

**DIAGNOSTIC ACCURACY IN ACUTE APPENDICITIS: A PROTOCOL
BASED ON MODIFIED ALVARADO SCORE AND
ULTRASONOGRAPHY AT KENYATTA NATIONAL HOSPITAL**

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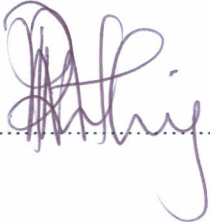
**A DISSERTATION SUBMITTED IN PART FULFILLMENT OF THE
REQUIREMENTS FOR THE DEGREE OF MASTER OF MEDICINE (MMED) IN
GENERAL SURGERY, UNIVERSITY OF NAIROBI.**

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DECLARATION

I declare that this dissertation is my original work and has not been presented at any other University.

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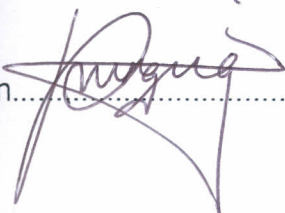
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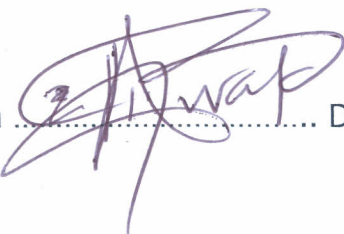
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DEDICATION

I dedicate this work to my loving family. To my beautiful wife Beth for her unwavering support and encouragement. To Michelle and Jeremy for being such a source of joy and motivation to soldier on.

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I give all honour to God for the saving grace in His Son; In Him I live, In Him I move and in Him I have my being.

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LIST OF ABBREVIATIONS

CT scan	Computed tomography scan
CRP	C - reactive protein
KNH	Kenyatta National Hospital
MAS	Modified Alvarado score
PPV	Positive predictive value
NPV	Negative predictive value
ROC	Receiver operating characteristics
AUC	Area under the curve
US	Ultrasonography
CI	Confidence interval

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ABSTRACT

Background: Acute appendicitis remains the most common indication for surgical intervention in acute abdomen. The negative appendicectomy rate is 25% at KNH according to a recent study.¹¹ Diagnosis of acute appendicitis continues to be a challenge. This is especially so for the less experienced clinicians who are the majority in our setup. There is need for an easily available and cost effective protocol to aid the clinician in making an accurate diagnosis of acute appendicitis.

Objective: To determine the diagnostic accuracy of a protocol that combined modified Alvarado scoring and ultrasonography for equivocal cases in acute appendicitis at Kenyatta National Hospital.

Design: A prospective observational study

Setting: KNH accident and emergency and general surgery departments

Patients and methods: Patients presenting with suspected acute appendicitis were scored using the modified Alvarado scoring system. Patients who scored 7 and above proceeded to surgery while those who scored the equivocal range of 4 to 6 underwent ultrasound scanning for suspected appendicitis as described by Puylaert.²⁶ Confirmation of appendicitis was based on histopathology as the reference standard.

Results: A total of 100 patients were recruited in the study over a period of 8 months from July 2011 to March 2012. The ratio of male to female patients was 1.2:1. The range of ages of presentation was 7 to 55 years with a median age of 26. The mean age was 27.9 years with a standard deviation of 11.4. Fifty four patients had a modified Alvarado score of 7 and above while 46 patients scored between 4 and 6 and underwent ultrasonography. The area under the curve for the receiver operating curves was 0.60 and 0.58 for ultrasonography and MAS plus ultrasonography respectively. There was no statistical difference between the PPV of MAS between 4 and 6 and of ultrasonography in the equivocal cases. Ultrasonography had sensitivity, specificity, PPV and NPV values of 93.5%(95% CI,78.5-99.2), 26.7%(95% CI,7.8-55.1), 72.5%(95% CI,56.1-85.3) and 66.7%(95% CI,22.2-95.6) respectively. The overall sensitivity, specificity, PPV and NPV of the protocol was 97.5%(95%CI,91.2-99.7),19%(95% CI,5.4-41.9),81.9%(95% CI,72.6-89.1) and NPV 66.7%(95% CI,22.2-95.7) respectively. The crude negative appendicectomy rate for the series was 21%. The calculated negative appendicectomy rate with the protocol factored in was 18%. The

protocol had a missed appendicitis diagnosis rate of 2%. The overall accuracy of the protocol in the diagnosis of acute appendicitis was 81%.

Conclusions: The diagnosis of acute appendicitis is first and foremost a clinical diagnosis with scoring systems and imaging being necessary adjuncts in the equivocal cases. The use of a protocol based on modified Alvarado score and ultrasonography is a useful and easily available tool in the diagnosis of acute appendicitis. The protocol can aid the clinician to 'rule-in' appendicitis. However, the specificity of the protocol is still low in the KNH setting and may largely be dependent on the learning curve of ultrasonography technique.

INTRODUCTION

Appendicitis was first described in 1886 by Reginald Fitz and remains the commonest cause of acute abdomen requiring surgical intervention both in Kenya and elsewhere.^{1,2,3} Accurate diagnosis of acute appendicitis remains a major challenge the world over and is perhaps more pronounced in constrained resource setups.^{4,5} Accuracy in diagnosis of acute appendicitis by clinical acumen has been found to be largely dependent on experience.⁴ Aids to assist in diagnosis of acute appendicitis exist but many are complex, expensive and unavailable especially in poor settings. Numerous scoring systems have been devised to aid the clinician.⁶ Perhaps the best well known is the modified Alvarado score. Various imaging modalities are available but their use is dependent on levels of resources. Ultrasonography has been used and studied widely in diagnosis of appendicitis.⁷ The aim of this study was to determine the diagnostic accuracy of a protocol based on the use of modified Alvarado score combined with ultrasound imaging in diagnosis of acute appendicitis at Kenyatta national hospital. The main outcome measure was the negative appendicectomy rate.

LITERATURE REVIEW

Reginald Fitz first described appendicitis as an entity in 1886. Diagnosis of acute appendicitis has remained a challenge despite great advances in technology. A negative appendicectomy rate of 20% has generally been accepted in a review of trends in management over thirty years.⁸ It is known that negative appendicectomy rates vary widely principally due to differences in experience. John, *et al* found the sensitivity of clinical acumen in diagnosis of acute appendicitis to range between 71% and 97% depending on the experience of the clinician.⁴ Clinical acumen still remains the mainstay in the diagnosis of acute appendicitis.

Pruekprasert found that in the hands of an experienced surgeon clinical acumen was superior to either modified Alvarado or C-reactive protein measurements.⁹ CRP measurements and the Alvarado score were quoted to be of value to the inexperienced surgeon.⁹ Disparities in clinical acumen will continue to exist since the apprenticeship nature of surgical training is both time and situation dependent. Various scoring systems have been devised to assist in improving accuracy in diagnosis of appendicitis. These include Alvarado, Teicher, Christian, Fenyo and Lindberg.⁶

Modified Alvarado score

In a re-evaluation of published data, the modified Alvarado scoring system was found by the Abdominal Pain Study Group to meet the set criteria in terms of reduction in morbidity and mortality.⁶ The score was first described by Alvarado in 1986.¹⁰

This scoring system awards points for symptoms (migration of pain, anorexia, and nausea or vomiting), physical signs (right lower quadrant tenderness, rebound tenderness, and pyrexia), and laboratory values (leukocytosis). Whether to include a right to left shift is dependent on the laboratory in use. The modified Alvarado score does not include the left shift.

