Clinical Prediction Rules in acute appendicitis: Which combination of variables is more effective at predicting?

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Abstract

Background: Clinical prediction rules have been designed to reduce diagnostic variability and improve the effectiveness of the diagnostic process. However, there are no unanimous criteria regarding which of them is the most efficient for the diagnosis of right iliac fossa pain.

Aim: The primary aim of this study was to assess the diagnostic efficacy of the most commonly used clinical prediction rules. The second aim was to identify the combination of the smallest number of clinical and analytical variables that would allow a cost-effective diagnostic approach to assess the right iliac fossa pain.

Methods: A retrospective observational study was conducted of 458 patients who were evaluated for right iliac fossa pain between January 2010 and December 2016. The selected scores (Alvarado, AIR, RIPASA, and AAS) were applied to all cases to validate their effectiveness and simultaneously establish the smallest number of variables that were needed for an efficient diagnosis. Univariate and multiple regressions were used for validation.

Results: Of the four scores tested, the Alvarado score was the most efficient diagnostic approach. However, the most reduced and predictive combination of the evaluated variables included anorexia, white blood cell count> 8275 leukocytes/μL, neutrophilia (>75%), abdominal pain < 48 hours, migrating pain to the right lower quadrant and axillary temperature out the range of 37-39ºC.

Conclusions: A new and effective score for predicting appendicitis in patients presenting with right iliac fossa pain has been established.

Introduction.

Acute appendicitis (AA) is one of the most common surgical pathologies in emergence units, with a lifetime risk between 7–9% [1, 2, 3]. It is more frequent between children and young adults. Its incidence seems to be conditioned by different factors such as sex, age, ethnicity and the season of the year [2, 4]. However, most of the patients who present with acute right iliac fossa pain (RIFP) do not have appendicitis. The differential diagnosis can be difficult and remains a clinical challenge [3].

Considered as a progressive disease whose natural evolution is toward perforation, early diagnosis and treatment are necessary to reduce morbidity and mortality [5, 6], and surgery is the gold standard of treatment [7]. Currently, two types of appendicitis are thought to exist: uncomplicated (nonperforating) and complicated (perforating) appendicitis [6]. The etiology and pathogenesis of AA remain largely unknown and predicting a mild or fulminate course of appendicitis is not possible. However, recent studies suggest that with a logistic regression model, this could be predicted (6). Regardless, delaying an appendectomy increases the risk of perforated appendicitis, which is associated with a higher incidence of short- and long-term morbidity [8, 9]. Hence, appendectomy is recommended as soon as possible [10, 11].

Diagnosis is based on the clinical history, examination, and laboratory and imaging tests [12]. Ultrasonography (US), abdominal computed tomography (CT) and magnetic resonance imaging (MRI) are most commonly used. These can reduce the negative appendectomy rate, which has been reported to be as high as 15% [13]. US is noninvasive, avoids radiation and is associated with a sensitivity rate between 71% and 94% and a specificity rate between 81% and 98% [14, 15]. This technique is therefore reliable to confirm the presence of appendicitis but unreliable to exclude appendicitis [3]. Furthermore, one should bear in mind that US is highly operator dependent [3]. Inconclusive US findings, mostly due to failure visualizing the appendix, mandate additional imaging studies. Abdominal CT for suspected appendicitis has sensitivity and specificity rates between 76–100% and 83–100%, respectively, and therefore, CT is superior to US [15, 16]. However, the radiation exposure of abdominal CT is a concern, particularly in children and pregnant women [16].

There is an evident lack of uniformity between the different guidelines regarding diagnosing and managing AA [7]. In an attempt to standardize the diagnostic approach to this pathology, clinical prediction rules (CPRs) have been introduced, seeking to provide a more objective approach to diagnosing RIFP and avoiding unnecessary operations [12, 17].

Both clinical and biochemical variables have been used in CPRs to increase the value of individual variables. Since the initial proposal of Alvarado [18], there are currently approximately 12 CPRs available for AA diagnosis [12].

