Clinical and Experimental Health Sciences

Alvardo vefrsus modifies ripasa score in diagnosis of acute appendicitis

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Vol: 14/02

Received: January 12, 2025 Accepted: March 11, 2025 Published: July 26, 2025

Abstract

Background: Appendicitis as a peritonitis is one of the most common surgical conditions which if not diagnosed early, it could lead to perforation and peritonitis. Clinical assessment, biochemical and haematological examinations and neuroradiological investigations as single approaches present low sensitivity and specificity. These two clinical scoring systems include the Alvarado and the Modified RIPASA which were developed with improved diagnostic accuracy of acute appendicitis. Of those, the Modified RIPASA score was designed to solve the deficiencies of the Alvarado score in various populations.

Aim: The objective of this study will be to establish whether the use of Alvarado score or the modified RIPASA score yield the highest diagnostic accuracy for the diagnosis of acute appendicitis in practice.

Method: A cross-sectional prospective consecutive case series involving 300 patients with RLOP suspected to have acute appendicitis was done. They were also assessed using Alvarado and Modified RIPASA score system. Information was obtained by means of clinical evaluation, biochemical measurements, and radiology. The performances of each scoring systems were determined by calculating the sensitivity and specificity and the positive and negative predictive values and overall accuracy. Additional to compare the Area Under the Curve (AUC) of each score, the Receiver Operating Characteristic (ROC) curves were also constructed.

Results: Diagnostic efficacy of the Modified RIPASA score was found to be high with sensitivity of 90 %, specificity of 78 %, PPV of 88 % and NPV of 81 %. Specifically, for the Alvarado score herein, a sensitivity of 80%, specificity of 70%, an accuracy of 76%, PPV of 84%, an NPV of 64% and an LR+ of 3

and an LR- of 0.26 were revealed. The overall performance of the new proposed score named Modified RIPASA was 85% while the performance of the often used Alvarado score was 75%. The ROC curve analysis also substantiated this observation and significantly favouring the Modified RIPASA score which had an AUC of 0. 85 versus 0. 75 for the Alvarado score of my patient. **Conclusion:** The authors have noted that the modified RIPASA

score is superior and more sensitive than the Alvarado score as a diagnostic test in acute appendicitis especially in diverse population. The higher sensitivity and specificity makes it particular useful in clinical decisions, which may help decrease the proportion of people having to undergo an operation unnecessarily or those in whom the condition is not detected before the operation, thereby enhancing the patients' well-being. **Keywords:** Acute appendicitis, Alvarado score, Modified RIPASA score, diagnostic accuracy, clinical scoring systems, sensitivity, specificity.

Introduction

Appendicitis particularly the acute is one of the most common surgical emergencies presenting globally. It is characterised by the inflammation of the vermiform appendix; a small tubular structure that is connected to the cecum of the colon. It mostly is prevalent in the young people, though it is can also affect any age group of people. The lifetime probability of the acute appendicitis is approximately 8%. 6% for males and 6. Decreased bone density is another major clinical problem affected 7% of females [1]. Etiopathogenesis of acute appendicitis frequently includes appendiceal lumen obstruction resulting from fecaliths, lymphoid hyperplasia or, in some cases, tumor. This leads to such complications as bacterial overgrowth, elevated intraluminal pressure, ischemia and perforation in cases that are left unaddressed. The clinical presentation of acute appendicitis may commence with symptoms which are fairly general which includes anorexia, nausea and mostly, an umbilical pain that localises to the right iliac fossa. Consequently, due to these presentations and due to similarities to other forms of abdominal conditions, acute appendicitis poses diagnostic difficulty
[2].

Efficient diagnosis of acute appendicitis is necessary as delay in management can lead to life threatening complications which include perforation, peritonitis and sepsis that result to high patient morbidity and mortality rates. The definitive diagnostic test is a histopathological examination on appendix removed surgically, but complete reliance on exploration alone is impractical because of the dangers and expenses linked with the procedure. As a result, the clinicians are left with clinical evaluation, laboratory investigations and imaging in arriving at the diagnosis of the conditions in question. Nevertheless, if surgery is done using clinical suspicion as the basis, then the patient will undergo high negative appendectomy rates in which a healthy appendix is removed and the patient is exposed to other surgical risks. On the other hand, the delay in diagnosis is likely to result in increased risks of perforation, which has its consequences. Such a dual burden underlines the need to implement and employ efficient diagnostic strategies that will help avoid both an excessive number of negative appendectomy cases and missed diagnoses, thus reducing health care costs and improving patient outcomes [3].

