Acute appendicitis. Update of clinical scores

Ann. Ital. Chir., 2019 90, 3: 231-237
pii: S0003469X19029440

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Acute appendicitis. Update of clinical scores

OBJECTIVES: *Evaluate Alvarado Score's (AS) accuracy related with C-reactive protein (CRP). Evaluate the accuracy rate of ultrasonography (US).*
MATERIALS AND METHODS: *We analyzed data on 290 patients admitted to Emergency Department (ED) of Sant'Andrea Hospital (Rome – Italy) presenting abdominal pain in lower quadrants between Jan2009-Apr2015. AS, laboratory tests, images and report from CT-scan and US were collected. Histological examination is considered as Gold Standard. We calculated Specificity(Sp), Sensitivity(Se), Accuracy(Ac), positive predictive value(PPV), and negative predictive value(NPV). We use Exact Fisher Test (EFT) for samples less than 50 units, and Chi square test (χ^2). CRP were assessed as possible laboratory marker to be added to AS.*
RESULTS: *Two hundred and forty patients (82%) were enrolled following the inclusion criteria. The variations obtained from the AS with C-reactive protein show no difference. CT-scan vs US results show a higher Sp for US despite CT ($p= 0.0509$ $\chi^2=3.803$. Se and NPV are higher in CT compared to the US (Se: $p=0.000315$ $\chi^2= 12.88$ NVP: $p=0.015$. We evaluated Ac of US and CT within the individual groups (low(L), Intermediate(I), High(H): L; 37 patients show no statistically significant difference (EFT=1; $p>0.05$). I: show superiority of CT-scan in Se and NPV (FE:0.0162 $p<0.05$; FE:0.0432 $p<0.05$). Regarding H only Se show an acceptable p-value ($p<0.0021$).*
CONCLUSION: *Alvarado score (AS) can be used as the first diagnostic approach in the diagnosis of acute appendicitis (AA). Ultrasound must be considered the first level instrumental examination; necessary and sufficient in low risk patients (0-3 pt) to exclude, with a high reliability rate, the diagnosis of acute appendicitis.*

KEY WORDS: Acute Appendicitis, Alvarado Score, CT scan, Ultrasound, Peritonitis

Introduction

Acute abdominal pain is the principal cause of access in Emergency Department (ED) and accounts in Italy for 5-10% of all visits[1]. Acute appendicitis (AA) is the main cause of emergency abdominal surgery and in one third of cases presents atypical clinical and laboratory findings[2-3]. The lifetime risk of appendicitis is 8.6% for male and 6.7% for female; however, the risk of undergoing appendectomy is much lower for male than for female (12 vs 33%) and it occurs most often between the ages of 10 and 30, with a male /female ratio of 1.4:1. [4-5] Additional investigations such as ultrasound, CT-scan are used on one hand to minimize the rate of "white appendicitis", on the other to highlight the complicated cases thus reducing morbidity and mortality associated with missed perforations[6] and finally to avoid any legal issue. Notwithstanding these techniques the rate of appendicitis not confirmed by histology is still between 5 and 25%[7]. This percentage shows that the number of "unnecessary" appendectomies is relatively independent from pre-operative instrumental examinations, while it derives from the lack of a standardized diagnostic protocol that allows an acceptable diagnostic accuracy.

Pervenuto in Redazione Dicembre 2018. Accettato per la pubblicazione Gennaio 2019
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The modified Alvarado Score (AS) with the inflammatory marker C-reactive protein (CRP) seems to be able to guide the surgeon in early and appropriate diagnosis[8], being the "first step" to decide further investigations, especially in atypical clinical presentation. A systematic review by Olhe et al showed that AS was highly accurate and specific, especially in male, to rule out the diagnosis of acute appendicitis rather than to confirm it[9]. Other authors tried to increase the accuracy rate of the AS using other parameters such as sex, age and associated comorbidities. In pediatric patients, Blitman suggested that a CT- scan can be avoided with a low Alvarado and an ultrasound negative, considering the high negative predictive value of these two tests in combination[10]. In obese patients (BMI> 25-30) an AS modified according to their weight and age was demonstrated to be accurate[11]. In contrast, the AS was less predictive in fertile women, with an increase in false positives[12].

