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# A Diagnostic Score for Reliable Confirmation of Acute Renal Colic Among Patients With Acute Abdominal Pain

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**Abstract.** *Background/Aim: Diagnostic scores (DSs) for confirmation of acute renal colic (ARCO) have rarely been evaluated. Patients and Methods: A cohort of 1,333 patients with acute abdominal pain (AAP) were studied, including 59 patients with confirmed ARCO. The most significant diagnostic findings (in multivariate logistic regression analysis) were used to construct DS formulas for the diagnosis of ARCO. Meta-analytical techniques were used to detect the summary sensitivity and specificity estimates for each data set (clinical symptoms, signs and tests, as well as DS formulas). Results: In hierarchical summary receiver operating characteristic analysis (HSROC), the values for area under the curve (95% confidence interval) for i) clinical symptoms ii) signs and tests, and iii) DS were 0.650 (0.612-0.688), 0.724 (0.680-0.768) and 0.962 (0.940-0.984), respectively. In HSROC analysis of the area under the curve values, differences were significant between i) and iii) (p<0.0001) and between ii) and iii) (p<0.0001). Conclusion: The present study is the first to provide evidence suggesting that the DS can be used for clinical confirmation of ARCO in patients with AAP, with a high diagnostic accuracy without radiological or laboratory analyses.*

Acute renal colic (ARCO) is the most common urological emergency and in the USA over one million patients per year with ARCO visit emergency units (1). Similarly, the incidence of ARCO is also increasing globally, as shown by a i) steady rise in the emergency visits, ii) use of imaging, and iii) use of drugs for ARCO (2, 3). The clinical findings of ARCO include flank or lower abdominal pain, characterized by loin radiation. These symptoms are non-specific, however, and computerized tomography (CT) has become the standard diagnostic modality for ARCO (2). Although CT is useful for the detection of kidney stones, the radiation exposure from CT is a concern because ARCO is a recurrent disease, with relapses in 30-50% of patients (4, 5). To our knowledge, there are very few data on the testing of diagnostic scoring (DS) for ARCO, which prompted us to re-evaluate the accuracy of the clinical diagnosis of ARCO among patients with acute abdominal pain (AAP). The present study evaluated the relative accuracy of i) clinical symptoms, ii) signs and test, as well as iii) DS in confirming ARCO.

## Patients and Methods

A cohort of 1,333 patients with AAP were included, of whom 59 had ARCO. The clinical symptoms (n=22), signs (n=14) and laboratory tests (n=3) were recorded for each patient. The diagnosis of ARCO was confirmed by considering all clinical symptoms, clinical signs and results of the laboratory tests together and following the diagnostic criteria of AAP as previously described (6-11).

*Identifying DS models.* A multivariate logistic (stepwise) regression analysis (SPSS Statistics 26.0.0.1; IBM, Armonk, NY, USA) was used to disclose variables with an independent predictive value. All the variables of clinical history and diagnostic findings presented in Tables I and II were included in the analysis as binary data *e.g.*, ARCO=1 and other diagnosis of AAP=0, where was a positive (PE) and negative (NE) endpoints as defined therein. Using the coefficients of the regression model, a DS was built and its predictive value for ARCO was studied. The coefficient of the multivariate analysis shows the relative risk of a patient with a given clinical symptom, sign or test of having ARCO.

The DS formula derived for ARCO was: −3.26 × gender (female=1, male=0) + 2.60 × duration of pain (PE=1, NE=0) +

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*Key Words:* Acute renal colic, symptoms, signs, tests, diagnostic score, HSROC, diagnostic accuracy.

Table I. *Clinical history of patients with acute renal colic (ARCO) versus other cause of abdominal pain.*

| Clinical history variable | Positive endpoint | Negative endpoint | Frequency | | | |
|---|---|---|---|---|---|---|
| | | | TP | FN | FP | TN |
| 1. Location of initial pain | Right or left loin | Other | 20 | 39 | 11 | 1,263 |
| 2. Location of pain at diagnosis | Right or left loin | Other | 11 | 48 | 11 | 1,263 |
| 3. Duration of pain at diagnosis | ≤12 hours | >12 hours | 39 | 20 | 422 | 852 |
| 4. Intensity of abdominal pain | Intolerable pain | Subjectively moderate or weak pain | 27 | 32 | 189 | 1,085 |
| 5. Progression of pain from onset to diagnosis | Weaker or worse pain | Subjectively same pain than at the onset | 42 | 17 | 790 | 484 |
| 6. Type of pain | Colicky pain | Steady or intermitted pain | 31 | 28 | 387 | 887 |
| 7. Aggravating factors | No aggravating factors | Movement, coughing, respiration, food or other | 29 | 30 | 327 | 947 |
| 8. Relieving factors | No | Yes | 30 | 29 | 404 | 870 |
| 9. Previous similar pain | No | Yes | 41 | 18 | 831 | 429 |
| 10. Vertigo | Yes | No | 3 | 56 | 37 | 1,233 |
| 11. Nausea | No | Yes | 26 | 33 | 541 | 733 |
| 12. Vomiting | Yes | No | 30 | 29 | 540 | 734 |
| 13. Appetite | Normal appetite | No appetite | 27 | 32 | 329 | 945 |
| 14. Previous indigestion | Yes | No | 17 | 42 | 262 | 1,010 |
| 15. Jaundice | No | Yes | 58 | 1 | 1242 | 30 |
| 16. Bowels | Normal | Diarrhea, constipation, blood, mucus or white stools | 53 | 6 | 962 | 312 |
| 17. Micturition | Abnormal | Normal | 2 | 57 | 19 | 1,255 |
| 18. Drugs for abdominal pain | No | Yes | 58 | 1 | 1220 | 53 |
| 19. Previous abdominal surgery | Yes | No | 17 | 42 | 316 | 957 |
| 20. Previous abdominal diseases | Yes | No | 11 | 48 | 222 | 1,050 |
| 21. Consumption of alcohol | No | Yes | 56 | 3 | 1209 | 64 |

FN: False-negative; FP: false-positive; TN: true-negative; TP: True-positive.