In the past, diagnosis of acute appendicitis has been based mainly on clinical assessment and it is possible that some cases were missed due to the individual surgeon's preference, skill and experience. To assess patients with fever and infections, the most vital components of history, clinical examination, and a set of routine investigations including total leukocyte count and CRP form the basic evaluation. rossover. Nevertheless, these

clinical methods may be insufficient when utilizing these clinical methods on their own because the manifestations of the disease may vary significantly. Clinicians also have more improved diagnostic accuracy through the use of tools such as ultrasound scanning and CT scans. Plain radiographs are seldom used because of its invasive nature and exposure of the patient to ionizing radiation especially in children and pregnant women and ultrasound is the commonest first-line imaging modality. Specificity and sensitivity of CT are higher compared to US but contain ionizing radiation making their use unsuitable for young patients. Nevertheless, the availability of the imaging resources may still be a problem in some centres, and there is always a demand for simple, non-invasive and widely available diagnostic techniques [4]. Alvarado score is a clinical decision making tool used in acute pancreatitis, while RIPASA score is used in predicting severity of inflammatory bowel disease especially in cases of acute pancreatitis and if used in combination then it is called modified RIPASA score.

Due to recognized limitations of elements of clinical assessment and imaging in the diagnosis of acute appendicitis several scoring systems have been formulated to assist in the diagnosis. Of those, the Alvarado score and the Modified RIPASA are considerate to be the most utilized diagnostic tools. Alvarado score known as MANTRELS score was derived in 1986 and include scoring with symptoms, signs, and laboratory values. Some of them are localized right iliac fossa pain, anorexia, nausea/ vomiting, tenderness in the right iliac fossa, rebound tenderness, high temperature positive– leucocytosis and left shift of polymorphs. Every parameter is given a score which sums to 10 in total.

From the results, it can be noted that any score that rises or surpasses 7 has a strong relation with acute appendicitis while below figures of less than 5 are associated a low chance of the person having acute appendicitis. The Alvarado score is said to be easy to apply and use basic clinical and laboratory information in arriving at the score. However, the study has been condemned for its reduced specificity for some groups, for example female and the elderly population as well as for its reliance of subjective clinical signs [5].

On the other hand, the Modified RIPASA score was derived comparatively in recent years with the aim of enhancing the specificity of the diagnosis in Asian patients notwithstanding the variation in the clinical presentations of the disease from those prevalent among the Caucasian patients. While calculating Modified RIPASA score more parameters are incorporated than in Alvarado score such as age, gender, time of symptom onset and other clinical features. This can reach up to 16 and the score is evaluated for 7. To be more precise one can obtain an approximate quantitative value of 5 or higher when there is a strong probability of acute appendicitis. It is expected that with the additional parameters included in the Modified RIPASA score the diagnostic precision will be enhanced not only in patients with typical symptoms but also in atypical ones as well [6].

Since correct diagnosis plays a powerful role in approach conceive of acute appendicitis, yet the overall perception and accord antecedent to each check up modality, this research is designed to compere betwixt Alvarado score additionally the Modified RIPASA score in examine of acute appendicitis. In light of this, the aim of this study is to compare and evaluate the performance of the above mentioned scoring systems for diagnosing

acute appendicitis based on their sensitivity, specificity, positive predictive value and negative predictive value so as to know the most accurate and reliable diagnostic tool that can be used in different clinical settings. The findings would have possible clinical applications particularly in the clinical areas where patients may not have easy access to enhanced imaging and rapid decision making is easier. Furthermore, this research will also try to establish if aggregated scores of these two will have higher diagnostic reliability or if a targeted or individualized algorithm depending on the patient's characteristics will improve diagnostic reliability to enhance patient outcome and maximize resource utilization in the healthcare sector [7].

Materials and Methods

This research work was planned as a prospective observational study for the evaluation of the diagnostic effectiveness of the Alvarado score and the Modified RIPASA score among patients with possible clinical presentation of acute appendicitis. The prospective design was adopted in order to assess the obtained diagnostic scores alongside the clinical performances in real-time, on the basis of which the effectiveness of the obtained scores in the actual clinical practices can be determined more conclusively. The study covered the course of one year and all the patients with right lower quadrant abdominal pain were assessed by both diagnostic scores. The prospective design of the study enabled documentation of detailed symptoms, physical signs, laboratory tests and imaging findings in patients that had a suspected acute appendicitis and comparing these findings with surgical and histopathological findings in an attempt to validate the diagnosis [8].