The most tested one is the Alvarado score, introduced in 1986 ([8]. This score has proven to be very efficient at “ruling-out” appendicitis with an overall sensitivity and specificity of 96% and 81%, respectively [17]. However, of the 8 variables used in the initial scale of Alvarado, new variables and weightings have been added to the successive scales developed, leading to a progressive complexity of CPRs and, therefore, making their use less efficient [12].

Nonetheless, the use of such CPRs appears useful to determine the likelihood of AA, distinguishing between low-, intermediate- and high-risk cases. Likewise, they allow identifying the cases in which image methods must be implemented [14]. Taken together, these diagnostic requirements highlight the need to perform a systematic clinical evaluation of patients with RIFP, which can be done efficiently with the use of CPRs, but the simplification of CPRs may make them more useful.

The aim of this study was to validate the effectiveness of the currently available CPRs in performing a correct diagnosis and to develop a new simplified and efficient scoring system.

Materials And Methods:

A retrospective observational study was conducted. The clinical records of 458 patients who were evaluated for suspected AA from January 2010 to December 2016 were reviewed. All patients underwent surgery using an open (25) or a laparoscopic (433) approach. Diagnostic confirmation was obtained through the anatomopathological report, which indicated AA by the presence of inflammatory cells

(leukocytes, lymphocytes or plasma cells) in the surgical specimen or indicated negative appendectomy (NA) in the absence of these cells [19].

The information collected included demographic and personal data, clinical features, and analytical data at admission, as well as interventional reports, and postoperative outcomes. With this information, the Alvarado, RIPASA (Raja isteri pengiran anak saleha appendicitis), AIR (appendicitis inflammatory response) and AAS (adult appendicitis score) scores were established for the selected patients.

The data obtained were entered into an anonymized database created in Microsoft Excel (Microsoft Corporation. Redmond, WA 98052. USA) and were analyzed using IBM SPSS Statistics version 20.0 (IBM Corporation Armonk, New York 10504. USA). In the descriptive analysis, the quantitative variables are reported as the median and the interquartile range (IQR). The qualitative variables are reported as frequencies and percentages of the total number of patients (N, %). Associations between the qualitative variables were analyzed by the Pearson chi-square ($\chi 2$) test. Comparisons of the quantitative values were carried out using the nonparametric Mann–Whitney U test. To determine the diagnostic efficiency of these scales, an analysis was performed using receiver operating characteristic (ROC) curves, with a calculation of the area under the curve (AUC) for each scale. Then, the scores were stratified according to a low, medium or high probability of presenting AA according to established literature guidelines the Alvarado [17, 18], RIPASA [20], AIR [21] and AAS [22] scales.

To elaborate a new score (the HMC score), a univariate logistic regression was performed for each variable. In addition, the white blood cell count (WBCC) was categorized to establish a cut-off point. With this aim, a univariate binary logistic regression was performed with each decile, considering statistical significance when $p < 0.05$. Those with $p < 0.1$ were included in the multivariate analysis by the Wald method. After an automatic adjustment, a multivariate regression model was performed to identify those variables that behaved as independent factors of a confirmed diagnosis of AA. Finally, the AUC of the new scale was established.

The data were treated confidentially and anonymously according to the provisions of Spanish Organic Law 15/1999 of December 13 of the Personal Data Protection (LOPD).

Results

We analyzed 458 patients who fulfilled the inclusion criteria: abdominal pain with suspected AA and underwent an appendectomy. Of these, 404 (88.2%) patients had a histological confirmation of appendicitis, and 54 (11.8%) had a normal appendix. In 36 patients, the intraoperative appearance of the appendix was considered normal; however, in 10 of these patients (27.8%), the histological report confirmed the presence of AA. The median age of all patients was 31 years (IQR: 18.0–48.0 years). In the distribution by sex, a male predominance was observed (266 patients: 58.1%), and 60.9% of the patients with histologically confirmed appendicitis were males ($p < 0.001$). US was performed in all cases and was suggestive of AA in 260 (60%) patients, including 243 patients with histological confirmation of AA (sensitivity 63.8% and specificity 67.3%).

The scales under investigation were applied to all patients in our cohort, and all scales showed statistically significant results in terms of predictive ability and diagnostic performance (Table 1).