Table II. *Clinical signs and investigations of patients with acute renal colic (ARCO) versus other cause of abdominal pain.*

| Clinical signs and investigations | Positive endpoint | Negative endpoint | Frequency | | | |
|---|---|---|---|---|---|---|
| | | | TP | FN | FP | TN |
| 1. Mood | Distressed or anxious | Normal | 20 | 39 | 207 | 1,067 |
| 2. Colour | Normal or pale | Jaundiced, flushed or cyanosed | 58 | 1 | 1,192 | 82 |
| 3. Abdominal movement | Normal | Poor/nil | 55 | 4 | 1,184 | 89 |
| 4. Scar | Yes | No | 17 | 42 | 329 | 944 |
| 5. Distension | No | Yes | 58 | 0 | 1,178 | 93 |
| 6. Tenderness | Right or left loin | Other | 9 | 50 | 6 | 1,268 |
| 7. Mass | No | Yes | 59 | 0 | 1,240 | 34 |
| 8. Rebound | No | Yes | 42 | 17 | 660 | 614 |
| 9. Guarding | No | Yes | 36 | 23 | 590 | 684 |
| 10. Rigidity | No | Yes | 54 | 5 | 984 | 289 |
| 11. Murphy's sign, positive | No | Yes | 58 | 1 | 1,150 | 123 |
| 12. Bowel sounds | Normal | Abnormal | 50 | 9 | 1,094 | 1,80 |
| 13. Renal tenderness | Yes | No | 51 | 8 | 310 | 964 |
| 14. Rectal digital tenderness | Normal | Abnormal | 49 | 10 | 920 | 354 |
| 15. Body temperature | <37.1˚C | ≥37.1˚C | 42 | 8 | 664 | 518 |
| 16. Leucocyte count | <10,000/mm$^3$ | ≥10,000/mm$^3$ | 26 | 16 | 590 | 449 |
| 17. Urine | Haematuria or erythrocytes >10/HPF | Normal or bacteriuria | 40 | 13 | 8 | 1,107 |

FN: False-negative; FP: false-positive; HPF: high-power field; TN: true-negative; TP: true-positive.

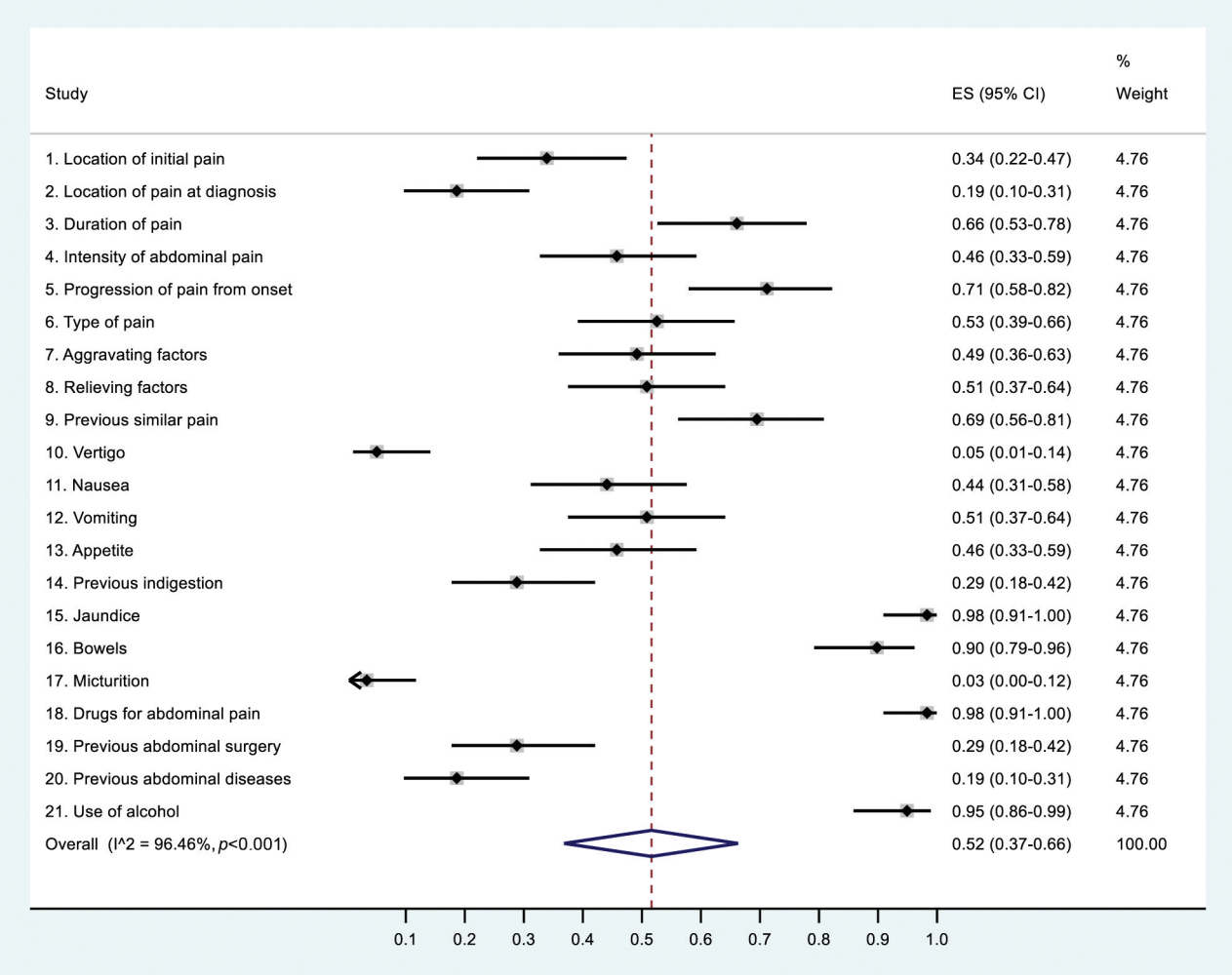


Figure 1. *Sensitivity of history-taking in acute renal colic (random-effects model). ES: Estimated sensitivity; CI: confidence interval.*

1.54 × appetite (PE=1, NE=0) + 6.89 × tenderness (PE=1, NE=0) + 3.23 × renal tenderness (PE=1, NE=0) + 7.56 × urine (PE=1, NE=0) − 8.06.