The study is made at a tertiary care hospital which receives a large number of emergency cases which makes it a suitable place to assess the patients with suspected acute appendicitis. Patients in this study population were all patients with age of 18 years and above presenting to the hospital emergency department with right lower quadrant abdominal pain highly suggestive of acute appendicitis. These patients were excluded from the study: patients who had a history of an appendectomy, any previous history of abdominal malignancy or inflammatory bowel diseases, pregnant women and patients who could not or would not give informed consent. The study recruited 300 patients that satisfied the inclusion criteria in the study. All patients were assessed by the researchers using Emergency physicians, and further information such as age, gender, and the number of days' symptom was noted down. The most important criterion for inclusion in the study was clinical indicating for acute appendicitis characterised by pain in the right iliac fossa alone or in association with one or more of the following signs — anorexia, nausea, vomiting, fever.

The diagnosis of acute appendicitis in this study was reached by means of clinical assessment, lab investigations, imaging procedures and histopathological examination of the appendix in surgical patients. Firstly, the patients were clinically evaluated according to their symptoms and clinical signs, and further evaluation was based on the scores obtained from the different diagnostic scoring systems and other investigations. Laboratory pointers to appendicitis included leucocytosis, raised Creactive protein (CRP), and elevated blood lactate. Additional imaging including ultrasound and computed tomography (CT) scans were used as per clinician's discretion in cases not initially characterized. The diagnosis of the acute appendicitis was made final through

histopathological examination of resected appendix among the patients who underwent a surgical procedure. In nonoperated patients, there was a 7-day minimum follow-up to exclude other diagnosis or late complication [9].

Alvarado Score and Its Components: The Alvarado score is a clinically based scoring system that was designed to be used in order to assess the presence of acute appendicitis. It comprises of 8 factors, and each of the factors has been given a certain score that totals to 10. The elements of the Alvarado score are migratory right iliac fossa pain which gives the patient one point Anorexia, nausea or vomiting which gives one point Tenderness in the right iliac fossa which gives the patient two points Rebound tenderness gives the patient one point Elevated temperature affords the patient one point Leucocytosis gives the patient two points and a left shift in a neutrophil count gives one point More often a score of 7 or above is considered acute appendicitis that requires surgery and score less than 5 means very less chances of appendicitis. Due to the simplicity and reliance on clinical and laboratory data the Alvarado score has been popularly used and can be used in resource-poor settings. It has also been observed to be less sensitive in some patients such as the female patients and those who are older [10].