Table 1: Summary of the modified Alvarado score

	MANIFESTATION	VALUE
Symptoms	Migration of pain	1
	Anorexia	1
	Nausea/vomiting	1
Signs	RLQ tenderness	2
	Rebound tenderness	1
	Elevated temperature ($\geq 37.3^{\circ}\text{C}$)	1
Laboratory value	Leukocytosis ($\geq 10,000/\mu\text{L}$)	2
Total points		9

A prospective study of 116 patients by Ongaro at Kenyatta National Hospital in 2005 found that the use of modified Alvarado score would have reduced negative appendicectomy rates from 25% to 11.2%. The sensitivity of the scoring system was found to be 91 %.¹¹

The modified Alvarado score has been studied widely and there exists little controversy on the management of patients who score 7 and above. The diagnosis of acute appendicitis in this group is almost always accurate. Patients who score 3 and below are unlikely to have acute appendicitis. The patients who score between 4 and 6 pose the greatest diagnostic challenge with the score being regarded as equivocal in this subset.¹²

The modified Alvarado score has been found to be a useful tool for admission criteria. with one study giving a negative appendicectomy rate of 12.5%.¹² In this study by Al Qahtani in Saudi Arabia, no patients with a score less than 4 had appendicitis.¹² A high Alvarado score is an easy and satisfactory aid in diagnosis of acute appendicitis in children and men. There is however an unacceptably high false positive rate among women of 33% versus 22% in the others.¹³ Alvarado scoring in children is a useful tool in taking the decision for admission in suspected acute appendicitis.¹⁴

Using MAS, Khan and Rehman found a negative appendicectomy rate of 15.6% and a positive predictive value of 84.3% in a study of 100 patients. They recommended Alvarado score as an easy, simple and complementary tool for the diagnosis of acute appendicitis especially for the junior surgeons.¹⁵

Modified Alvarado score had a positive predictive value of 98.1% in a study of 100 patients with acute appendicitis.¹⁶ It has been shown there is no statistical difference in the use of Alvarado score between emergency medicine residents and the general surgery residents in terms of suspecting the diagnosis of acute appendicitis.¹⁷

Ultrasonography in appendicitis

When the diagnosis is not clear, modalities to help clarify the diagnosis for suspected appendicitis include admission and observation in a hospital setting, diagnostic imaging to and laparoscopy. Laparoscopy is perhaps the superior of all these as appendicectomy can proceed in the same setting, but it is not universally available. Imaging studies are cost effective in making a definitive diagnosis and can reduce the need for admission and observation in a hospital.^{18, 19} More importantly, imaging studies of patients with an uncertain diagnosis may reduce the rate of perforation, and thus reduce postoperative hospital stay, morbidity and mortality.²⁰

In patients with suspected acute appendicitis, US examination has been used with the option of more expensive and time consuming modalities in equivocal US findings. The combination of US and CT scanning was shown to significantly lower the negative appendectomy rate when compared with clinical acumen alone. There was no increase in complications such as perforation and length of in-hospital stay.²¹

Ultrasonography as an imaging modality is widely available in the country. Anecdotal evidence suggests that it can be found in most district and provincial hospitals. It is also in widespread use among private radiologists and radiographers in Kenya.

The American College of Radiology cites graded compression ultrasonography as an important adjunct in diagnosis of appendicitis. It recommends US as a safest option in pregnancy. MRI for inconclusive ultrasonography places detection of a normal appendix at 2%. Ultrasound is the preferred mode of imaging in children and in low pretest probability patients, US is the most effective and least costly strategy.

A meta-analysis of 26 studies that had a total of 9356 patients had several important conclusions. Whereas CT scan had the advantages of higher sensitivity especially in obese patients and ability to have a multi-planar retrospective data reconstruction, US had the merits of cost effectiveness, lack of ionizing radiation and ability to provide dynamic information through graded compression. Newer technology like tissue harmonic imaging have increased the depth and clarity in ultrasonography.²² There were no differences in the diagnostic performance of CT compared to US with regard to specificity of studies of any age group. [studies of children, OR=0.77(95% CI, 0.55, 1.09); studies of adults, OR=1.18(95% CI,0.61,2.28).²³

US is preferred to CT in children due to the greater radio-sensitivity of organs and tissues in children.²⁴ US was found to be also particularly useful in adult patients whose presentation warranted admission but not immediate surgery.²⁵

Pulyaert described a graded compression technique for evaluating the appendix with trans-abdominal sonography in 1986. His study had 60 consecutive patients with suspected acute appendicitis. The inflamed appendix was visualized in 25(89%) of 28 patients with confirmed appendicitis. The appendix was not visualized in the 32 patients without appendicitis. Ultrasonography was also able to pick 6 out of 7 perforated appendices. Parameters to check for included an outer diameter of more than 6mm, aperistalsis, noncompressibility and periappendiceal fluid.²⁶

Ultrasonography offers the added advantages of non invasiveness, short acquisition time, lack of radiation exposure and the potential to diagnose other causes of acute abdomen especially in young women. Poortman, *et al* suggested that ultrasonography should be incorporated as a first line imaging modality for the diagnosis of acute appendicitis in adults.²⁷

Graded compression ultrasonography has been found to be useful in aiding diagnosis of acute appendicitis both in pregnancy and among children.^{28, 29} Nicolas, *et al* in their study population of 125 patients concluded that a threshold 6mm appendix under compression is the most accurate US finding for appendicitis with a high positive and negative predictive value. A finding of an appendix greater than 6 mm had a PPV, NPV, sensitivity and specificity of 98 %.³⁰ US significantly improves diagnostic accuracy in suspected appendicitis while reducing the negative laparotomy rate to 8-15%.³¹

Balthazar *et al* correlated CT and US in a study of 100 patients and concluded that the accuracy of both modalities was similar.³² Compression graded technique ultrasonography compares favourably with unenhanced CT scanning.^{33, 34} Accuracy of ultrasonography was shown to decrease if the location of the appendix was retrocecal.³⁵ Undetectable appendix has often been found to be either catarrhal or phlegmonous.³⁶

It has been argued that the experience of the radiologist or sonographer has important ramifications in the outcome of sonographic findings though some studies have suggested differently. In a study by Keyzer, *et al* comparing US and unenhanced multi-detector row CT in patients suspected of having acute appendicitis the sensitivity, specificity, positive and negative predictive values, and accuracy were not significantly different between US and CT or between groups of radiologists (P values ranged from .389 to >.99), regardless of the patient's BMI (P values ranged from .073 to >.99). Use of imaging in detection of both acute appendicitis and alternative diagnoses outcome did not depend on radiologist expertise in gastrointestinal imaging, patient sex, age or body size of the patient.³⁷

A study by Zielke, *et al* revealed a role for US in suspected appendicitis by surgical residents. US had higher accuracy, sensitivity and specificity than clinical acumen alone.³⁸

Preeyacha, *et al* in their retrospective study concluded that ultrasonography has a negative predictive value of 95.1 %.³⁹ As such one can infer that ultrasonography would be of great value in decision making on MAS equivocal cases. The overall accuracy of ultrasonography was higher than that of surgeon's clinical impression in a study by David, *et al*.⁴⁰

Alvarado score in combination with other modalities

The Alvarado scoring system has been studied in combination with various other modalities in the diagnosis of acute appendicitis. Michael, *et al* combined the score with selective laparoscopy in adult females. The negative appendectomy rate was 0% compared with 18% in the control group.⁴¹ The addition of ultrasonography in negative or equivocal cases using the Alvarado score decreased the false negative rate by 75% in a study by Stephens and Mazzucco. In their study, combination of both modalities reduced false positives to zero.⁴²

A randomized control trial of ultrasonography in diagnosis of acute appendicitis incorporating the Alvarado score found had a sensitivity and specificity of 94.7% and 88.9%. The decision to do ultrasonography was based on the Alvarado score. Patients in the intervention ultrasonography-Alvarado group had a shorter mean time to operation than the controls.⁴³ Graded compression ultrasonography has been shown to be an accurate means of diagnosing or excluding acute appendicitis in clinically equivocal cases and to be of great value in establishing alternative diagnosis.⁴⁴

STUDY JUSTIFICATION

Acute appendicitis remains the most common cause of acute abdomen requiring surgical intervention. Accurate diagnosis still largely depends on the experience of the clinician. Various scoring systems and imaging studies are currently in use to increase accuracy of diagnosis while avoiding increase in complication rates. The negative appendectomy rate and complication rates are common outcomes used in surgical audits. The negative appendectomy rate in Kenyatta national hospital is 25% overall and higher in women.¹¹

The diagnosis and management of acute abdomen in KNH and other hospitals in Kenya is by clinicians of widely differing experience. The larger proportion of patients is handled by newly qualified clinicians. The availability of a validated tool to aid in the diagnosis of acute appendicitis is therefore highly desirable.