Table 1
Results of predictive ability and diagnostic performance of CPRs tested.

SCORE	Total = 458	NA = 54 (11,8%)	AA = 404 (88,2%)	p-value
Alvarado	6,00 [5,00–8,00]	5,00 [4,00–6,00]	6,00 [5,00–8,00]	**< 0,001**
RIPASA	7,50 [6,50–9,00]	7,00 [5,50–8,00]	7,50 [6,50–9,00]	**< 0,001**
AIR	5,00 [4,00–7,00]	4,00 [2,00–5,00]	5,00 [4,00–7,00]	**< 0,001**
AAS	11,00 [9,00–13,00]	9,00 [7,00–11,00]	11,00 [9,00–13,50]	**< 0,001**
AA: histological confirmation; NA: no histological support for AA.				

The AUC of each CPR based on the probability of AA diagnosis is shown in Table 2, and the ROC curves are shown in Fig. 1.

Table 2
AUC of the scales according to the histological confirmation of acute appendicitis.

Score	AUC	Confidence interval 95%		p-value
Alvarado	0,74	0,67	0,80	**< 0,001**
RIPASA	0,63	0,56	0,71	**< 0,001**
AIR	0,70	0,62	0,78	**< 0,001**
AAS	0,70	0,62	0,78	**< 0,001**

Of the 4 CPRs, the Alvarado score presented the most accurate diagnosis when the scores were high, assigning a high probability of AA to 206 patients, with diagnostic confirmation of 96.6%. Additionally, the Alvarado score places fewer patients in the intermediate probability of having AA (37,6%). In the low probability group, the AAS score was the most efficient, with 81.91% confirmed cases of AA.

On the other hand, the multivariate analysis identified the following variables as independent factors of confirmed diagnosis of AA: anorexia [increased the risk by 2.28 times ($p = 0.039$)], WBCC ≥ 8.275 leukocytes/μL [increased the risk by 5.16 times ($p < 0.001$)], neutrophilia (NTF) > 75% [increased risk of 3.18 times ($p = 0.002$)], migrating pain to the RIF [increased the risk by 2.37 times ($p = 0.021$)], and abdominal pain for less than 48 hours of evolution [increased the risk of AA by 2.11 times ($p = 0.028$)].

In contrast, a temperature between 37°C and 39°C was associated with a lower risk of AA than that in patients with a temperature out of that range [OR 0.42 ($p = 0.013$)] (Table 3).

Table 3
HMC Score.

Variable	Coefficient B	Score	p-value
Anorexia	0.825	8	**0.039**
WBCC ≥ 8.275	1,640	16	**0.001**
NTF > 75%	1,157	12	**0.002**
Pain migration to RIF	0,861	9	**0.021**
Pain evolution < 48 h.	0,745	7	**0.028**
T > 37 ºC < 39ºC	-0,873	-9	**0.013**
(WBCC: white blood cell count; NTF: neutrophilia; RIF: right iliac fossa; T: temperature).			

The novel CPR built with these six variables was able to establish three levels of risk among our cohort: low probability (≤ 25 points): 24.9% of patients, medium probability (26–40 points): 47.9% of patients, and high probability (≥ 41 points): 27% of patients (Fig. 2). The AUC was 0.81 [95% CI (0.74–0.87) ($p < 0.001$)].

Discussion

To improve the effectiveness of the diagnostic process, the ideal scoring system should work as an effective and accurate tool that accelerates and improves the decision-making process and simultaneously reduces the need for complementary imaging studies [22].

The aim of this study was to validate the effectiveness of the most commonly used CPRs and to develop a new streamlined and efficient scoring system.

In this sense, the most efficient of the CPRs evaluated was the Alvarado score, which has been confirmed in multiple previous studies [3, 17]. This score enables risk stratification in patients with RIFP with the quantification of eight variables. The other CPRS shows a lower diagnostic efficiency with an increase in the number of variables evaluated.