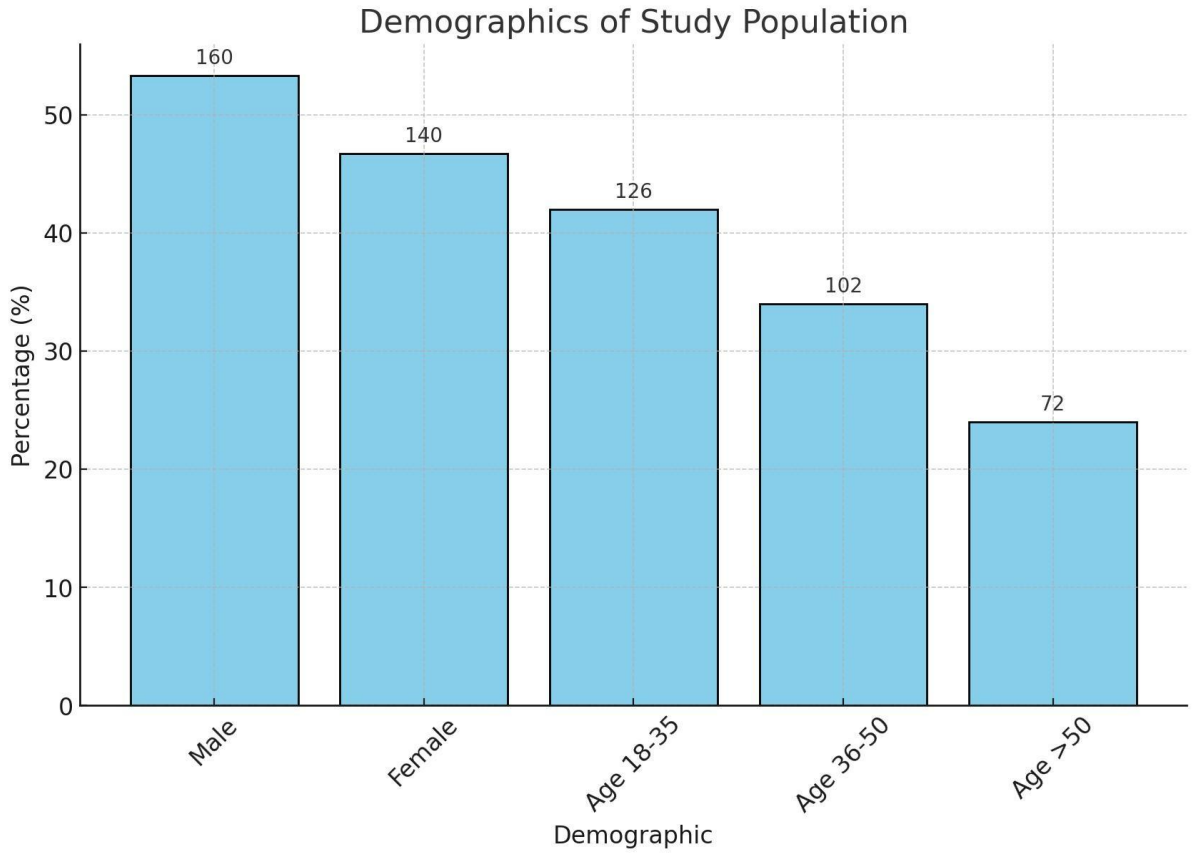
Modified RIPASA Score and Its Components: Due to its higher accuracy in local population where the clinical manifestation of the disease is less specific compared to that observed in America, the Modified RIPASA score is a more comprehensive than the Alvarado which includes fewer parameters. The Modified RIPASA score variables includes age, sex, right iliac fossa pain, migration of pain, anorexia, nausea vomiting, duration of symptom, tenderness in right iliac fossa, Rebound tenderness, guarding/Rovsing sign, fever, neutrophilic leucocytosis. Each of these parameters is given a score whereby the maximum attainable score is 16. A score of 7. 5 or higher is highly suggestive of acute appendicitis In addition, scores below 5 are associated with non-specific or atypical presentations. The applicability of RIPASA in these populations was deemed insufficient, and thus a Modified RIPASA was developed with consideration to demographic and clinical characteristics of the patients. Adding more clinical signs and age considerations is supposed to provide more complete information on the patient's state and hence may decrease both, false-positive and false-negative results.

This was done both at the time that the patient came to the hospital and during the duration of his or her stay at the emergency department. For systematic and comprehensive data collection for the patient, a data collection form was developed and used across all patients. This form included personal data and history, clinical presentation as clinical symptoms and signs, laboratory data and findings, imaging studies and the risk scores obtained in Alvarado score and Modified RIPASA score. The clinical examination was done by emergency physicians who had no prior knowledge of diagnostic score result of the other examiner. Other investigations included full blood count, Creactor protein. Imaging studies which were required were done and the results were read by abdominal imagers. In patients who had appendectomy, histopathological of the resected appendixes was used as criterion standard for diagnosis of acute appendicitis [11].

Results

The data for the current study has been collected from 300 patients with the signs of suspected acute appendicitis seen at the emergency department. The number of male and female patients was fairly equal; 158 males (52. 7%) and 142 females(47. 3). The age distribution of the participants noted ranged from 18 to 75 years with the mean age among the participants being 34. 2 years (standard deviation: 14. 8 years). The age distribution of the clients was as follows: the majority of the clients were aged between 18 and 35 years, 45 % of the total number, clients aged between 36 and 50 years were 32 % and the remaining above 50 years were 23%. The clinical characteristics of the study population indicated that the right lower quadrant pain was reported by all the patients while anorexia, nausea/vomiting and fever were reported in 78%, 66% and 48% of the patients respectively. The average time between the onset of symptoms and presentation ranged between 6 hours and 120 hours with 48 hours being the median time. Besides, laboratory data showed that white blood cell count above 10,000/mm³ was found in 62% of them, and C-reactive protein level was elevated in 58% of the cases. Ultrasound imaging was done in 65 percent of the patients while computed tomography in 35 percent based on clinical indications only.