*Statistical analysis*. STATA/SE version 16.1 (StataCorp, College Station, TX, USA) was used for further statistical analyses. The statistical tests presented were two-sided, and p-values under 0.05 were considered statistically significant. Using 2×2 tables, sensitivity and specificity with 95% confidence intervals (95% CI) for clinical symptoms, signs and tests were determined. Meta-analytical technique (metaprop) was used to create separate forest plots for sensitivity and specificity for each set of data, including each diagnostic variables. We calculated the summary estimates of sensitivity and specificity, positive and negative likelihood ratios, and diagnostic odds ratio using a random-effects bivariate model and fitted the summary hierarchical receiver operating characteristic (HSROC) curves, including all diagnostic variables in the DS model, using ARCO as an endpoint.

## Results

*Basic patient data*. In ARCO study group there were 59 patients (14 females and 45 males) *versus* 1,274 patients in the non-ARCO group (683 females and 591 males) including the following patients with AAP: 616 with non-specific abdominal pain, 271 with acute appendicitis, 124 with acute cholecystitis, 53 with acute small bowel obstruction, 50 with non-organic dyspepsia and 160 other patients with AAP, with a mean±SD age of 37.5±21.7 years.

*The clinical symptoms in ARCO*. The sensitivity of the clinical symptoms for detecting ARCO was 52% (95% CI=37-66%). The sensitivity was higher than 52% for eight of the symptoms. The five best clinical symptoms (progression of pain from the onset to diagnosis, jaundice,

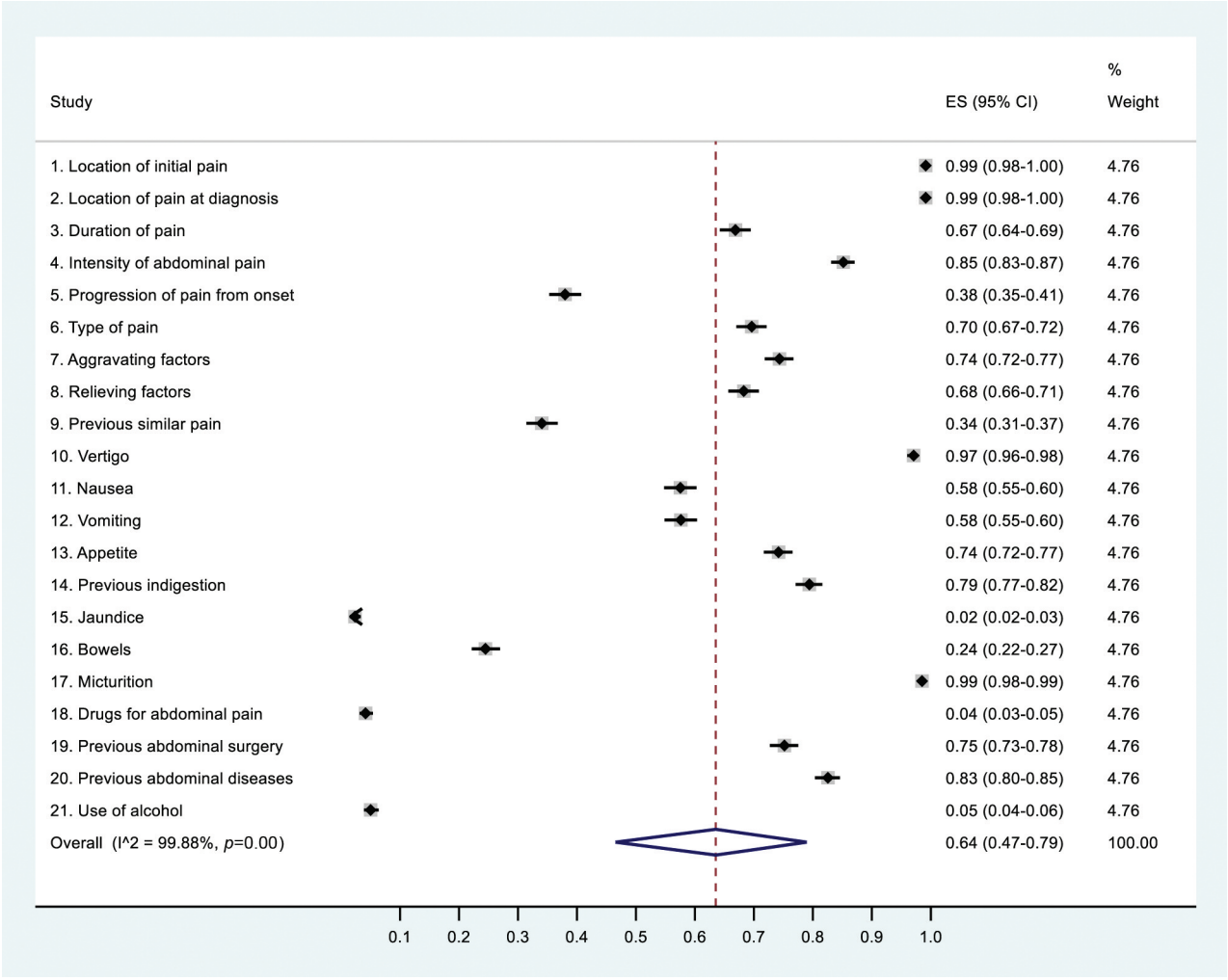


Figure 2. *Specificity of history-taking in acute renal colic (random-effects model). ES: Estimated specificity; CI: confidence interval.*

bowel function, drugs for abdominal pain and consumption of alcohol) had 71-98% sensitivity in ARCO (Figure 1). The specificity of the clinical symptoms in confirming ARCO was 64% (95% CI=47-79%) (Figure 2). Altogether, 13 symptoms had specificity higher than 64%. The five most specific symptoms of ARCO (location of initial pain, location of pain at diagnosis, intensity of abdominal pain, vertigo, and micturition) had 85-99% specificity (Figure 2).

*The clinical signs and tests in ARCO*. The sensitivity of the diagnostic signs and tests for ARCO was 79% (95% CI=65-90%) (Figure 3), and 10 findings had sensitivity exceeding 79%. The five highly accurate findings (skin colour, abdominal movement, distension, mass, positive for Murphy's sign) had 93-100% sensitivity (Figure 3). The specificity of the signs was only 42% (95% CI=23-62%) (Figure 4), while nine signs had individual specificity higher than 42%. The five most accurate signs (mood, scar, tenderness, renal tenderness and urine), however, had 74-100% specificity (Figure 4).