The newly developed CPR (the HMC score) group included six variables: anorexia, abdominal pain with less than 48 hours of evolution, migratory pain to the RIF, WBCC > 8.275 leukocytes/µL, NTF > 75%, and axillary temperature between 37ºC-39ºC. The score performs well as a predictor of AA with an area under the ROC curve of 0.81 ($p < 0.001$), with an improved diagnostic performance over the other scales (Fig. 3).

It is composed of three symptoms and three clinical data categories, which are easily identifiable by the patient and the evaluator, respectively. The HMC score has the advantage of being simpler (with fewer items) than the previous ones (Alvarado, RIPASA, AIR, and AAS), eliminating subjective data such as the

degree of defense/rebound in the abdominal exploration (AIR and AAS), and data that are not always collected in the patient's medical records.

This score established a cut-off point for the leukocyte count. Although it has already been shown that individual or combined analytical tests have limited or little specific value when predicting AA, their simultaneous negativity allows practically negating the diagnosis of AA [23]. In a prospective study of 1,032 patients, Lau [24] concluded that the elevation of the WBCC and the percentage of neutrophils simultaneously increased the diagnostic specificity for AA. In another study, Atema [25] found that a WBC count of > 20,000 associated with symptoms for more than 48 hours was associated with a positive predictive value of 100%.

Among patients with AA, the reported sensitivity and specificity rates of leukocyte counts were 60%-87% and 53%-100%, respectively [26], with different leukocyte cut-off points: 11,000 leukocytes/μL in the study of Bilic [27] and 10,400 leukocytes/μL reported by Narci [28]. Our leukocyte cut-off point was 8,275 leukocytes/μL, which increased the sensitivity of the test and, when combined with NTF (> 75%), the specificity was also increased. The percentage of neutrophils is by itself considered the best diagnostic marker for AA and is also related to its severity [25].

Another aspect introduced by the HMC scale is in reference to body temperature. Fever is one of the variables present in most of the RIFP diagnostic scales (Alvarado, RIPASA, and AIR). However, many authors believe that the predictive value of fever for AA is limited [29, 30]. Andersson [31], in a study of 496 patients, demonstrated that a temperature > 37.7 °C had a sensitivity and specificity of 70% and 65%, respectively, for the diagnosis of AA. In a later study, Andersson found that the mean temperature in nonsurgical abdominal pathology was 37.7ºC, and only its persistence in serial physical evaluations would indicate the presence of complicated AA [32]. Therefore, temperature, as an independent variable, is not as useful [3, 29]. In our scale, an axillary temperature between 37ºC and 39ºC was associated with a lower risk of AA. For that reason, and in agreement with these authors, our data support the idea that temperature is not a good predictive value of AA pathology. Its presence in patients evaluated for RIFP should alert clinicians to the possible existence of other intra-abdominal pathologies, such acute gastroenteritis, pelvic inflammatory disease, etc.

Otherwise, it is well established that the diagnostic approach to RIFP is conditioned by certain characteristics of the patient, such as age and sex [2, 4]. When comparing the global cohort of female patients with AA, we found that the HMC scale presented an AUC = 0.84 [0.77–0.90] ($p < 0.001$), which was higher than the AUC of the other CPRs. The data were even more obvious when we analyzed the group of women between the ages of 15 and 64 with an AUC of 0.86 [0.78–0.93] ($p < 0.001$). Additionally, the diagnostic approach in women of childbearing age is particularly difficult because of the overlap of gynecological symptoms with those of AA itself, causing an increase in NA due to diagnostic errors [33]. It has been postulated that CPR scores fail to properly evaluate this subgroup of patients because the scores cannot adequately exclude the presence of gynecological pathologies. In fact, a diagnostic scale has been developed for the management of acute abdominal pain in women of reproductive age [34].

When we applied the HMC score to women between 15 and 64 years old, we obtained a very high degree of success for the diagnosis of AA because of the 44 patients in this age subgroup with an HMC score ≥ 41, only one of them had a diagnosis recorded as AN, which improves the data provided by other authors [35]. However, female patients with a score ≤ 25 had the highest rate of NA (20 out of 44). These results support those collected in other studies that also showed high rates of NA in women of childbearing age [29, 36] and support the early implementation of imaging tests in these patients [37].