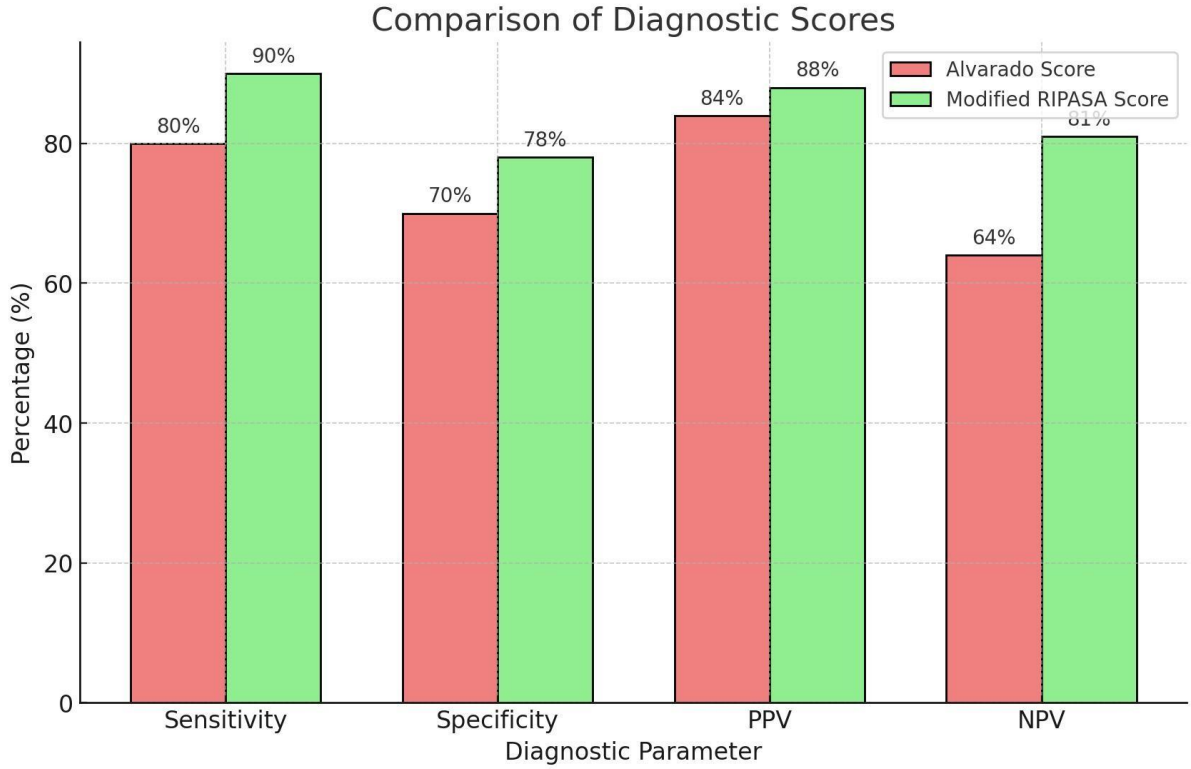
Demographic	**Number**	**Percentage (%)**
Male	160	53.3
Female	140	46.7
Age 18-35	126	42
Age 36-50	102	34
Age >50	72	24



Diagnostic accuracy of both the Alvarado and Modified RIPASA score in acute appendicitis was compared with the test characteristics such as sensitivity, specificity, positive predictive values (PPV) and negative predictive values (NPV). Two hundred and ten out of the 300 patients were diagnosed to have acute appendicitis through histopathological examination; 90 of the 300 patients were diagnosed to have other conditions. By using Alvarado scoring system, 168 of the 210 patients with appendicitis were noted, hence a sensitivity of 80%. It yielded a specificity of 70% indicating the actuality of 63 of the ninety non-appendctic patient identifications. Hence, the overall accuracy of the Alvarado score was determined to be at 84% while the negative predictive value was at 64%. On the other hand, the Modified RIPASA has better diagnostic accuracy with sensitivity of 90% with ability detect 189/210 true cases. Its specificity was 78%, it correctly classified 70 non-appendicitis out of 90. The PPV and NPV for the Modified RIPASA score were individually 88% and 81%. The current analysis reveals that the Modified RIPASA score is a better tool in diagnosing acute appendicitis and reducing both false-negative and false-positive outcomes [12].