In multiple studies ultrasonography showed a sensitivity around 85% and a specificity higher than 90%[13], using as signs of AA the increased diameter of the appendix, parietal thickening and peri-appendicular involvement. In 2004 a multicenter study by Wind et al. [14], evaluated different strategies for radiological assessment of patients admitted to the emergency department with acute abdominal pain and showed that ultrasound in past years in Europe has been used as the first instance exam for the diagnosis of AA. Nevertheless, the practical use remains controversial. Ultrasound, in fact, don't seems to reduce number of "unnecessary" appendectomies. However, given the absence of radiation, US is still recommended in high-risk groups such as children and fertile women in pregnancy, especially during the first trimester of gestation. CT-scan showed higher sensitivity and specificity than ultrasound becoming the gold standard for diagnosis of AA in USA[15,16-30], while in Europe it is evaluated case by case.

Primary objective of the present study was to evaluate the accuracy of modified Alvarado score with inflammatory markers such as C-reactive protein (CRP). Secondary objectives were to reduce the number of CT-scan performed in ED in suspected AA and to evaluate the accuracy of US in the diagnosis of AA.

Materials and Method

We retrospectively analyzed data collected from electronic database on patients admitted to ED of Azienda Ospedaliera Sant'Andrea (Rome – Italy) presenting abdominal pain in lower quadrants between January 2011 and April 2015. Inclusion criteria were: comprehensive report of clinical emergency room and hospitalization, with all parameters to calculate the AS, blood sample with dosage of C-reactive protein at the admission (T0), CT-scan and/or US, appendectomy or other abdominal or pelvic surgery, with histological diagnosis. Exclusion criteria were age less than 10 and higher than 95 years. AS and the laboratory tests (PCR, leukocytosis and neutrophilia) were collected from medical records of patients at the time of entry and 24-48 h after admission and prior to surgery. If value of PCR was greater than 0.5 mg/dl, one point to total count of AS was added. The weight and height of each individual patient and the Body Mass Index (BMI) was recorded Images and report of US and CT were obtained. Histological examination was considered the gold standard for diagnosis.

Specificity (Sp = TN / (TN + FP), sensitivity (Se = TP / (TP + FN), Accuracy (Ac = (TP + TN) / (P + N), positive predictive value (PPV = TP / (TP + FP), and negative predictive value (NPV = TN / (TN + FN) of each diagnostic test were calculated. The significance of categorical variables obtained by different tests was analyzed using the *Exact Fisher Test (EFT)* for samples less than 50 units, and the *Chi square test* (χ^2) for the others. The SPSS (Statistical Package for Social Science) was used for computations. A level of p-value <0.05 was considered significant for all tests.

Results

A total of 292 patients were evaluated and 240 (82%) were enrolled following the evaluation of the inclusion criteria. Fifty-two patients were excluded for: absence of surgery (n° 20), age not between 10 and 95 years (n° 32).

In the cohort of the study 123 were males (51.2%) and 117 females (48.7%), with an average of 34.5 years (SD ± 18.7).

Age was 10-20 years in 71 (29.6%), 93 (40%) between 20 to 40 in 93 (40%) and > 40 years in 76 (30.4%) > 40 aa, with a minimum 10 aa (4 pt) and a maximum 93 aa (1 pt). Of the 240 patients screened, 14 (5.8%) were underweight (BMI < 18.4). All Two hundred and forty patients elected underwent surgery: 84 performed open surgery (35%) and 156 laparoscopic surgery (65%) with a conversion rate of 2.5%.

Histological examination of the surgical specimen was available in all 240 patients with the following diagnoses: AA in 188 (78.3%); other abdominal or pelvic diseases in 52 cases (21.7%). The main differential diagnosis obtained in our study are summarized in Tabl I.

AS of all patients was measured, and we divided patients in three different risk's classes: High (145 60.42%) with a score ≥ 7; Intermediate (58, 24.17%) with a score between 4-6; Low: (37, 15:42%) with a score ≤ 3. The average was 6.40 ± 2.71.

