_{LC+} formula (Se=93%, Sp=91%) in AA diagnosis was reached when the patients with DS_{LC+}

values falling between -2.33 and -0.41 were considered as "grey zone" patients, for whom follow-up was appropriate before the decision to operate ($n=77$). Taken together, i) the female AAP patients with DS_{LC+} value below -2.33 should not be operated, ii) those with DS_{LC+} value between -2.33 and -0.41 should be followed-up and iii) all AAP-women with the DS_{LC+} value higher than -0.41 should be operated without delay.

Male DS_{LC-} and DS_{LC+} . The same considerations can be made among male patients with AAP. Our present data suggest that male patients with a DS_{LC-} value below -2.00 should not be operated. Those men with DS_{LC-} values between -2.00 and -0.48 should be followed-up, whereas all those with DS_{LC-} values above -0.48 should be operated with no delay. In males with LC available ($n=476$), the AA predictors were the same as earlier but added with the LC and rectal digital examination. When the men with a DS_{LC-} value between -1.74 and -0.14 were considered equivocal ($n=67$, follow-up required), the Se of this DS_{LC-} in AA was 93%, with a Sp of 93% and an efficiency of 93%. As to the males and DS_{LC+} the present analysis implicates that the

Figure 8. Pooled specificities of the clinical signs and tests in acute appendicitis (random-effects model) in men. ES: Estimated sensitivity; CI: Confidence interval.

Figure 9. Sensitivities of diagnostic scores without leucocyte count (DS_{LC-}) in women at six different cut-off levels (DS I-VI).

Figure 10. Specificities of diagnostic scores without leucocyte count (DSLCL-) in women at six different cut-off levels (DS I-VI).

Figure 11. Sensitivities of diagnostic scores with leucocyte count (DSLCL+) in women at six different cut-off levels (DS I-VI).

patients with a DS_{LC+} value below -1.74 should not be operated, while those with DS_{LC+} values between -1.74 and -0.14 could be safely followed-up. This leaves only the male patients with DS_{LC+} values above -0.14 , who should be immediately operated.

A right iliac fossa tenderness (RIFT) Study Group in UK suggested that female patients (272/964, 28.2%) with AAP

were more than twice as likely as males to undergo surgery with histologically normal appendix as a result (*i.e.* negative appendectomy, FP) (120/993, 12.1%) (RR=2.33, 95% CI=1.92-2.84, $p<0.001$). Although several AA risk scorings (5, 9-15) demonstrate different predictive factors for AA diagnosis, as far as we know, only the RIPASA scoring provides gender-specific data (19). The present study is the

Figure 12. Specificities of diagnostic scores with leucocyte count (DSLCLC+) in women at six different cut-off levels (DS VII-XII).

Figure 13. Sensitivities of diagnostic scores without leucocyte count (DSLCLC-) in men at six different cut-off levels (DS I-VI).

second to provide such data, while reporting the diagnostic performance of the DS_{LC-} and DS_{LC+} models in both genders: The aim was to elaborate the optimal combination of symptoms, signs and tests in the DS formulas with and without LC and using six different combinations (DS_{LC-} and DS_{LC+}) as diagnostic predictors of AA. Our DS is in line with APPEND score (20) that the LC testing was not an important

predictor of AA diagnosis, while APPEND score does not account for the significance of gender in AA. Alvarado (9) and Appendicitis Inflammatory Response (21) scores emphasize LC analysis as a significant predictor of AA diagnosis and APPEND score identified neutrophil percent and neutrophil/lymphocyte ratio as important predictors of AA. AA diagnosis strategies in the future may include early markers of

Figure 14. Specificities of diagnostic scores with leucocyte count (DSLCL-) in men at six different cut-off levels (DS I-VI).

Figure 15. Sensitivities of diagnostic scores with leucocyte count (DSLCL+) in men at six different cut-off levels (DS VII-XII).

inflammation *e.g.* interleukin 6 (IL-6) blood levels of which were shown to increase even 3-fold from the reference levels in perforated AA (22), suggesting that IL-6 analysis may be useful in predicting AA complication risk. Although the IL-6 analysis is promising, the current antigen test method precludes its use as a rapid test in AA so far (23, 24).

Conclusion

In conclusion, our gender-specific DS reached very high AUC values (0.948-0.956) in both genders, and using the ROC comparison test, there was no statistically significant difference in the AUC values of DS_{LC-} and DS_{LC+} between

Figure 16. Specificities of diagnostic scores with leucocyte count (DSLCL-) in men at six different cut-off levels (DS VII-XII).

Figure 17. Hierarchical summary receiver operating characteristic (HSROC) curve of the six DSLCL- in women.

Figure 18. Hierarchical summary receiver operating characteristic (HSROC) curve of the six DSLCL+ in women.

women and men. Kularatna *et al.* (15) reviewed available DS formulas in AA and showed between 84% and 96% AUC values in AA diagnosis. Although, weakness of the

meta-analysis is heterogeneity and quality of included studies, it seems that the Tzanakis score (13) with ultrasound (US) and inflammatory markers reached the

Figure 19. Hierarchical summary receiver operating characteristic (HSROC) curve of the six DSLC- in women.

Figure 20. Hierarchical summary receiver operating characteristic (HSROC) curve of the six DSLC+ in men.

highest diagnostic performance with 96% AUC in AA. This is equal with the AUC values obtained in the present study. However, the advantage of our DS is that this scoring does not need US or LC analysis to reach a high diagnostic accuracy in AA.

Conflicts of Interest

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

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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