The modified Alvarado score is an easy and reproducible score with useful utility among clinicians at different levels of experience. Though ultrasonography is a widely available modality in our setting, it has not been routinely employed in diagnosis of acute appendicitis. The combination of ultrasonography and modified Alvarado scoring in diagnosis of acute appendicitis has been studied elsewhere. The scoring and ultrasonography protocol has been shown to improve accuracy in diagnosis of acute appendicitis. There is paucity of data and studies on combining modified Alvarado scoring and ultrasound scanning in management of acute appendicitis in the region.

This prospective observational study sought to establish whether the combined use of a simple clinical scoring system and ultrasonography in a protocol could lead to lower negative appendectomy rates at KNH. Positive results would encourage an affordable protocol based criteria in diagnosis and management of acute appendicitis at KNH and across the country.

STUDY QUESTION

What is the overall negative appendicectomy rate at KNH following the use of a protocol based on modified Alvarado scoring and ultrasonography in the diagnosis of acute appendicitis?

STUDY OBJECTIVES

Main objective

To determine the diagnostic accuracy of a protocol based on modified Alvarado score and ultrasonography in diagnosis of acute appendicitis at KNH.

Specific objectives

- 1) To determine the predictive value of modified Alvarado scoring for suspected acute appendicitis at KNH.
- 2) To determine the sensitivity, specificity and predictive values of ultrasonography for equivocal cases of suspected acute appendicitis at KNH.
- 3) To determine the overall accuracy of a protocol based on combined use of modified Alvarado score and ultrasonography for diagnosis of suspected acute appendicitis at KNH.

PATIENTS AND METHODS

Study setting

The study was conducted at KNH accident and emergency and surgical wards. KNH is a national teaching and referral hospital in Kenya. It serves Nairobi city and its environs and also serves as one of the referral centers for the country and its neighbours.

Study population

All patients above 5 years of age with suspected acute appendicitis seen at the accident and emergency department and in the surgical wards.

Inclusion criteria

All patients above 5 years with suspected acute appendicitis that consented to be included in the study.

Exclusion criteria

- 1) Patients with generalized peritonitis
- 2) Patients with previous abdominal surgery
- 3) Patients with blunt or penetrating abdominal trauma
- 4) Patients who declined to give consent

Study design

Prospective observational study

Sample size

A previous study by Neford had a sample size of 116.¹¹

Appendicitis had a prevalence of 32.5% and 37.5% in the retrospective and prospective arms respectively in the study by Mungai.¹ The average was calculated as 35%.

This was an observational study to evaluate diagnostic accuracy.

Buderer's formula was used to calculate the required sample size for given values of specificity, sensitivity and absolute precision:

$$\text{Sample size (n) based on sensitivity} = \frac{Z_{1-\alpha/2}^2 \times S_N \times (1-S_N)}{d^2 \times \text{Prevalance}} \text{ and,}$$

$$\text{Sample size (n) based on specificity} = \frac{Z_{1-\alpha/2}^2 \times S_P \times (1-S_P)}{d^2 \times (1-\text{Prevalance})}$$

Where;

S_N = anticipated sensitivity

S_P = anticipated specificity

$Z_{1-\alpha/2}$ = Statistic for the level of confidence of 95%, 1.96

d = absolute precision desired (half the width of the confidence interval)

The prevalence estimates for appendicitis was taken to be 35%, an average for the retrospective and prospective arms of a study carried out in our set up. Taking the sensitivity and specificity of the score, the ultrasound and both combined to be above 70%, calculation was done for the required sample size for 0.1 value of precision.

For sensitivity or specificity above 90%, sample sizes of about **100** or even less would achieve a considerable precision of 10%. Using the formulae above Malhotra and Indrayan (2010) have developed a nomogram where different samples sizes can easily be read of the scale for different values of prevalence, sensitivity and precision.

The subset of patients scoring 4 to 6 on the modified Alvarado score was to be a minimum of **30** to allow for statistical analysis as stipulated in the Central Limit theorem.

All patients who met the eligibility criteria and who consented to be recruited into the study underwent diagnosis according to a protocol incorporating the modified Alvarado score and graded compression ultrasonography. Consecutive patients above 5 years with suspected appendicitis were recruited at the Kenyatta National Hospital accident and emergency department over a period of 8 months. Consent from minors was taken through the guardian or parent.

The chief investigator conducted training on modified Alvarado scoring, throughout the study period, of the medical officers and surgery residents working at the accident and emergency department.

Recruitment was done at the patient filtering rooms in accident and emergency department in KNH, by the medical officers on duty. The medical officers interviewed and examined the patients and on suspecting acute appendicitis, partially filled the MAS form (see appendix II). A complete blood count was then ordered.

The patients were then reviewed in the surgical review room by the principal investigator and/or surgery resident on call. The MAS was repeated by the investigator or surgical resident on call who then completed the scoring using the now available leukocyte count from the complete blood count results.

All patients who scored 7 and above on the MAS underwent surgery without further imaging. Patients who scored between 4 and 6 underwent graded compression ultrasonography as described by Puylaert. There was continuous appraisal on the technique of graded compression technique on the part of the ultrasonographers by the chief investigator.

Patients who scored 3 and below on the MAS were discharged or managed as per the clinician's prerogative. These were excluded from the study.

The patients who underwent ultrasonography were counseled before the procedure. The ultrasonography was done by qualified sonographers and diagnostic radiology residents on call. A global survey of the abdomen was done routinely using a convex low frequency probe and any other pathology noted. A Philips HD11 ultrasound system with high frequency (7.5-12 MHz) linear probes was then used to focus on the right iliac fossa. Gentle and graded progressive compression was initiated in the mid part of the abdomen, in front of the aorto-iliac bifurcation. The compression was done slowly to the point of maximum tenderness. Along the wall of the caecum the ileocaecal valve was recognized as a pseudo-tumoral shape bulging into the caecal lumen. The appendix was taken as the blind-ended tubular structure that originated from the base of the caecum.

The right iliac fossa findings were recorded in a standard form that contained the parameters described by Puylaert. (See appendix III). The standard parameters to be reported will include outer diameter, presence or absence of peristalsis, presence or lack of compressibility, appendicolith and periappendiceal fluid presence.

The possible scenarios in ultrasound imaging were lack of visualization of the appendix, normal appendix, features in keeping with various stages of acute appendicitis or obvious other pathology. All the patients sent for ultrasonography had initial equivocality using clinical examination and scoring and as such still underwent appendectomy. Exception was given to the patients who on ultrasonography demonstrated an obvious other pathology as expected in differential diagnoses of acute appendicitis. This subset was then managed as per the determined diagnoses and was analysed as a subset.

Appendectomy was carried out by the investigator or any other surgery resident on call. The intra-operative findings were recorded in the patients file for referral during analysis. The incision of access was the surgeon's prerogative. Patients with intra-operative alternative diagnoses were managed as warranted. A finding of an alternative diagnosis intra-operatively that had not been picked by the protocol was regarded as a false positive during analysis. This was based on the fact that the study was testing the accuracy of a diagnostic protocol.

The appendectomy specimen was preserved in formalin and transported to the histopathology laboratory at KNH for histopathology reporting.

Confirmation of the diagnosis of acute appendicitis was based on the histopathology. A finding of acute appendicitis on histopathology was regarded as the reference standard for acute appendicitis and formed the basis for calculation of negative appendectomy rate, sensitivity, specificity, PPV, NPV and accuracy in this study.