We also evaluated, the variations of AS with the addition of C-reactive protein, which has been measured at T0 in 234 patients out of 240 (97.5%). The data are shown in Fig. 1. There was no difference between two scores in general population.

TABLE I

Abdominal or pelvic disease	Frequency N°	(%)
Right ovarian cyst	7	2,92
Acute salpingitis	7	2,92
Chronic infiammation	7	2,92
Diverticulitis	6	2,50
Acute colecistitis	4	1,67
Appendiceal Cancer*	4	1,67
Left ovarian cyst	3	1,25
Endometriosis	3	1,25
Crohn disease	2	0,83
Uterine myoma	2	0,83
Torsione peduncolo ovarico	2	0,83
Extra uterin pregnancy	2	0,83
Peritoneal carcinomatosis	1	0,42
Colon adenocarcinoma	1	0,42
Inguinal protesis infection	1	0,42
Total	52	

*1 adenoma, 2 adenocarcinoma, 1 Linfoma

TABLE II - *CT-scan data.*

%	CT-scan
Sp	64
Se	98,75
PPV	89,77
NPV	94,11
Acc	90,47

TABLE III - US data.

%	US
Sp	84,44
Se	82,57
PPV	93,96
NPV	62,29
Acc	83

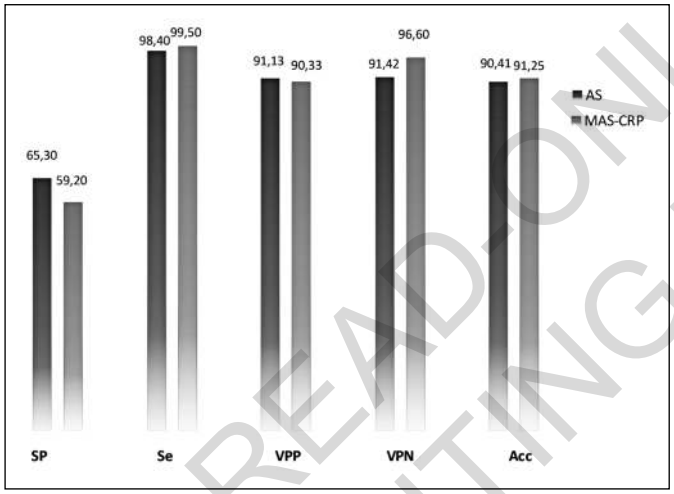

Fig. 1: Alvarado score vs Modified Alvarado, Score with CRP.

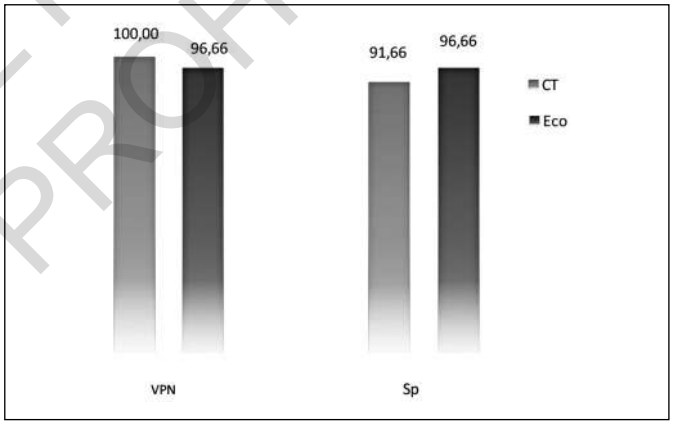

Fig. 2: Low risk.

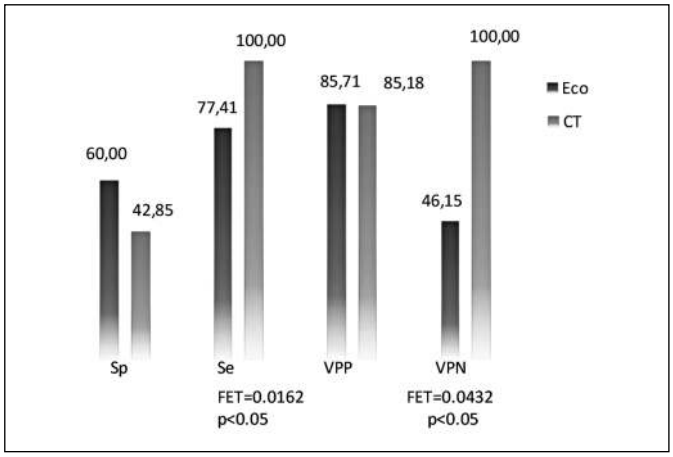

Fig. 3: Intermediate risk.