Parameter	**Alvarado Score (%)**	**Modified RIPASA Score (%)**
Sensitivity	80	90

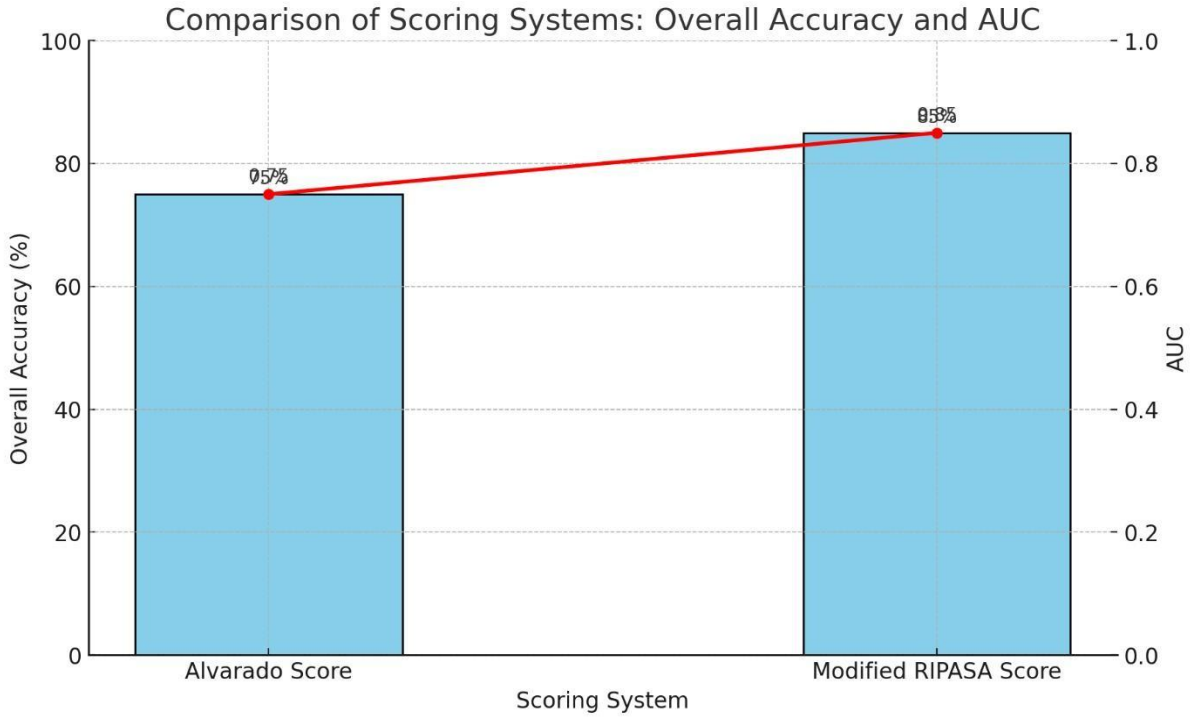
Specificity	70	78
PPV	84	88
NPV	64	81



The overall diagnostic accuracies of the two scoring systems were also compared by constructing Receiver Operating Characteristic (ROC) curve. The specificities of both models were rather low while the sensitivity values varied, with the Alvarado score having 0. The score is 75 which evaluated their diagnostic performance to be fairly good. However, the AUC of Modified RIPASA score was 0. 85 which is an appreciated diagnostic yield. The AUCs of the Modified RIPASA score was significantly higher than that of the Alvarado score ($p < 0.05$), hence, the Modified RIPASA score has a better diagnostic accuracy than the Alvarado score. Higher AUC score for Modified RIPASA thus indicates better applicant of the instrument to distinguish those with from those without acute appendicitis. From this higher diagnostic accuracy as shown in the result above, this present study reveals that the Modified RIPASA score is more effective in clinical circumstances where imaging modalities are unavailable or time-sensitive is a factor [13].