*DS in confirming ARCO*. The most important predictors of ARCO were gender, duration of pain, appetite, tenderness, renal tenderness and urine. The most accurate level for the DS model (DS V; sensitivity=96%, specificity=99%) was reached when the patients with a DS value of between −3.29 and 0.69 were considered as "undefined" patients with ARCO for whom follow-up was required (n=46) (Figure 5). The DS formula was tested at five different cut-off levels to disclose the best diagnostic performance (Figure 5). The overall sensitivity and specificity of these DS models was 91% (95% CI=84-97%) and 98% (95% CI=96-99%),

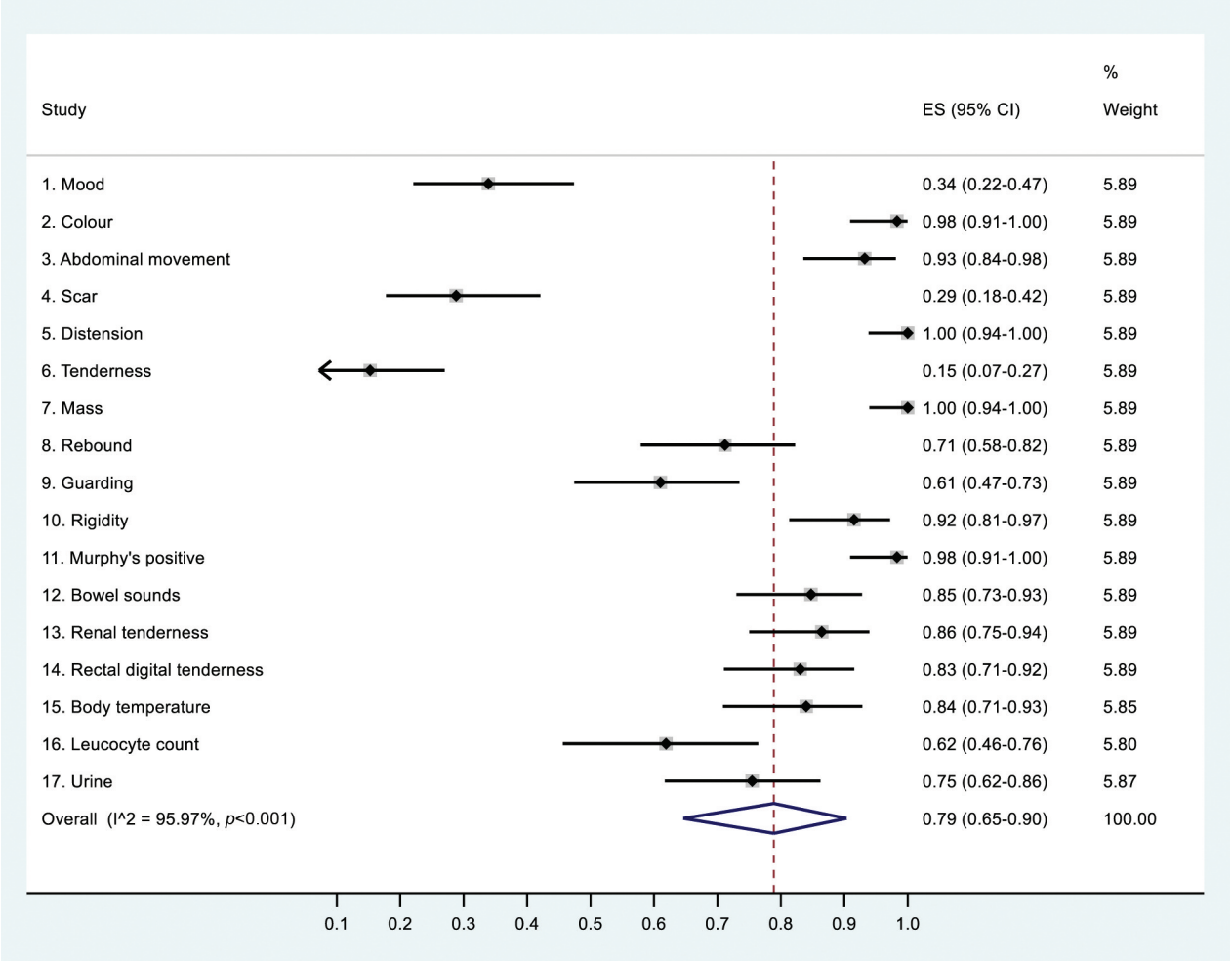


Figure 3. *Sensitivity of signs and tests in acute renal colic (random-effects model). ES: Estimated sensitivity; CI: confidence interval.*

respectively (Figures 5 and 6). Three of these models had sensitivity >91% and three models had specificity >98%. The best diagnostic DS model in these patients with ARCO (DS V, Figures 5 and 6) had sensitivity of 96% (95% CI=86-100%) and specificity of 99% (95% CI=98-99%).

*HSROC and AUC*. STATA (metandiplot) was used to draw the HSROC curves to visualise the pooled overall diagnostic accuracy of symptoms, signs and tests, and different DS models in detecting ARCO (Figures 7, 8 and 9). In HSROC analysis, the AUC (95% CI) values for i) clinical symptoms, ii) signs and tests, and iii) DS were 0.650 (0.612-0.688), 0.724 (0.680-0.768) and 0.962 (0.940-0.984), respectively. The differences between these AUC values (roccomp analysis) were as follows: Between i) and ii), $p$=0.199; between i) and iii), $p$<0.0001; between ii) and iii), $p$<0.0001.