Another group of patients with specific characteristics is the pediatric group. In this subgroup, the diagnosis of AA is a challenge both for the presence of nonsurgical pathologies that resemble appendicitis and for the difficulties of the anamnesis and exploration of these patients [14]. The rate of diagnostic errors increases as age decreases, and children 3 under three years of age have up to 5 times more risk of complicated AA [38]. Unable to provide data on patients under five years of age, our results show that NA was more frequent in pubescent girls between 10 and 14 years old (60% in our cohort), which are similar results to those found by Güller in a retrospective study of 7452 cases [39].

The HMC scale was shown to be an acceptable predictor of AA in pediatric patients, with an AUC = 0.74 (0.59–0.90; p = 0.019), a result not achieved when applying the other scales. A high score on this scale was 100% diagnosed by AA, which could have avoided the use of ultrasound, a conclusion similar to that derived from the study of Blitman in which the Alvarado score was applied [14]. On the other hand, authors such as Fleischman [40] showed that low scores of the appendicitis scales in children had good sensitivity to rule out AA and, therefore, to save diagnostic imaging tests with certainty and avoid unnecessary radiation risks.

Consequently, we believe that imaging tests improve the diagnostic accuracy, avoid errors and delays in definitive treatment, and should be performed in the diagnostic workup of doubtful diagnoses (intermediate scores) followed by CT scan when needed, a strategy supported by other authors [41, 42].

Finally, in elderly patients, the AA rate is approximately 10%, although with the aging of the population, these figures are increasing [43]. Comorbidities, the insidious onset of the disease and the delay in diagnosis with the high rate of perforations make AA pathology with high using and mortality rates in elderly patients [44]. The diagnostic scales for AA were designed with a young population, so their effectiveness in an elderly age group is not well documented [45]. For all this, and in the same way as other authors [44], we recommended the early use of imaging tests in these patients, especially in the presence of inconclusive clinical data.

In our study, 11.1% of the patients were within this age group, with only 3 results of NA. None of the CPRs tested were statistically significant when applied to this group to discriminate between AA and NA. Nevertheless, the HMC scale was statistically significant, with the best AUC for elderly patients out of all the scores (0.86), showing that it was also a good predictive model for these patients. However, this sample size seems to be too small to make suitable comparisons with other published data.

The major weaknesses of this study are its retrospective nature, which increases the potential for bias and that it is a single center study. Among the strengths, it stands out that all patients have been treated by a small number of surgeons, with an adequate level of criteria uniformity and that in more than 95% of the cases, the clinical data were complete. Obviously, the score developed requires a validation that is currently being implemented in our center.

Conclusion

In summary, we can affirm that the diagnostic probability scales for AA are useful tools to evaluate patients with RIFP, which can facilitate the diagnostic approach during emergency situations and save time and unnecessary tests. The diagnostic accuracy for AA can be increased, in probable or inconclusive cases in which the diagnoses are based on clinical data, with the implementation of US and CT studies.

Obviously, in western countries, access to image studies is relatively easy. However, frequently, this supposes an overload for the radiological services as in our center. The implementation and proper use of these tools in emergency services can help to select those patients who truly need an extension of the clinical evaluation with complementary imaging studies.

Finally, our data allow us to affirm that the HMC score improves the diagnostic effectiveness in the population groups studied with respect to the other scales that have been evaluated and previously validated and supported by the literature.

Declarations

- Ethics approval and consent tparticipate: Ethical approval through the Clinical Research Ethics Committee of Valladolid University was granted in January 2017.
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- Authors' contributions:
    - Dr. J.C. Martín del Olmo: study design, manuscript edition and critical revision.
    - Dr. J.R. Gómez López: data collection and collaboration in the manuscript edition.
    - Dra. M.L. Martín Esteban: data collection and analysis.
    - Dra. P. ConcejCutoli: data collection and analysis.
    - Dra. M.A. MontenegrMartín: data collection and analysis.
    - Dr. C. VaquerPuerta: critical revision of the study.
    - Dra. C. López Mestanza: design of statistical study.
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Figures