DATA MANAGEMENT AND ANALYSIS

Data was collected using a standard form for the biodata, history and examination findings. The modified Alvarado score was calculated. Ultrasonography findings were entered into a standard form. At the end of data collection, data was entered and analyzed using SPSS version 17.0. The study population was described using age and gender distributions which were presented as means and proportions respectively. Negative appendectomy rates were calculated and presented as a proportion. The MAS and the ultrasonography findings were compared with the histology findings using McNemar test. The degree of agreement was measured using kappa statistics.

Taking the histo-pathological findings as gold standard, the degree of agreement between the reference test and a) the MAS, b) the ultrasonography of the equivocal cases and c) both score and ultrasonography combined were reported using kappa statistic.

Predictive values were calculated for the various MAS and ultrasound findings. Specificity and sensitivity and their 95% confidence intervals were estimated for a) the ultrasound in equivocal cases and c) both score and ultrasound combined. Their positive predictive values and negative predictive values were computed. Receiver-Operating Characteristic (ROC) curves were drawn to determine the area under the curve for sensitivity and specificity of each technique. Negative appendectomy rates and the expected reduction achieved by combining the two diagnostic tools were calculated and presented as a proportion. All statistical tests were performed at 5% level of significance. (95% confidence interval).

ETHICAL CONSIDERATIONS

Approval to carry out the study was sought from the Surgery Department University of Nairobi and the Kenyatta National Hospital Ethics and Research Committee.

1. Patients recruited into the study signed a consent after a clear explanation of the nature, procedures and purpose of the study.
2. Minors consented and assented through their next of kin or guardians.
3. Total blood counts waiting time and ultrasonography did not jeopardize or unduly delay patient management decisions.

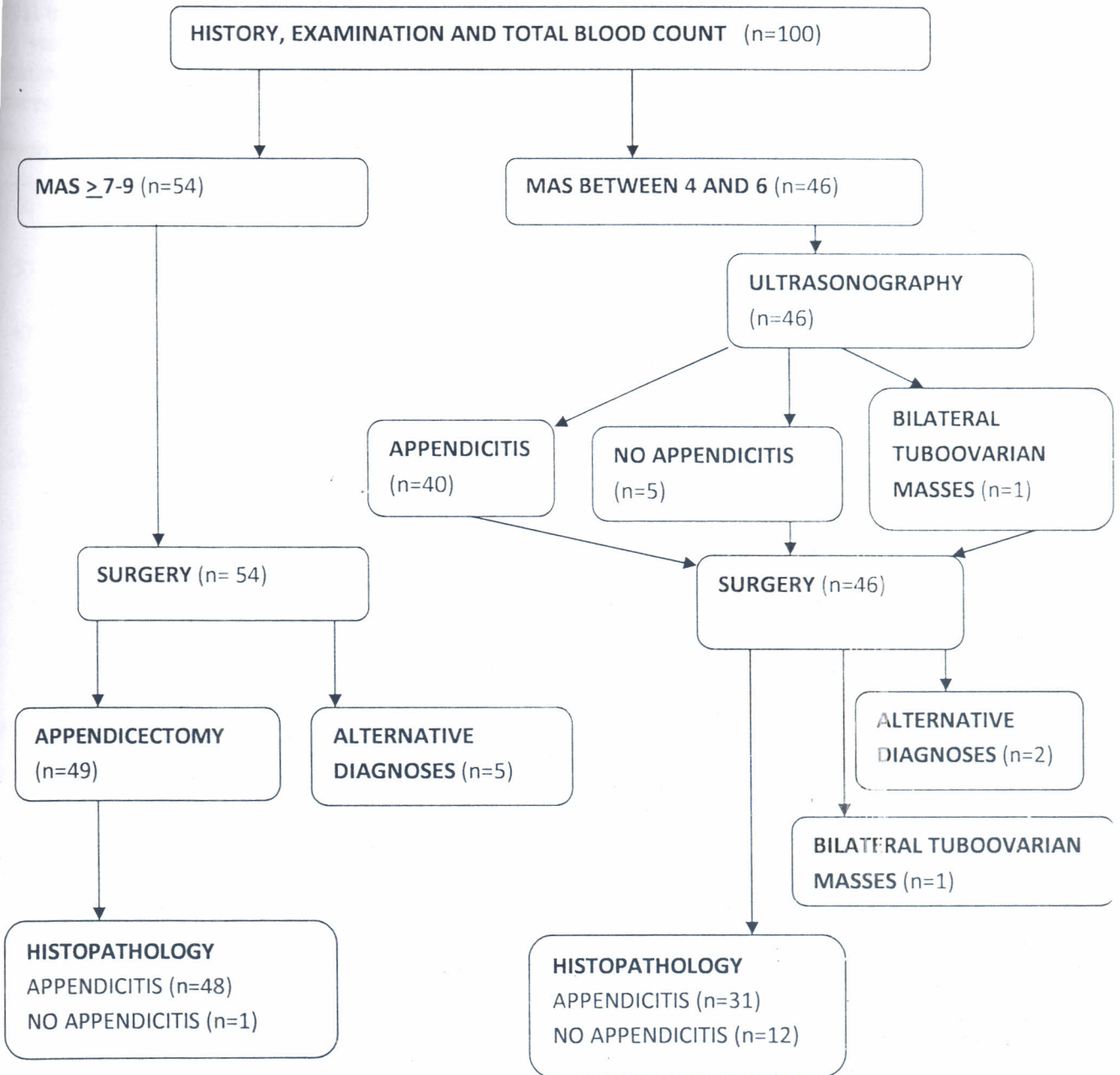
No patient who met the inclusion criteria refused to consent for the study.

RESULTS

In a period of eight months between July 2011 and April 2012 a total of 100 patients were recruited into the study.

The patient flow chart during the study is as shown in Figure 1

Figure 1: Patient flow chart



Baseline demographic patient characteristics

One hundred patients were recruited into the study over a period of 8 months from July 2011 to March 2012. The ratio of male to female was 1.2:1. The range of ages was 7 to 55 years with a median age was 26 years. The mean age was 27.9 years with a standard deviation of 11.4. Table 2 and figure 2 summarise the baseline demographic characteristics.

Figure 2: Distribution of patient population by gender

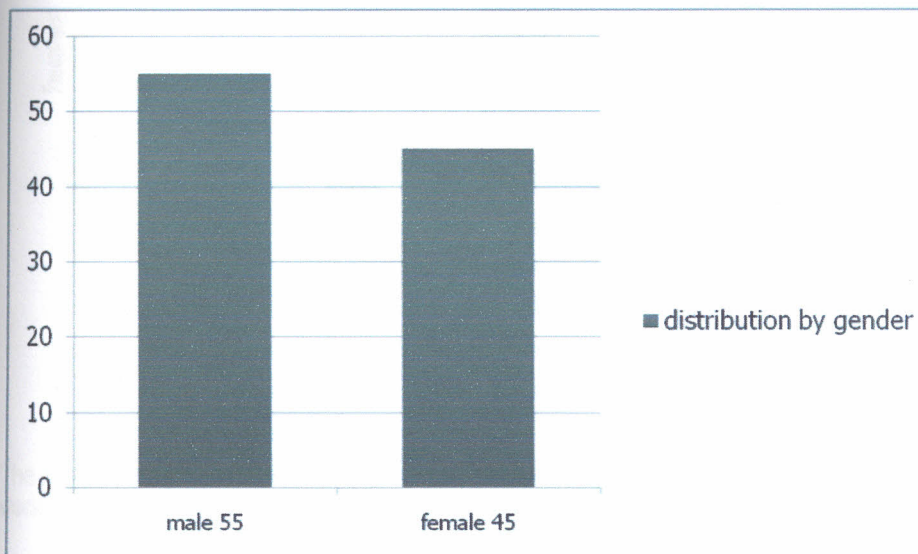
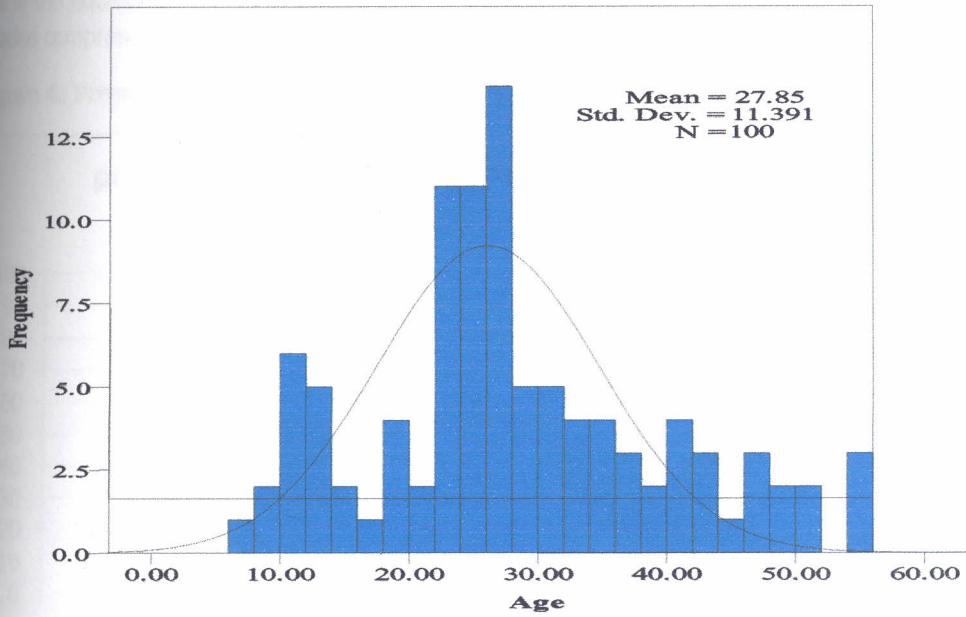