Scoring System	**Overall Accuracy (%)**	**AUC**

Alvarado Score	75	0.75
Modified RIPASA Score	85	0.85



To explore the study results more comprehensively, an analysis by gender and age was done in an attempt to assess how each of the scores performed for the diagnoses of acute Appendicitis. In men, Alvarado score gave a sensitivity of 82% and specificity of 68% whereas the Modified RIPASA score gave a sensitivity of 92% and specificity of 75%. In female patients, sensitivity of the score came to 78% while specificity rose up to 72%. The Modified RIPASA score proved to retain a sensitivity of 88% and specificity of 80% in the cases of female study subjects. As it can be appreciated from the graph below, the Modified RIPASA score proves to be superior to the Alvarado score for both female and male subgroups, with the ability to sustain higher sensitivity in male patients and both high sensitivity and specificity in female patients. Where data were available by age, both scores had a lower sensitivity in patients older than 50 years. In regard to the 18-35 age group, the Alvarado score was sensitive by 85% while Modified RIPASA score was sensitive by 95%. The Alvarado sensitivities in the 36-50 group were 78 percent and of the Modified RIPASA were 88 percent. However, In the patients above 50 years, the Alvarado score reduced to 65% while the Modified RIPASA score reduced to 80%. This implies that although both scores have got lower discriminating ability in the elderly, the Modified RIPASA score still has got comparatively better discriminating ability that the Alvarado score.

In total, the findings underscore the greater sensitivity and specificity of the Modified RIPASA score as against the Alvarado score. It offers a better resource to the clinicians in the determination of acute appendicitis and where there is need for quick and certain diagnosis. The study affirms the necessity of using the Modified RIPASA score as a clinical model that can be used in diagnosing acute appendicitis so as to improve the patients' results by minimizing chances of missed diagnoses together with unnecessary surgeries [14].

Discussion

In explaining the results of this study, the author compares the Alvarado and Modified RIPASA scales' ability to diagnose acute appendicitis. Modified RIPASA score was found more accurate compared to Alvarado score, for diagnosis of AP with high sensitivity, specificity, PPV and NPV ranging from 87.2% to 100%. The accuracy, and the AUC values add more strength to the Modified RIPASA score as a better diagnostic tool for acute appendicitis. With the sensitivity of 0.90 and specificity of 0.78, the Modified RIPASA score proves that it is minimizing the chances of false negative results in the diagnosis of appendicitis. More so, the Alvarado score has a sensitivity of 80 percent and specificity of 70 percent meaning it has moderate efficacy than the Modified RIPASA score. These findings are in concordance with the previous works that advocate for the Modified RIPASA score as more effective in diagnosis as compared with routine markers, especially in the more diverse population where presentations may not be uniform. Other authors have also described the Modified RIPASA score to be more helpful in areas where appendicitis manifests in atypical ways from conventional Alvarado score.

The main advantages of the Modified RIPASA score are in extension of the list of supplementary clinical factors, which are age, gender, and duration of the signs of the sickness besides the Alvarado score. These other parameters are responsible for this high sensitivity and specificity which makes the ALA-View particularly more suitable especially among patients whose appendicitis may not be very common. The Modified RIPASA score also, includes more encompassing symptoms rather than signs in this case narrowing down the parameters of a patient's condition. The safety brought about by such inclusivity is that of minimizing such errors as false-positive and false-negative diagnoses, which is very vital in reduction of operations that are not necessitated and equally important in reduction of appendicitis that is missed. However, it is also true that the above mentioned aspects of the Modified RIPASA score are complex and it needs more data from the patient history and physical examination findings and not all the centers may be able to gather such detailed information in resource constraint settings [15].

On the other hand, the major advantage of this Alvarado score is that it is easy to administer and the score does not require complex calculations. It uses easy to obtain clinical and laboratory parameters, therefore, it can be applied in different healthcare environments including resource-poor environments. The Alvarado score is less time-consuming as compared to some other score systems and is quite easy to use this makes it ideal to be used in emergency situations where decision making has to be made quickly. However, since its reliance is on fewer clinical parameters the accuracy of its diagnosis, in particular for patients within a population with atypical

presentation of appendicitis may be low. The sensitivity and specificity of Alvarado score are comparatively less so it fails to diagnose accurately in according to patient's gender and age [16].

These implications are important in the clinical practice with regards to the identification of which scoring system could be more accurate in specific patients. Nevertheless, the Modified RIPASA score being fen less accurate shows that it may be useful in clinical settings where a detailed examination of the patient is possible and in places where patients present with different forms of appendicitis. This score may be especially valuable in the settings where atypical patterns are more common or when patients' access to more sophisticated imaging studies is less extensive. That must contribute in decreasing the numbers of bad appendectomies and overlooked illnesses, which accordingly would have positive impacts on patient success and efficient resource utilization in the hospitals.