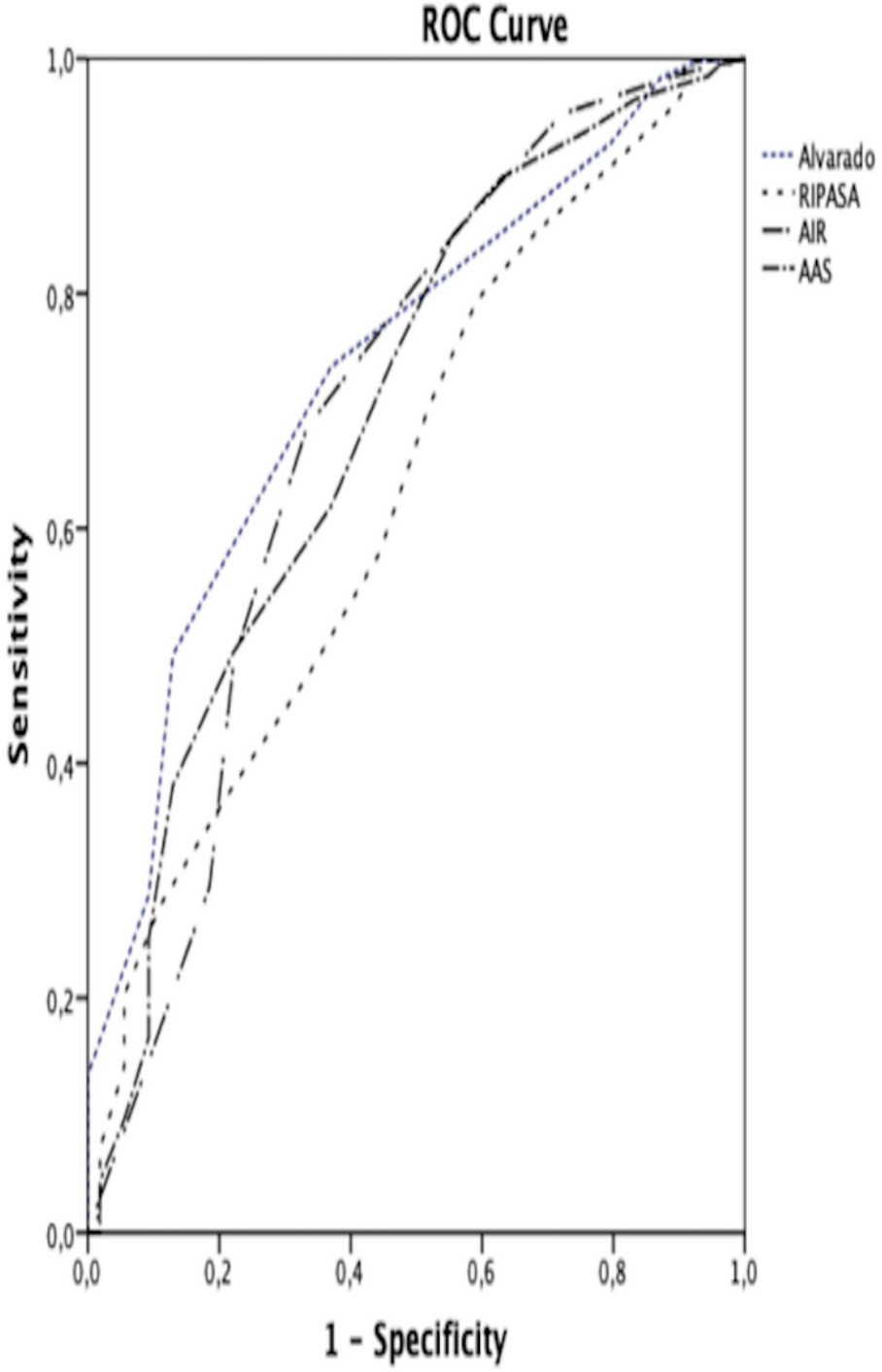

Figure 1

ROC curves of the CPR tested.