Table 2 summarises the measures of central tendency for the age of recruited patients.

Table 2: Measures of central tendency in the ages of recruited patients

Variable	Age in years
Mean (SD)	27.9 (11.4)
Median (IQR)	26 (22-35)
Min-Max	7-55

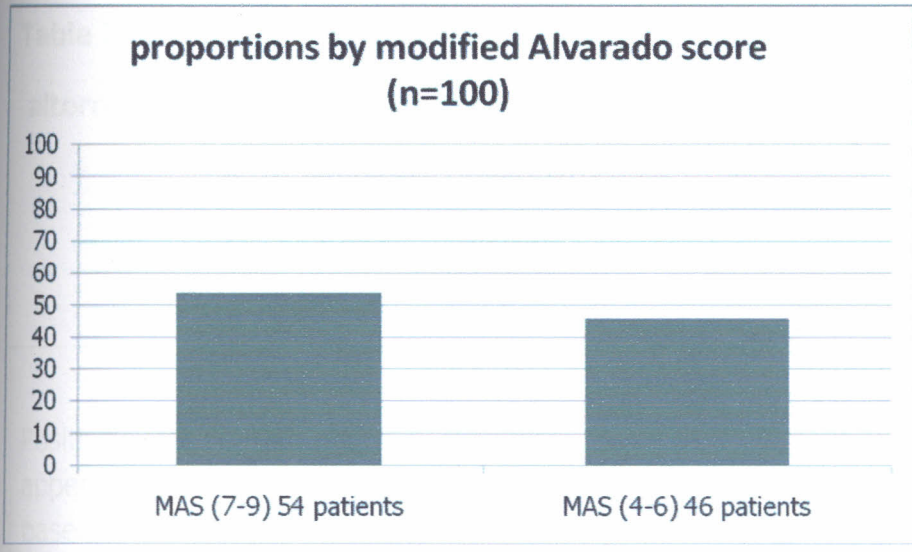
Figure 3: Age distribution by frequency



The frequency graph shows a main peak in incidence of acute appendicitis in the third decade.

Fifty four (54%) patients scored above 7 in the modified Alvarado score while 46(46%) fell in the equivocal 4 to 6 range. All the 46 patients in the equivocal range underwent graded compression ultrasonography.

Figure 4: Proportion of recruited patients by modified Alvarado score



Results of patients scored by modified Alvarado score

Forty eight out of 54 patients who scored between 7 and 9 on the modified Alvarado score underwent appendicectomy and were confirmed as positive on histopathology. One patient had no appendicitis on histopathology. Five patients were found to have alternative diagnoses at surgery. Two of these patients had perforated gastric ulcers, 1 patient had gangrenous small bowel while 1 patient had pelvic inflammatory disease. One patient had a mesenteric abscess. Table 3 summarises the findings of the patients who scored above 7 on the MAS based on histopathology of appendicectomy specimen and alternate diagnosis at surgery.

Table 3: Results of patients with modified Alvarado score (7-9) including alternative diagnoses seen at surgery for patients (n=54)

	Histopathology Appendicitis	Histopathology Normal appendix	Alternative diagnosis at surgery	Total
Positive for appendicitis based on MAS 7-9	48 (True positives)	1 (False positives)	<ul style="list-style-type: none"> 1.mesenteric abscess 2.gangrenous gut 3.pelvic inflammatory disease 4.perforated gastric ulcer 5.perforated gastric ulcer 	54

Positive predictive value = **48/54** (True positives / Total test positives)

PPV=88.9% (95% CI 80.5-97.3%)

Results of patients with modified Alvarado score between 4 and 6

Forty six patients had a modified Alvarado score of 4 to 6 and were regarded as equivocal. These underwent ultrasonography as per the protocol. Table 4 shows the results of the findings based on the equivocal score based on MAS between 4 and 6.

Table 4: Findings based on modified Alvarado score between 4 and 6 (n=46)

Modified Alvarado Score	Histology		Total
	Appendicitis	No appendicitis	
Equivocal for appendicitis (MAS 4-6)	31 (True positives)	15 (False positives)	46

Positive predictive value = **31/46** (True positives / Total test positives)

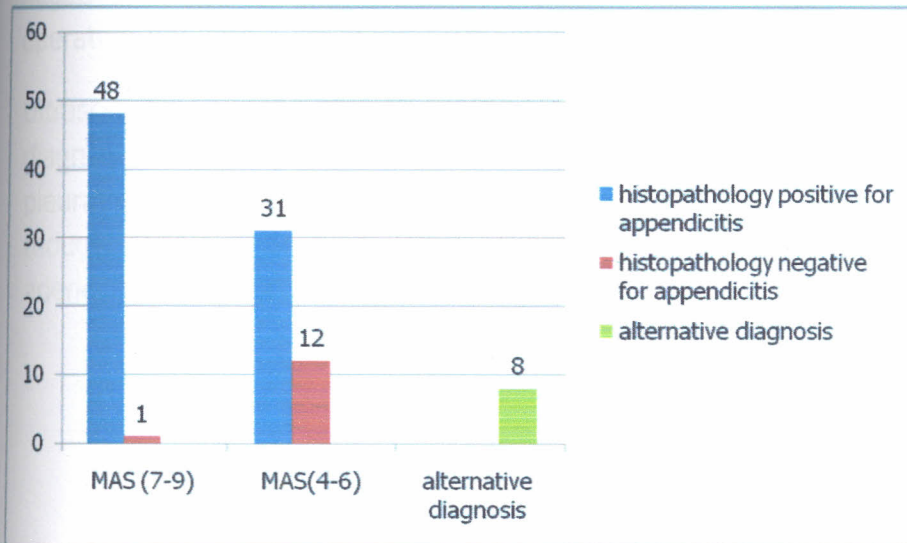
PPV=70.5% (95% CI 57.3-83.7%)

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Overall results of patients using modified Alvarado score 4-9

All the 100 patients recruited into the study underwent modified Alvarado scoring. Figure 5 summarises the findings of the scoring system compared with histopathology and intra-operative diagnoses.

Figure 5: Summary of modified Alvarado score findings in relation to intra-operative and histopathology results (n=100)



Results of subset of patients who underwent ultrasonography

A total of 46 patients underwent ultrasonography. Out of the 40 patients who had positive appendicitis findings on ultrasonography, 29 were confirmed as positive on histopathology while 11 patients were negative. Eight of these patients had negative histopathology for appendicitis while 1 patient was reported as metastatic adenocarcinoma with a normal appendix. Two patients had alternative diagnoses at surgery with right pyosalpinx and a frozen abdomen respectively.