In the low class of risk CRP within the AS obtained a reduction in the number of *false negatives* with consequent increase of the *sensitivity* of the test, but a parallel increase in the number of *false positive* in the *intermediate* and *high* risk classes, with a concomitant decrease in specificity.

One-hundred and five patients (43,7%) were subjected to a CT-scan in Emergency Department.

The CT scan in 83.8% (n = 88) was positive, with a report suggesting for "suspected acute appendicitis", while the remaining 16.2% was negative (no CT-signs of AA). Seventy-nine (75.2%) had positive CT-findings and definitive histological examinations; Sixteen (15.2%) had negative CT-findings and had other disease at the

Table IV

Risk	Ultrasonography FP	TP	FN	TN	Tot	CT-scan FP	TP	FN	TN	tot
Low	1	3	1	29	34	1	11	0	3	15
Intermediate	4	24	7	6	41	4	23	0	4	31
High	2	82	15	1	100	3	55	0	1	59

FP/TP: false/true positive FN/TN: false/true negative

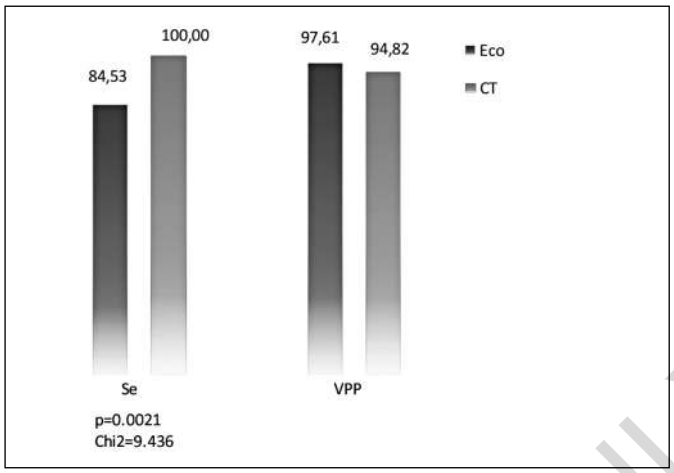

Fig. 4: High risk.

intraoperative examinations. Nine (0.08%) had positive CT-findings but resulted negative at definitive histological examination and one (0.01%) had negative CT-findings but resulted positive at the definitive histological examination. The 9 patients with false positive results were respectively affected by: Chronic Appendicitis (n = 4), Appendiculous neoplasia (n. = 4) and Crohn's disease (n ° = 1). The statistical data are exposed in Table II. The 73.7% of patients (n = 177) performed US. One-hundred and seventeen (66.1%) had positive US-findings for suspect AA, while 33.9% (n = 60) was negative. Of the 177 patients examined: One-hundred and nine (61.6%) had positive US-findings with a positive histological examination; thirty-eight (21.5%) had negative US-findings and were affected from other disease at the intraoperative examination. Seven (0.04%) had positive US-findings but negative histological examination and 23 (13%) had negative US-findings but positive histological examination. The data are shown in Table III. The results showed a higher Sp for US compared to CT (p= 0.0509 χ^2=3.803). Similarly, positive predictive value (PPV) was found to be higher for US than CT (94% vs 90%), without statistical significance levels (p = 0.269 χ^2=1.127). Sensitivity (Se), Negative Predictive Value (NPV) and Accuracy (Acc) were higher in CT compared to the US (Se: p=0.000315 χ^2= 12.88 VPN: p=0.015 (FET).

We evaluated the diagnostic accuracy indices of US and CT within the individual groups (low, Intermediate, High) of AS.