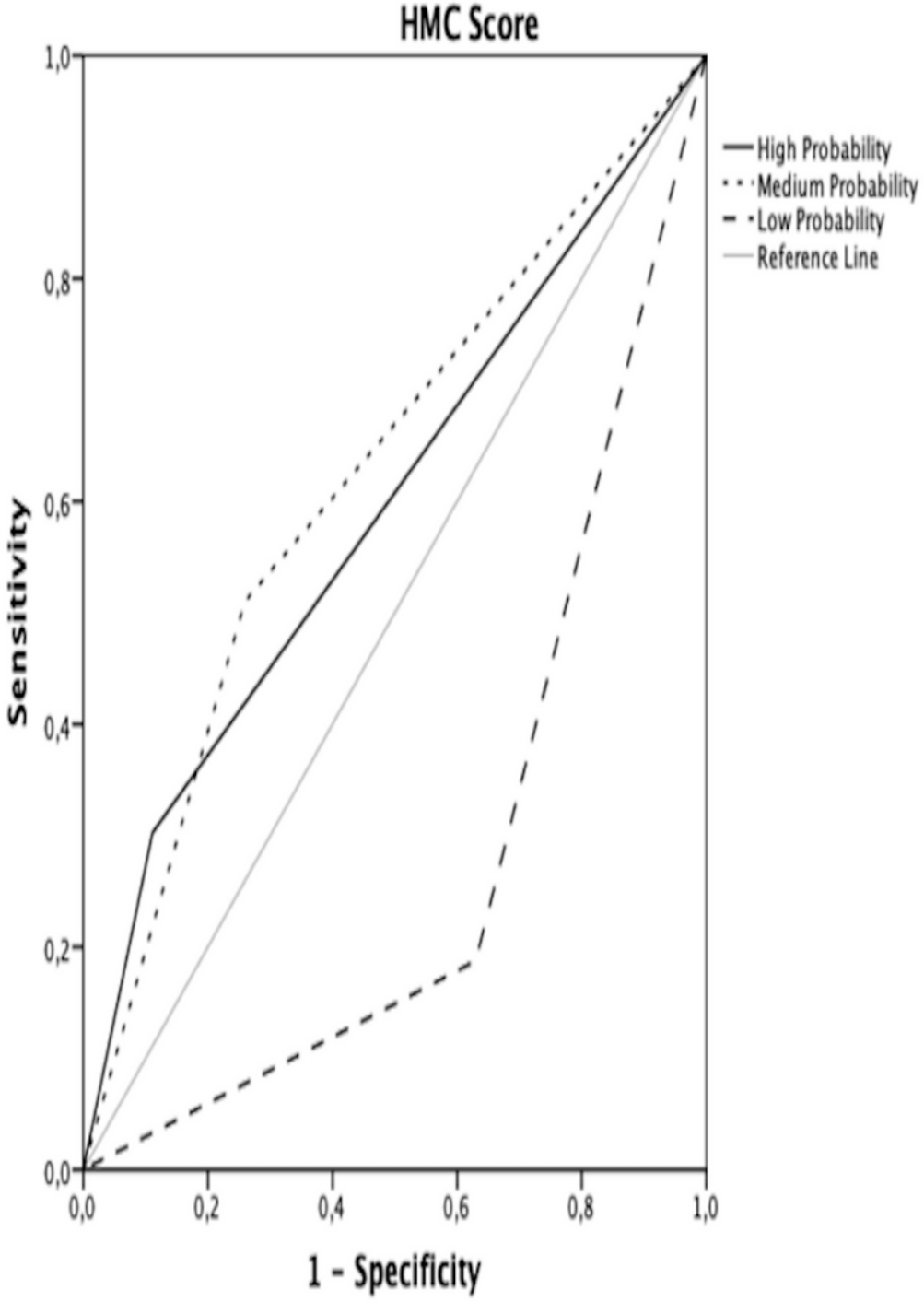

Figure 2

Stratification of the HMC score: low probability (≤ 25 points); medium probability (26-40 points); high probability (≥ 41 points).