Six patients were reported as to have no appendicitis on ultrasonography. Two of these patients had a positive histopathology diagnosis of acute appendicitis. Of the remaining 4 patients reported not to have appendicitis on ultrasound, 3 patients were found to be negative on histopathology. 1 patient did not undergo appendicectomy as the intra-operative findings agreed with the ultrasound findings of bilateral tubo-ovarian mass.

Ultrasonography was able to detect concurrent diagnoses in 4 patients. The concurrent diagnoses were; right hydronephrosis, right ectopic kidney, right tuboovarian mass and pleural effusion with ascites respectively. The patient with pleural effusion and ascites, though reported to have appendicitis on ultrasound turned out to have metastatic adenocarcinoma on histopathology.

A summary of the findings of ultrasonography in relation to the histopathology findings and alternative intra-operative findings is shown in Tables 5.

Table 5: Findings of ultrasonography for equivocal cases of suspected acute appendicitis (n=46)

Variable	Histopathology results			Total
	Appendicitis	Normal	Alternative diagnoses	
Ultrasonography Appendicitis	29	9	1. right pyosalpinx 2. frozen abdomen	40
	29 (true positives)	11 (false positives)		40
Ultrasonography No appendicitis	2 (false negatives)	3 (true negatives)	1. Bilateral tubo-ovarian masses	6
	2 (false negatives)	4 (true negatives)		6
Total	31	15		46

Key: Figures in **bold** used to calculate the performance of the ultrasonography

P=0.002 (McNemar test), Agreement = 71.7%, Kappa=0.239, p=0.056

$$PPV = 29/40 \text{ (true positives / total test positives)}$$

$$NPV = 4/6 \text{ (true negatives / total test negatives)}$$

$$\text{Sensitivity} = 29/31 \text{ (true positives / true positives + false negatives)}$$

$$\text{Specificity} = 4/15 \text{ (true negatives / true negatives + false positives)}$$

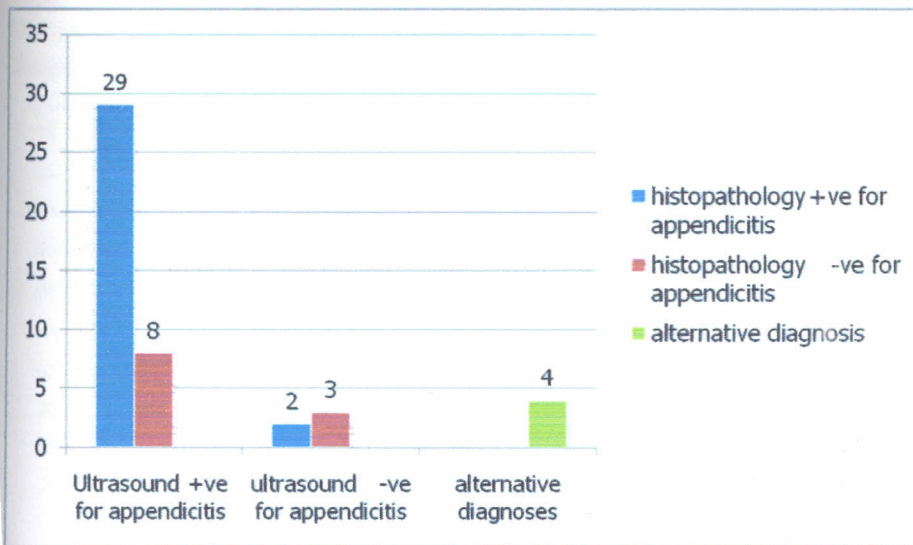
$$\text{Accuracy} = 29+4/46 \text{ (true positives + true negatives / total test population)}$$

The calculated PPV, NPV, sensitivity and specificity of ultrasonography are summarized in table 6.

Table 6: Sensitivity, specificity, PPV, NPV and confidence limits for ultrasonography

Measure	Proportion	95% CI	
		Lower	Upper
Sensitivity	93.5%	78.5%	99.2%
Specificity	26.7%	7.8%	55.1%
PPV	72.5%	56.1%	85.3%
NPV	66.7%	22.2%	95.6%

Figure 6: Summary of ultrasonography findings in comparison to intra-operative and histopathology findings (n=46)



Results of use of the combined modified Alvarado score (4-9) and ultrasonography protocol

A total of 100 patients who were recruited in the study underwent diagnostic screening using the study protocol which was base on modified Alvarado score with additional ultrasonography for the equivocal cases.

Ninety four (94%) of the patients were reported as acute appendicitis by the protocol. Of these 77 (81.9%) were confirmed on histopathology. Seventeen (29.1%) patients did not have appendicitis .Ten of these patients underwent appendicectomy and turned out negative on histopathology. 7 patients had alternative diagnosis made during surgery.

Six (6%) patients were reported to have no appendicitis on ultrasonography with 1 of the patients being reported as having bilateral tubo-ovarian masses. Two of these patients were positive for appendicitis on histopathology. Three patients who had no appendicitis on ultrasonography were confirmed as negative by histopathology. In the patient with bilateral tubo-ovarian masses on ultrasonography the diagnosis was confirmed during surgery.

Figure 7: Summary of findings using the protocol of combined modified Alvarado score and ultrasonography in comparison to intra-operative and histopathological findings (n=100)

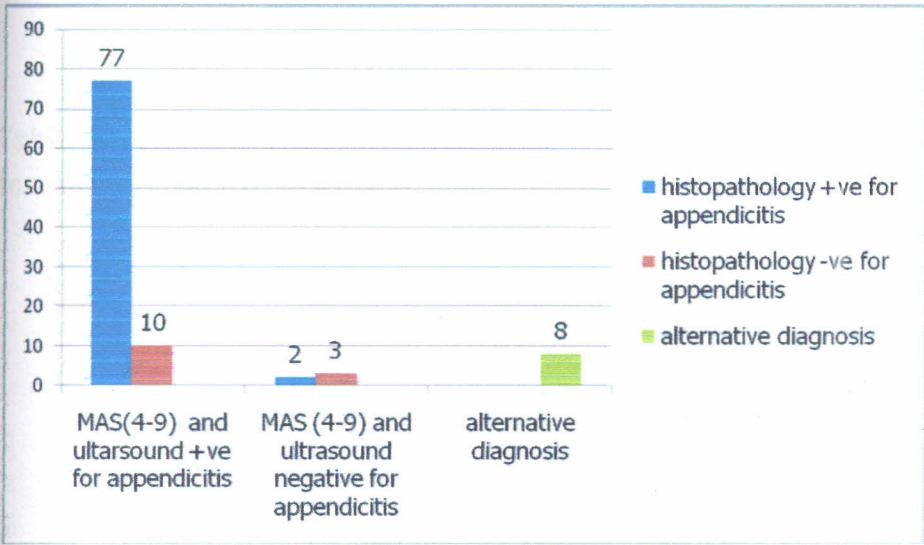


Table 7: Findings of combined MAS and ultrasonography for diagnosis of acute appendicitis (n=100)

MAS+Ultrasonography (diagnostic test)	Histology or alternative diagnoses		(alternative diagnosis)	Total
	Appendicitis	No appendicitis		
Appendicitis	77 (true positives)	17 (false positives)	(7)	94
No appendicitis	2 (false negatives)	4 (true negatives)	(1)	6
Total	79	21	(8)	100

P=0.001 (McNemar test), Agreement = 81%, Kappa=0.224, p=0.005

The figures in brackets represent the alternative findings intra-operatively.