## Discussion

The DS models for ARCO published so far are based on clinico-radiological prediction, which necessitates ultrasonography (US) or CT imaging in scoring. Moore *et al*. studied a retrospective cohort of patients undergoing CT for suspected ureteral stone. In multivariate analysis, five factors were predictive of a ureteral stone: male gender, duration of pain <6 hours, Caucasian, nausea or vomiting, and erythrocytes in the urine analysis, yielding a score of 0-13 (the STONE score) (12). The STONE score classifies patients into categories with different risk for ARCO: Low, intermediate and high risk. Moore *et al*. suggested the STONE score for ARCO screening and to reduce the need for unnecessary CT studies. Although the STONE may be a comprehensive test for ARCO, Fukuhara *et al*. pointed out

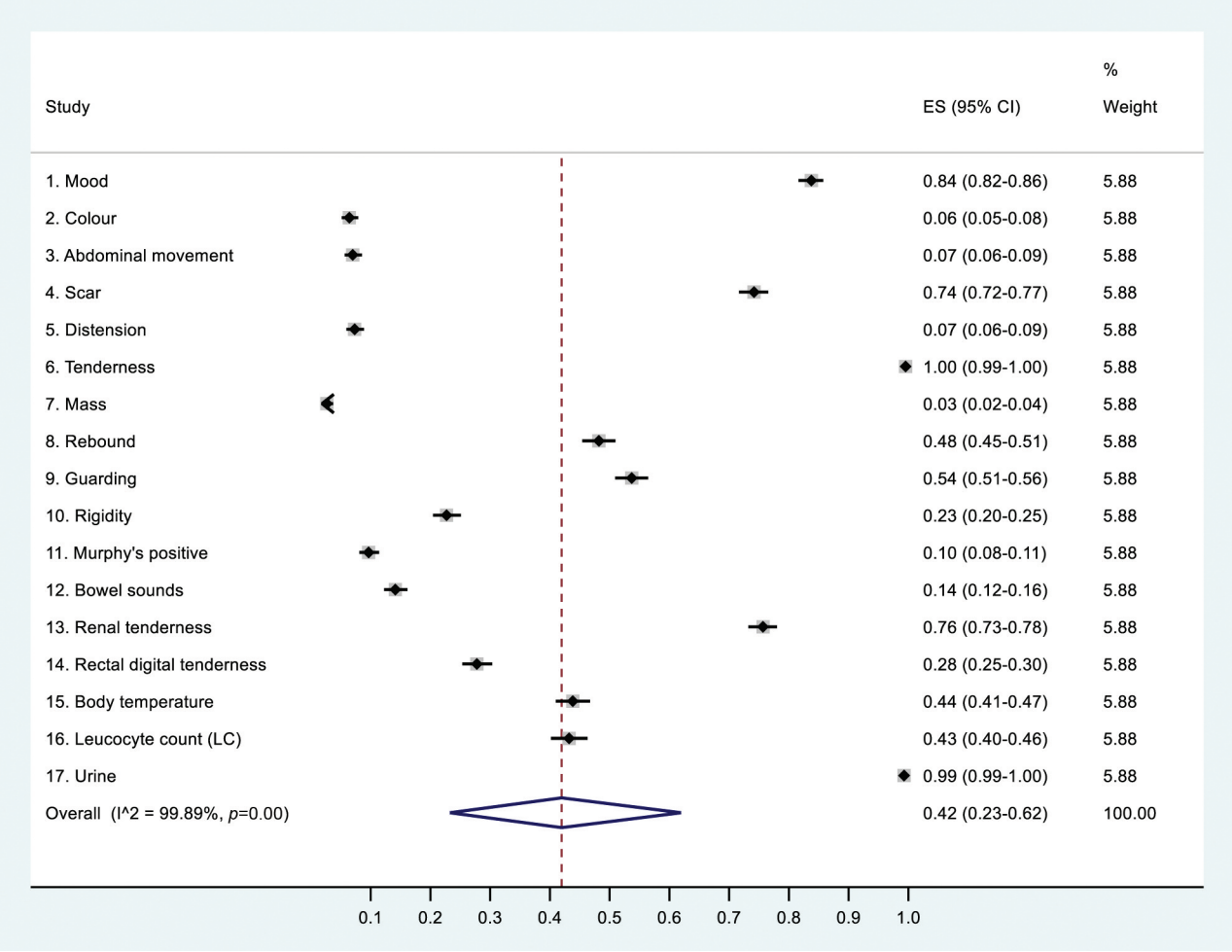


Figure 4. *Specificity of clinical signs and tests in acute renal colic (random-effects model). ES: Estimated specificity; CI: confidence interval.*

that the race factor (black *versus* non-black patients) may not be a suitable predictor for ARCO (13). In addition, in the study of Moore *et al*. (12), no ROC analysis with AUC values for the patients with ARCO were reported. Another bias of that study (12) is that the pretest probability for ARCO or the doctors' estimate for likelihood of ARCO could not have been investigated because only 2.9% of the patients had a non-ARCO diagnosis, which is likely to have affected the clinical prediction rule.

Fukuhara *et al*. investigated 124 patients with ARCO, and the evaluation of hydronephrosis (HN) with US was found to be a key factor in their DS because HN was weighted 4/13 points (13). Although some studies have pointed out the importance of HN in the diagnosis of ARCO (14), US may lead to false-positive/negative findings because US is a user-dependent modality and its accuracy in HN may vary according to the experience level of the test performer (15). Fukuhara *et al*. correlated US scoring with the final diagnosis, reporting the diagnostic performance of their DS as high as AUC=0.95 (13). They also validated the STONE score using ROC analysis, reaching an AUC of 0.88 (95% CI=0.82-0.94) in their cohort of patients with ARCO. However, there are several limitations in their study: i) Small sample size, ii) selected cohort, iii) their study was conducted only on weekdays and during working hours. There were only 40 non-ARCO patients and therefore the diagnostic efficiency of their DS among patients with AAP is unclear. In addition, the reliable diagnosis of HN by US needs much training (15).

Al-Terki *et al*. reviewed a cohort of 200 patients with ARCO, showing that in multivariate analysis, serum creatinine, leucocyte count, the largest diameter of the stone in CT and stone place in CT were significantly associated with ARCO, with their DS model reaching AUC=0.945 (16).