In 37 low-risk patients Sp and PPV of US and CT scan were not statistically significantly different (Fisher exact test=1; p>0.05) (Table V). All 203 intermediate and high risk patients undergone a radiological examination (US, CT-scan or both). The statistical analysis and data are shown in table 4 and in graphs III and IV. The analysis showed superiority of CT-scan in sensitivity and negative predictive value for intermediate risk (FE:0.0162 p<0.05; FE:0.0432 p<0.05).

Discussion

Our results updated and reviewed the accuracy of clinical predictive rule in the diagnosis of AA, confirming the usefulness and applicability of AS in clinical practice with or without the use of CRP. Moreover we underlined the power of US as first diagnostic step especially in selected group of patients with low risk AS, encouraging a critical reduction of CT-scan performed in ED.

In the last three decades, considering the stable rate of AA not confirmed at pathological examination associated with the increased risk of legal issues, defensive medicine brought surgeons to utilize more and more often CT-scan and Ultrasonography to confirm the diagnosis. Clinical predictive rules (Cpr) based on clinical, laboratory and radiological data, should be considered in order to reduce the misdiagnosis rate and percentage of appendectomy performed without correct indication[17].

The validity of AS has been summarized in a recent meta-analysis including 5960 patients in 29 studies:[8] According to Ohle et al, the score's performance is dependent on the cut-off value: a clinical cut-off score of less than five can be applied to rule-out appendicitis with a sensitivity of 99% and specificity of 43%. In our results Se and Sp of AS were higher (98.40 and 65.30 respectively) and no differences were registered between AS and MAS-CRP. During the following years a lot of studies have been published trying to increase the specificity and sensibility of AS. Wen Liu et al. demonstrated with the RIPASA score an higher rate of diagnostic accuracy but an inferior specificity[18]. Other famous scores

used in in daily practice are: the Paediatric Appendicitis score (PAS) [19]. The Appendicitis Inflammatory Response (AIR) score[20], and the most recently Adult Appendicitis Score (AAS) [21]. Thirumallai et al on 234 patients evaluate the potential association of AS with CRP demonstrated a really powerful negative predictive value (NPV) especially in patients with AS between 4-6, or <3 (respectively 72% and 86%)[22]. In our study conducted on patients with abdominal pain in lower quadrant there was no significant difference between AS and Modified Alvarado Score with C-reactive Protein (MAS-CRP).

Resuming all literature about clinical scores, in the last consensus conference organized by World Society of Emergency Surgery (WSES) held in Jerusalem during July 2015, a team of expert defined the diagnostic efficiency of clinical scoring systems and their role in the management of patients with suspected appendicitis. Three different statement were proposed[23]: 1. AS (with a cut-off score < 5) is sufficiently sensitive to exclude acute appendicitis (LoE 1, GoR A) 2. AS is not sufficiently specific in diagnosing acute appendicitis (LoE 1, GoR A) 3. An ideal (High sensitivity and specificity), clinically applicable, diagnostic scoring system/clinical rule remains outstanding. This remains an area for future research.

Our results agree with these statements showing an high rate of Se and Negative Predictive value (99.5 and 96.6 respectively). Moreover the association with radiological techniques appears indispensable in high and intermediate groups to confirm the diagnosis. In fact the typical symptoms and laboratory signs may be absent in 20-33% of patients and, when they are present, can be similar to other conditions, especially in early stage[24-25]. Regarding the instrumental evaluation, CT-scan and Ultrasonography are compared in a lot of studies in literature. Soreide in a recent Pubmed search under term of appendicitis found over 20.000 articles, but few randomized trials, especially in imaging, have been undertaken with resultant variable level of evidence[26]. Scott et al suggest that low risk patients admitted to hospital and considered for surgery could have appendicitis ruled in or out by abdominal CT. A negative CT would generally allow the discharge of the patient with appropriate short outpatient-department follow-up. In our study these group of patients (AS 0-3) has a NPV of US of 96.6%, and no significant differences were registered with same CT-scan's group according to Blitman et al.[10] and the study of Toprak H. et al. [27] Parker et al compared costs from two different protocols: CT-scan only vs CT-scan plus US. The final spending review was about 24 mln USD per year[28]. Considering the results of our analysis a total of 32 patients of 240 (13,3%) had a not-necessary CT-scan evaluation; Ten patients with low risk AS having a negative US, 8 patients with intermediate AS with positive US and finally 14 patients with high risk AS with positive US evaluation. Not considering the spending review related with these abuse of CT-scan evaluations, we can't forget the toxic damage of ionizing radiation exposure[29] for these patients. In view of the increased use of CT-scan in children and concerns regarding radiation based imaging, the National Cancer Institute and the American Paediatric Surgical Association recommend use of non-radiation based imaging such as US where possible[30]. Currently, over 50% of children undergoing appendectomy in North America have still radiation based imaging[31]. Universal imaging of patients with CT is not without health consequences: it has been estimated that the benefit of universal imaging in avoiding 12 unnecessary appendectomies could result in one additional cancer death[32]. Performing serial US seems to improve accuracy and reduce the number of CT performed[33]. Our analysis shows that, with correct clinical evaluation based on CPR and AS, the US evaluation takes a central role in patients with suspected AA with acceptable diagnostic rate.