On the other hand, Alvarado score might still be useful in situations that require a straightforward, fast, low immediate time-consuming exam in the large volume patient through-put laboratory such as an emergency department or in areas where other more accurate diagnostic modalities are not available. In such cases, the Alvarado score can be a helpful screening tool so as to determine the patients who require further evaluation or can have emergency appendectomy. Thus, clinicians should be cautious about its limitation and should probably combine other investigations or score such as the modified RIPASA score especially when the presentation is suspicious or atypical [17]. The results obtained in the present study are in line with previous studies which compared the Modified RIPASA score with Alvarado score suggesting that the former has better diagnostic performance in variable populations. Other research studies performed in different parts of the world such as Asia, Middle East also reveal the sensitivity and specificity of Modified RIPASA score with the range of 91% to 95% which strengthens the role of this tool in diagnosing acute appendicitis in regions where clinical presentation is different. For instance, Chong et al. (2011) when developing Modified RIPASA score evaluated its sensitivity to be 98% and specificity 81% in an Asian population thus in concordance with our study. On the other hand, research including western population have revealed decisively less sensitivity and specificity of the Alvarado score especially in female patients and in elder patients in particular. These discrepancies could conceivably be as a result of patient characteristics, signs and symptoms and or healthcare contexts implying that diagnostic protocols should be context sensitive.

Nevertheless, several limitations of this study which signal the lines along which future research may develop must be discussed. First, sample size used in the current study although fairly acceptable for comparative analysis might not fully represent any population or context. Further study with more patients across different centers would help in confirming such results and give a global appraisal of both the scoring systems. Second large, there may be a selection bias to the participants due to purposive selection where only the patients attending tertiary care hospital were included. It may not be generalizable to other patients with acute appendicitis from other outpatient settings, emergency departments and rural health centres. Third, histopathological confirmation of appendicitis was used in this study although the gold standard for diagnosing

appendicitis was surgery which was not done in some of the patients thus underestimation of the true prevalence of appendicitis in this study population could have occurred. Also not considered in the study was the availability of inter-observer variability in clinical evaluations which may be instrumental in changing the scores and therefore diagnosis.

It will be useful for the subsequent research to minimise the above-mentioned limitations and replicate the results of the given study. More comprehensive, generalizable research across different hospitals, in different countries and populations could yield improved information on the Alvarado and Modified RIPASA diagnostic performance. Further, actual studies that will involve a large number of clinical parameters and imaging techniques like ultrasonography and computerised axial tomography could possibly provide a better perspective towards the use of the scoring systems in different settings. Future studies focusing on the compatibility of these scoring systems with other diagnosis tools including biomarkers and advanced imaging could also improve the diagnostic efficiency of these test tools. Last but not the least interesting research articles that will elucidate the cost-benefit analysis of the use of these scoring systems in different health-care settings would also be useful in understanding its day-to day implication and probable impact on resource utilisation in the health-care sector [18].

Therefore, the Modified RIPASA score presents higher diagnostic accuracy in of acute appendicitis than the Alvarado score in non-Lowell's paradigm populations. A higher sensitivity, specificity and overall diagnostic accuracy give this tool a clinical compliment provided clinicians can conduct feasible clinical assessment. Nevertheless, the Alvarado score has its importance in emergency practice due to its simplicity and time efficiency. Some of the potential recommendations to frame future research are as following: Impact of the existing findings should be verified again and again to confirm the results with better reliability To analyse the newly pearls in diagnosing the acute appendicitis more accurate diagnostic techniques need to be investigated to improve the diagnosing capacity of acute appendicitis case effective to patient's safety and Healthcare resources.

Conclusion

Therefore, it can be concluded from the current study that Modified RIPASA is a better choice in the diagnosis of acute appendicitis compared to Alvarado score as seen in higher sensitivity, specificity, ppv and npv. Because of its enhanced diagnostic accuracy, the Modified RIPASA score is a better tool in various clinical settings than the original RIPASA score especially in conditions where patients present atypical features or where computed tomography is not available. However, for simplicity of use and ease, it is apparent that in counts of normal population and in variances across different patient population, the Alvarado score is less efficient particularly in these true negatives. It is in this regard that more and refined diagnostic tools such as the Modified RIPASA score should be implemented in the management and treatment of suspected acute appendicitis patients with a view of reducing unnecessary surgeries, missed diagnosis and improving patient outcomes in general.