Sensitivity= **77/79** (true positives/true positives + false negatives)

Specificity= **4/21** (true negatives/true negatives + false positives)

PPV= **77/94** (true positives/ total test positives)

NPV= **4/6** (true negatives/total test negatives)

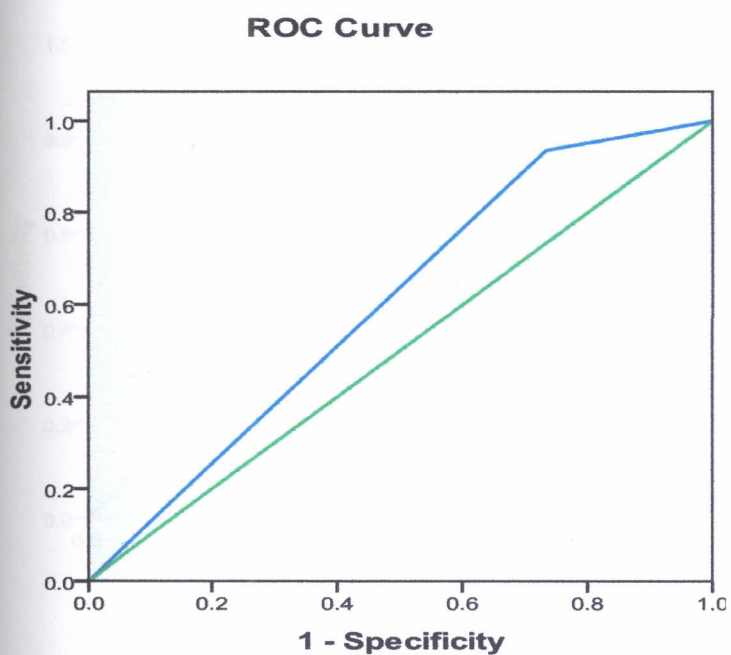
Table 8: Summary of sensitivity, specificity, PPV, NPV and confidence limits for the diagnostic protocol.

Measure	Proportion	95% CI	
		Lower	Upper
Sensitivity	97.5%	91.2%	99.7%
Specificity	19.0%	5.4%	41.9%
PPV	81.9%	72.6%	89.1%
NPV	66.7%	22.2%	95.7%

Receiver- operating characteristic curves

Receiver operating curves were drawn using the calculated sensitivities and specificities for a) ultrasonography in the equivocal group (46 patients) and b) the protocol combining MAS and ultrasonography for the study (100 patients). Figure 8 shows the ROC curve for ultrasonography in the equivocal group.

Figure 8: ROC curve for ultrasonography in the equivocal range

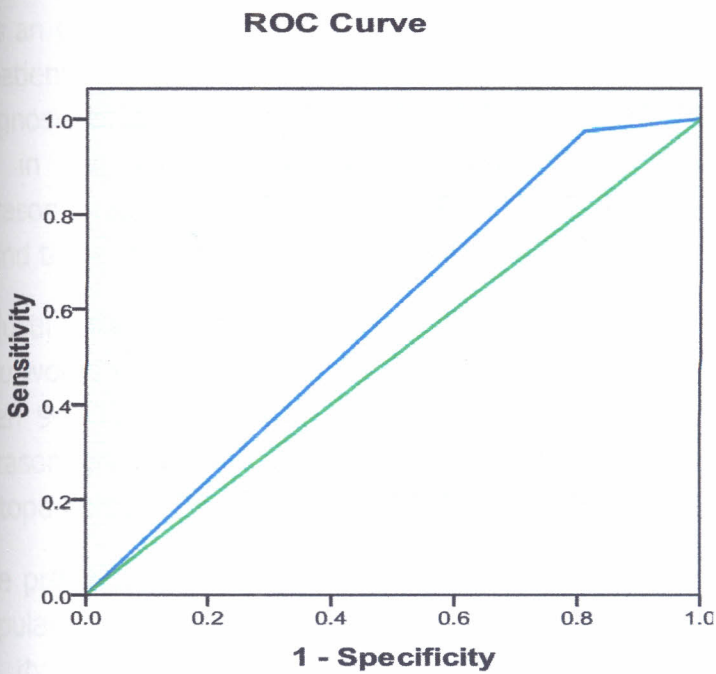


Diagonal segments are produced by ties.

Area under the curve = 0.601

Figure 9 shows the plot of the ROC curve for the protocol based on MAS and ultrasonography as used in combination during the study.

Figure 9: Receiver operating characteristic curve for the protocol based on MAS and ultrasonography



Diagonal segments are produced by ties.

Area under the curve = 0.585

The ROC curves for both ultrasonography in the equivocal cases and the protocol as a whole were 0.6 and 0.58 respectively.

Overall accuracy of the protocol

The sensitivity, specificity, PPV and NPV values of the diagnostic protocol were 97.5 % (95% CI, 91.2-99.7), 19 % (95% CI, 5.4-41.9), 81.9 % (95% CI, 72.6-89.1) and 66.7 % (95% CI, 22.7-95.7) respectively.

Overall accuracy = $\frac{77+4}{100}$ (true positives + true negatives / true positives + true negatives + false negatives + false positives)

The overall accuracy of the protocol was 81%.

Negative appendicectomy rate

The overall crude negative appendicectomy rate during the study period was 21%. This was an observational study and therefore there was no interventional arm. There were 7 patients who, though reported as acute appendicitis by the protocol, had alternative diagnosis at surgery and these did not have appendicectomy done. A further 4 patients fell in the category of true negatives; 3 who did not have appendicitis on ultrasonography and 1 patient who had bilateral tubo-ovarian masses. These were found to be true to the intra-operative diagnosis and histopathology findings.

Adjusting for use of the MAS and ultrasonography protocol, the total number of patients who would have gone for surgery with acute appendicitis as the diagnoses would have been 94. This takes into account the 6 patients who were reported as negative on ultrasonography. Out of the 94 patients, 77 were confirmed as acute appendicitis on histopathology. The adjusted negative appendicectomy rate was calculated as 18%.

The protocol would have missed a diagnosis of acute appendicitis in 2% of the study population. This is derived from the fact that there were 2 patients reported as negative by the diagnostic protocol, who were confirmed to have acute appendicitis on histopathology.

DISCUSSION

This study set out to establish the diagnostic accuracy of a protocol based on modified Alvarado score and ultrasonography in acute appendicitis at Kenyatta national hospital.

One hundred patients were recruited into the study over a period of 8 months from July 2011 to March 2012. The demographic characteristics revealed a male to female ratio of 1.2:1 and a peak incidence in the third decade with a mean age of 27.9 years. These findings were similar to two studies done previously at KNH. Ongaro found had a mean age of 27.1 years and a similar interquartile range.¹¹ Kimaro's study also showed nearly similar findings with a male to female ratio of 1.9:1.⁴⁵ A study on the epidemiology of appendicitis in the United States of America surveyed 250000 patients and the male to female ratio was 1.4:1. However the peak incidence was in the second decade which differed with the findings in our setup.⁴⁶ A study by Paterson, et al suggested that there was no significant difference in the male to female ratio in the United Kingdom.⁴⁷

Modified Alvarado scoring showed that a higher number of patients (54 vs 46) were seen in our setup with unequivocal findings as opposed to those in the equivocal range of 4 to 6. It remains to be elucidated if this suggests delays in health seeking behavior.

A modified Alvarado score of 7 and above had a positive predictive value of 88.9%. In this study 47 (97.9%) of the patients who were predicted to have appendicitis by a high score had confirmed appendicitis on histopathology. This gave a crude negative appendicectomy rate of 11.1% that is in keeping with what Ongaro found in his study in 2007.¹¹ A high Alvarado score was however unable to distinguish between appendicitis and other mimicking diagnosis in 5 cases. A systematic review by Ohle et al found out that a high Alvarado score was less sensitive as a 'rule in' score than as a 'rule out' for those below 5.⁴⁸ Our study suggests that a high Alvarado score is a useful tool to set aside patients for immediate appendicectomy without further diagnostics. This contrasts with a study by Saidi and Chavda that suggested that the scoring system has no value over clinical acumen.⁴⁹

An intermediate modified Alvarado score of 4 to 6 had a positive predictive value of 70.5%. In this subset of 46 patients, the negative appendicectomy rate was above 32%. As has been observed by numerous other studies, this subset has continued to pose diagnostic challenges for the clinician with approaches that range from in patient observation to further imaging using different modalities.^{50,51}

The addition of ultrasound to the equivocal group improved the positive predictive value from 70.5% to 72.5%. Since the Alvarado score of 4 to 6 cannot be used to rule out appendicitis, *ultrasonography added the important component of negative predictive value of 66.7%*. It further was able to detect an alternative diagnosis in 1 case and concurrent other diagnosis in 4 cases. The additional information by ultrasonography may be useful in reducing pre-operative delays due to diagnostic dilemmas. *The utility of ultrasound has been advocated in many studies both as an adjunct to improve diagnosis in the equivocal cases and to determine who needs further imaging with a superior modality.* In a study by Rasoul, et al in Iran, ultrasonography had a PPV of 90.4% and a sensitivity of 55.4%.⁵² In comparison ultrasonography had a PPV of 72.5% and a sensitivity of 93.5% in our study.