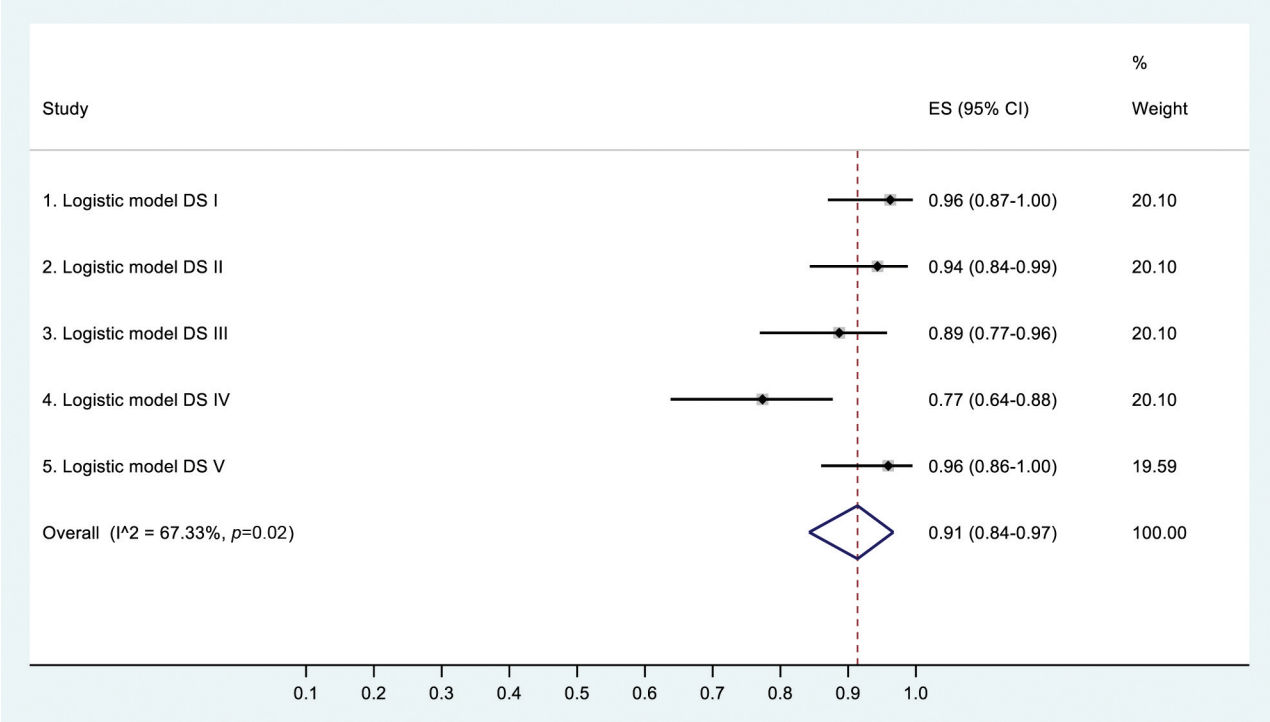


Figure 5. *Sensitivity of diagnostic scores at five different cut-off levels (DS I-V). ES: Estimated sensitivity; CI: confidence interval.*

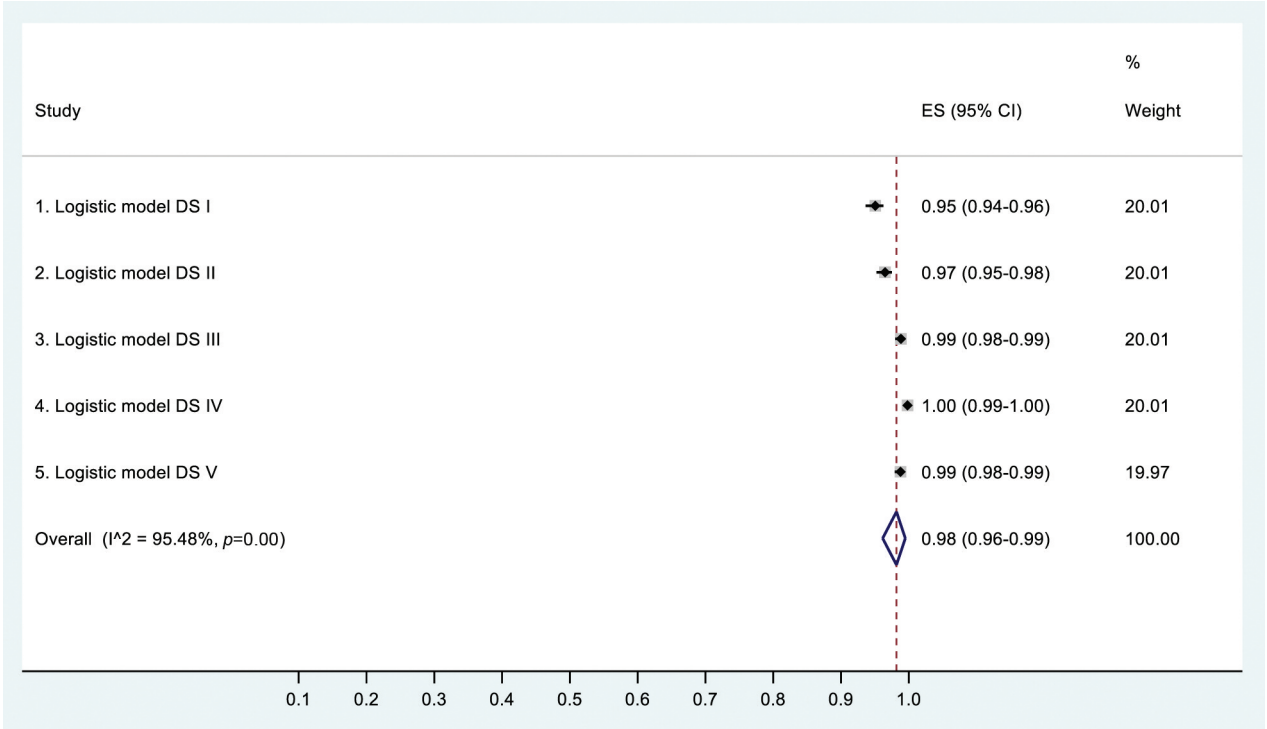


Figure 6. *Specificity of diagnostic scores at five different cut-off levels (DS I-V). ES: Estimated specificity; CI: confidence interval.*