The limits of this study are represented by the retrospective nature of collected data, and the powerless number of patients in single groups. On the other hand, the histological evaluation of surgical specimen taken as a gold standard and the consequent absence of lost to follow-up patients give power to our results.

Conclusion

The AS can be used as the first diagnostic approach in the diagnosis of AA, orienting the surgeon for the correct use of instrumental devices that he needs for the diagnosis of certainty.

Ultrasound must be considered the first level instrumental examination; necessary and sufficient in low risk patients (0-3 pt) to exclude, with a high reliability rate, the diagnosis of acute appendicitis.

CT-scan could be considered the second level instrumental examination, useful in intermediate and high risk patients (4-10 pt) who present an unreliable or negative ultrasound.

Riassunto

Lo scopo dello studio è stato quello di valutare l'accuratezza dell'Alvarado Score (AS) in relazione alla proteina C-reattiva (CRP) per l'appendicite acuta ed il livello di precisazione diagnostica ottenibile con l'ecografia (US). Sono stati analizzati i dati di 290 pazienti ricoverati presso il Dipartimento di Emergenza dell'Ospedale Sant'Andrea di Roma, che presentavano dolore addominale nei quadranti inferiori tra gennaio 2009 e aprile 2015. Sono stati raccolti i punti dell'AS, gli esami di laboratorio, immagini e referti di TC ed ecografia, considerando come "gold standard" l'esame istologico.

Abbiamo calcolato Specificità (Sp), Sensibilità (Se), Precisione (Ac), valore predittivo positivo (PPV) e valo-

re predittivo negativo (NPV). Abbiamo usato *Exact Fisher Test* per campioni inferiori a 50 unità, ed il *Chi square test* (χ^2). La PC Reattiva è stata valutata come possibile marker in aggiunta ai AS.
Sono stati arruolati nello studio 240 pazienti (82%) in rispetto dei criteri di inclusione.
L'aggiunta della PCR agli AS non ha dimostrano differenze. Il confronto tra TC e US ha mostrato una maggiore specificità degli ultrasuoni rispetto alla tomografia computerizzata (p= 0.0509 χ^2=3.803. Sensibilità e valore predittivo negativo sono risultati più alti nella CT rispetto agli US (Se: p=0.000315 χ^2= 12.88 NVP: p=0.015). Abbiamo valutato la accuratezza di US e CT all'interno dei singoli gruppi (basso (L), intermedio (I), alto (H): nel L 37 pazienti non hanno mostrato differenze statisticamente significative (EFT = 1; p> 0,05). Negli I hanno presentato la superiorità della CT in termini di sensibilità e valore predittivo negativo (FE: 0,0162 p <0,05; FE: 0,0432 p <0,05). Nel gruppo H solo la sensibilità ha mostrato un valore p accettabile (p <0,0021).
In conclusione il punteggio Alvarado (AS) può essere usato come primo approccio diagnostico nella diagnosi di appendicite acuta (AA) L'ecografia deve essere considerato l'esame strumentale di primo livello, necessario e sufficiente in pazienti a basso rischio (0-3 pt) per escludere, con un alto tasso di affidabilità, la diagnosi di appendicite acuta.

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