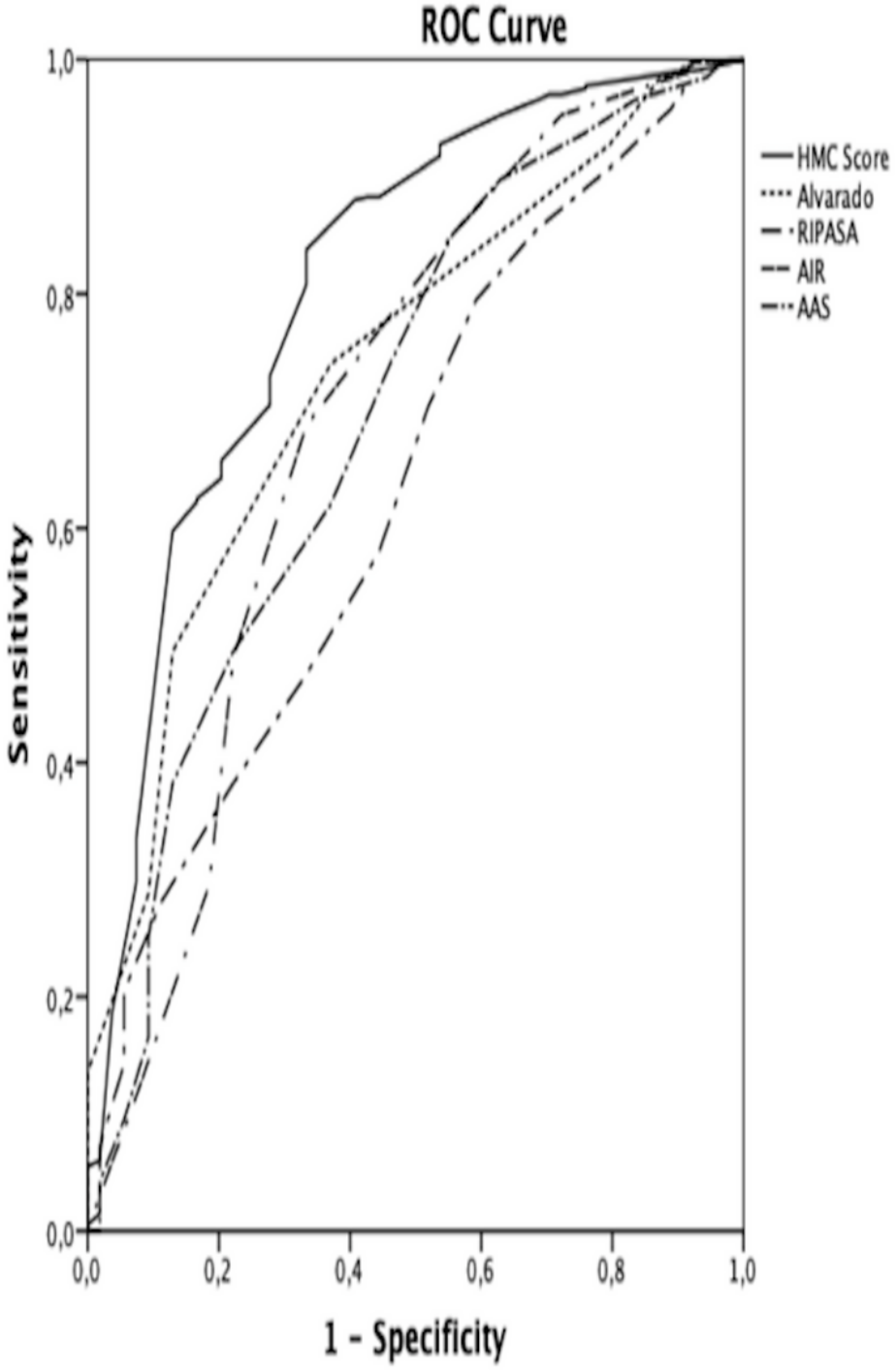

Figure 3

Comparative ROC curves of the CPR tested versus HMC score: HMC (AUC: 0.81); Alvarado (AUC: 0.74); AIR (AUC: 0.70); AAS (AUC: 0.70); RIPASA (AUC: 0.63).