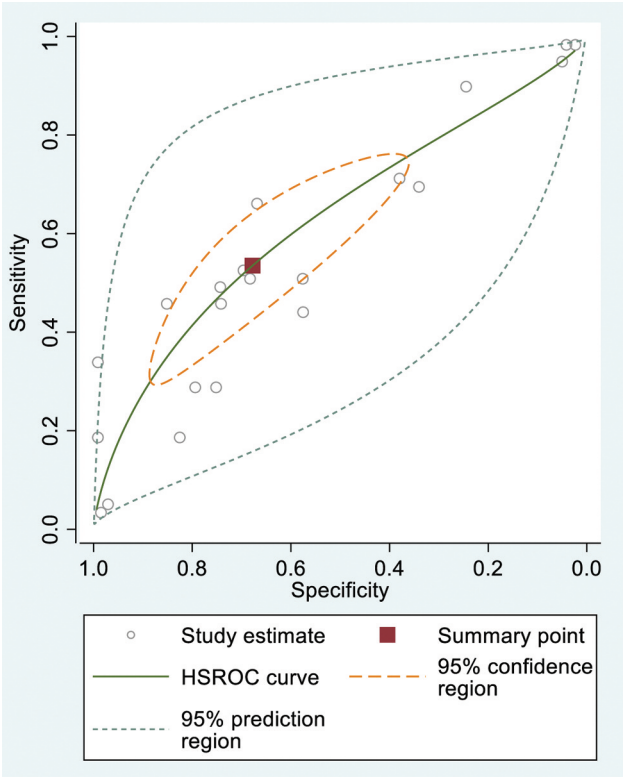


Figure 7. *Hierarchical summary receiver operating characteristic (HSROC) curve of the history-taking in acute renal colic.*

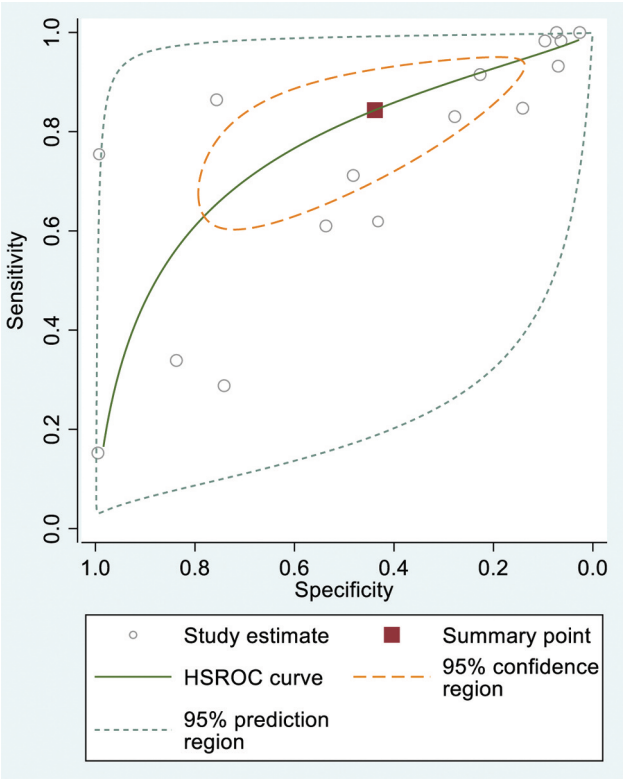


Figure 8. *Hierarchical summary receiver operating characteristic (HSROC) curve of the clinical signs and tests in acute renal colic.*

Table III. *Diagnostic score (DS) for acute renal colic (ARCO) model. The DS model is shown at five different cut-off levels of the DS derived from symptoms, signs and tests, with the -positive endpoint (PE) being ARCO and the -negative endpoint (NE) being another cause of abdominal pain. In DS model V 46 patients were excluded including four ARCO patients and 42 non-ARCO patients.*

| | | Frequency | | | |
|---|---|---|---|---|---|
| Logistic DS model | DS Cut-off | TP | FN | FP | TN |
| 1. DS I | –3.29 | 51 | 2 | 55 | 1,060 |
| 2. DS II | –2.23 | 50 | 3 | 39 | 1,076 |
| 3. DS III | –0.69 | 47 | 6 | 13 | 1,1,02 |
| 4. DS IV | 1.01 | 41 | 12 | 2 | 1,113 |
| 5. DS V | DS values between –3.29 and –0.69 excluded | 47 | 2 | 13 | 1,060 |

FN: False-negative; FP: false-positive; TN: true-negative; TP: True-positive. Logistic regression analysis formula for DS: –3.26 × gender (female=1, male=0) + 2.60 × duration of pain (PE=1, NE=0) + 1.54 × appetite (PE=1, NE=0) + 6.89 × tenderness (PE=1, NE=0) + 3.23 × renal tenderness (PE=1, NE=0) + 7.56 × urine (PE=1, NE=0) – 8.06. For PE/NE details see Tables I and II.

Their patient cohort was fully selected, however, including only patients with suspicion of ARCO and no other patients with AAP were included.

Rana *et al.* conducted a prospective study including 132 patients with ARCO. They validated the diagnostic performance of the Al-Terki DS including serum creatinine, leucocyte count, the largest diameter of the stone in CT and stone place in CT. The AUC value of the clinico-radiological DS was 0.93 (17). However, this study was also limited by the highly selected patient cohort, only including patients with ARCO.

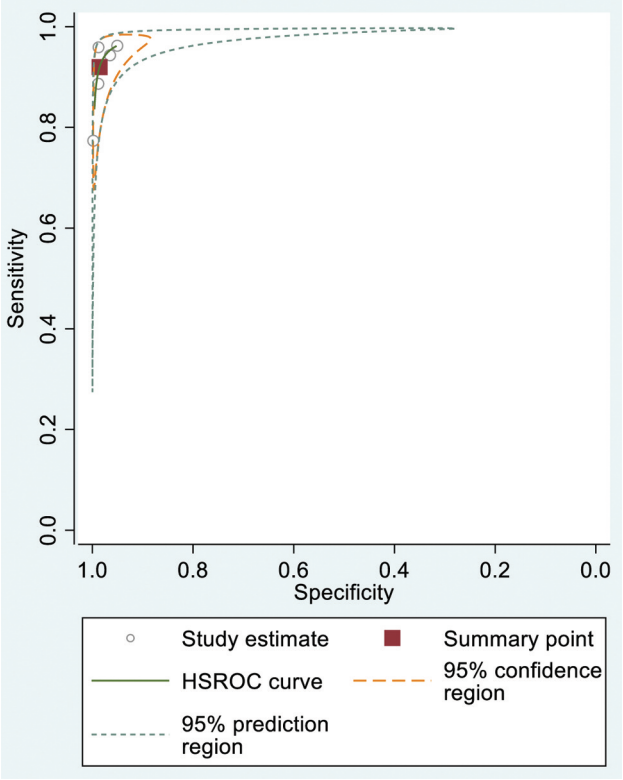


Figure 9. *Hierarchical summary receiver operating characteristic (HSROC) curve of the five diagnostic score (DS) models. Please see Table III for details of the logistic models.*

## Conclusion

Only few trials with US or CT imaging have studied the applicability of DS models in patients with ARCO. We were unable to perform direct comparisons to previous DS trials because the present study is the first to provide evidence that DS can be used for diagnosis of ARCO among patients presenting with AAP. Taken together, as determined by the AUC values of the HSROC tests, the DS for ARCO is superior to both i) symptoms and ii) signs and tests. The major advantages of our DS is that this model does not need US, CT or laboratory analyses to reach high accuracy for ARCO.

## Conflicts of Interest

The Authors report no conflicts of interest or financial ties to disclose.

## Authors' Contributions

All Authors contributed to the collection and analysis of data, drafting and revising the manuscript, read and approved the final article.

## Acknowledgements

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## References

1 Scales CD Jr, Tasian GE, Schwaderer AL, Goldfarb DS, Star RA and Kirkali Z: Urinary stone disease: advancing knowledge, patient care, and population health. Clin J Am Soc Nephrol *11(7)*: 1305-1312, 2016. PMID: 26964844. DOI: 10.2215/CJN.13251215

2 Fwu CW, Eggers PW, Kimmel PL, Kusek JW and Kirkali Z: Emergency department visits, use of imaging, and drugs for urolithiasis have increased in the United States. Kidney Int *83(3)*: 479-486, 2013. PMID: 23283137. DOI: 10.1038/ki.2012.419

3 Heers H and Turney BW: Trends in urological stone disease: a 5-year update of hospital episode statistics. BJU Int *118(5)*: 785-789, 2016. PMID: 27128735. DOI: 10.1111/bju.13520

4 Chen TT, Wang C, Ferrandino MN, Scales CD, Yoshizumi TT, Preminger GM and Lipkin ME: Radiation exposure during the evaluation and management of nephrolithiasis. J Urol *194(4)*: 878-885, 2015. PMID: 26055822. DOI: 10.1016/j.juro.2015.04.118

5 Gottlieb M, Long B and Koyfman A: The evaluation and management of urolithiasis in the ED: A review of the literature. Am J Emerg Med *36(4)*: 699-706, 2018. PMID: 29321112. DOI: 10.1016/j.ajem.2018.01.003

6 Eskelinen M and Lipponen P: Usefulness of history-taking in non-specific abdominal pain: a prospective study of 1333 patients with acute abdominal pain in Finland. In Vivo *26(2)*: 335-339, 2012. PMID: 22351680.

7 Meklin J, Eskelinen M, Syrjänen K and Eskelinen M: Leucocyte count does not improve the diagnostic performance of a diagnostic score (DS) in distinguishing acute appendicitis (AA) from nonspecific abdominal pain (NSAP). In Vivo *34(6)*: 3327-3339, 2020. PMID: 33144440. DOI: 10.21873/invivo.12171

8 Meklin J, Eskelinen M, Syrjänen K and Eskelinen M: Gender-specific performance of a diagnostic score in acute appendicitis. In Vivo *34(6)*: 3687-3703, 2020. PMID: 33144486. DOI: 10.21873/invivo.12217

9 Eskelinen M, Meklin J, Syrjänen K and Eskelinen M: Performance of a diagnostic score in confirming acute cholecystitis among patients with acute abdominal pain. Anticancer Res *40(12)*: 6947-6956, 2020. PMID: 33288589. DOI: 10.21873/anticanres.14719

10 Eskelinen M, Meklin J, Syrjänen K and Eskelinen M: Pediatric acute appendicitis score in children with acute abdominal pain (AAP). Anticancer Res *41(1)*: 297-306, 2021. PMID: 33419824. DOI: 10.21873/anticanres.14776

11 Eskelinen M, Meklin J, Syrjänen K and Eskelinen M: A diagnostic score (DS) is a powerful tool in diagnosis of acute appendicitis in elderly patients with acute abdominal pain. Anticancer Research *41(3)*: 1459-1469, 2021. DOI: https://doi.org/10.21873/anticanres.14904

12 Moore CL, Bomann S, Daniels B, Luty S, Molinaro A, Singh D and Gross CP: Derivation and validation of a clinical prediction rule for uncomplicated ureteral stone—the STONE score: retrospective and prospective observational cohort studies. BMJ *348*: g2191, 2014. PMID: 24671981. DOI: 10.1136/bmj.g2191

13 Fukuhara H, Kobayashi T, Takai S, Tawara T, Kikuta M, Sugiura A, Yamagishi A, Toyohara T, Nakane M and Tsuchiya N:

External validation of the CHOKAI score for the prediction of ureteral stones: A multicenter prospective observational study. Am J Emerg Med *38(5)*: 920-924, 2020. PMID: 31337599. DOI: 10.1016/j.ajem.2019.07.018

14 Daniels B, Gross CP, Molinaro A, Singh D, Luty S, Jessey R and Moore CL: STONE PLUS: Evaluation of emergency department patients with suspected renal colic, using a clinical prediction tool combined with point-of-care limited ultrasonography. Ann Emerg Med *67(4)*: 439-448, 2016. PMID: 26747219. DOI: 10.1016/j.annemergmed.2015.10.020

15 Herbst MK, Rosenberg G, Daniels B, Gross CP, Singh D, Molinaro AM, Luty S and Moore CL: Effect of provider experience on clinician-performed ultrasonography for hydronephrosis in patients with suspected renal colic. Ann Emerg Med *64(3)*: 269-276, 2014. PMID: 24630203. DOI: 10.1016/j.annemergmed.2014.01.012

16 Al-Terki A, El-Nahas AR, Abdelhamid U, Al-Ruwaished MA, Alanzi T and Al-Shaiji TF: Development and validation of a score for emergency intervention in patients with acute renal colic secondary to ureteric stones. Arab J Urol *18(4)*: 236-240, 2020. PMID: 33312734. DOI: 10.1080/2090598X.2020.1761143

17 Rana RS, Nazim SM and Ather MH: Predicting emergency interventions in patients with acute ureteral colic using acute renal colic scoring system in a Pakistani cohort. Int Urol Nephrol *53(1)*: 21-26, 2021. PMID: 32813207. DOI: 10.1007/s11255-020-02607-7

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