Kimaro, a diagnostic radiology resident then, in 2011 did a study on the correlation of ultrasonography as compared to clinical and surgical findings among patients in KNH. His study revealed sensitivity, specificity, PPV and NPV values of 92%, 58.3%, 95% and 47% respectively.⁴⁵ Our study in comparison had values of 93.5%, 26.7%, 72.5% and 66.7% respectively. The sensitivities in both studies were comparable. In our study the ability to pick the true negatives was quite low. This may be explained in part by the different methodology used in the two studies. Kimaro conducted the ultrasonography in all the patients in his series showed a negative appendicectomy rate of 10.7%.⁴⁵ In our study the ultrasonography was done by the different ultrasonographers or radiology residents on call.

There was an attempt to mitigate against inter-observer bias in ultrasonography in our study by using a standard data collection tool. It is known that ultrasound imaging remains heavily dependent on the user. Some authors have suggested that with adequate training ultrasonography can be a useful tool even among non radiology colleagues. Christian et al found that bedside ultrasound to detect acute appendicitis had a sensitivity of 65% [95% confidence interval (CI) 52-76], specificity of 90% (95% CI 81-95), positive predictive value was 84% (95% CI 71-92), and negative predictive value was 76% (95% CI 65-84).⁵³ In our study ultrasonography had a higher sensitivity but a low specificity. The differences in the specificity of ultrasonography, as suggested by the various comparable studies, seem to be largely dependent on the learning curve. It is expected that with further training, the utility of ultrasonography in diagnosing acute appendicitis would improve.

Combined use of a protocol based on modified Alvarado score and ultrasonography has been studied and been advocated by a number of authors.

The overall results for the protocol based on modified Alvarado score and ultrasound in our study were sensitivity, specificity, PPV and NPV values of 97.5% (95% CI,94.1-100), 19%(95% CI,2.2-35.8), PPV of 81.9%(95% CI, 74.1-89.7) and NPV of 66.7% (95%CI, 46.5-86.9).

The crude negative appendicectomy rate in our study was 21%. The adjusted negative appendicectomy rate after incorporating the protocol was calculated as 18%.This indicates a better performance than what has been generally accepted over the years, with negative appendicectomy rates being about 20%.⁸ The protocol would have missed a diagnosis of acute appendicitis in 2% of the study population. This is derived from the fact that there were 2 patients reported as negative by the diagnostic protocol, who were confirmed to have acute appendicitis on histopathology.

A study by Emmanuel et al in Tanzania had an overall negative appendicectomy rate of 33.1%.⁵⁴ Khan and Rehman found a negative appendicectomy rate of 15.6%. They advocated for the scoring system as an easy, cheap and complimentary tool for diagnosis of appendicitis.¹⁵ A study by Stephens and Mazucco achieved a false positive of zero by combining modified Alvarado score and ultrasonography .⁴² Debnath et al showed that graded compression ultrasonography was an accurate means of diagnosing or excluding appendicitis in clinically equivocal cases.⁴⁴ In our study the specificity was lower than expected and therefore ultrasonography could not be advocated as a tool for excluding appendicitis. However the positive predictive value and high sensitivity suggest that the use of the combined protocol is a good tool to enable the clinician to make a timely decision. This is in keeping with the findings by Douglas et al who in their randomized control trial concluded that patients in the Alvarado-ultrasonography group had a shorter mean time to operation than controls.⁴³

The AUC in the ROC curves were both above 0.5 and hence the protocol can usefully distinguish between those with and without acute appendicitis. It is expected that the AUC would improve with increased accuracy in ultrasonography use.

STUDY LIMITATIONS

- Ultrasonography was not carried out by a designated person and this may have caused inter-observer/operator errors. There was an attempt at mitigating against this by the use of standard ultrasonography descriptions using Puylaert's graded compression method. The use of different sonographers and radiology residents to do the ultrasonography was thought to be a strength in the study as it mirrored the reality of practice in our setting.

CONCLUSIONS

- The diagnosis of acute appendicitis is first and foremost a clinical diagnosis with scoring systems and imaging being necessary adjuncts in the equivocal cases. This reality is underscored by the fact that even a high modified Alvarado score has low specificity.
- The use of a protocol based on modified Alvarado score and ultrasonography of value and is an easily available tool in the diagnosis of acute appendicitis. The protocol can aid the clinician to 'rule-in' appendicitis. However the ability of the protocol to pick true negatives for appendicitis is still low and may largely be dependent on the learning curve of the ultrasonographer.

RECOMMENDATIONS

- There is need for continued training in ultrasound imaging among the clinicians in order to improve its accuracy as an imaging modality that shows great promise in the diagnosis of acute appendicitis.
- Further interventional studies using combined scoring and imaging protocols may further help to clarify and establish an algorithm for diagnosing acute appendicitis in our set up in order to bring down the negative appendicectomy rate further.

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APPENDIX II

DATA COLLECTION SHEET AND MODIFIED ALVARADO SCORING.

Name _____ Study number _____

IP/Casualty number _____ Age _____

Sex _____

<u>Modified Alvarado scoring</u>		Yes	No	Score
Symptoms	. Migration of pain	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text" value="1"/>
	. Anorexia	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text" value="1"/>
	. Nausea/ vomiting	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text" value="1"/>
Signs	. RLQ tenderness	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text" value="2"/>
	. Rebound tenderness	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text" value="1"/>
	. Elevated temperature (above 37.3°C)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text" value="1"/>
Laboratory	. Leukocytosis (≥ 10,000/ μ L)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text" value="2"/>
	Total	<input type="text"/>	out of	<input type="text" value="9"/>

APPENDIX III

ULTRASONOGRAPHY FINDINGS

Name _____ Study number _____

IP/Casualty number _____ Age _____

Sex _____

	Yes	No
Appendix visualized	<input type="checkbox"/>	<input type="checkbox"/>
Appendix compressible	<input type="checkbox"/>	<input type="checkbox"/>
Appendicular diameter (6mm and above)	<input type="checkbox"/>	<input type="checkbox"/>
Periappendicular fluid present	<input type="checkbox"/>	<input type="checkbox"/>
Peristalsis present	<input type="checkbox"/>	<input type="checkbox"/>
Appendicolith seen	<input type="checkbox"/>	<input type="checkbox"/>

Other findings _____

CONCLUSION _____

APPENDIX IV

CONSENT FORM

DIAGNOSTIC ACCURACY IN ACUTE APPENDICITIS: A PROTOCOL BASED ON MODIFIED ALVARADO SCORE AND ULTRASONOGRAPHY AT KENYATTA NATIONAL HOSPITAL

Name _____

Study No

Hospital No

This study is being carried out by Dr Mbuthia Mwangi, a postgraduate student in the department of surgery; University of Nairobi. The purpose of this study is to investigate the diagnostic accuracy of a protocol based on the modified Alvarado score and ultrasonography in diagnosis of acute appendicitis at Kenyatta National Hospital. The information gathered will be useful both in your treatment and for other patients in future who will present in a similar manner and have suspected acute appendicitis.

There is no harm or risk to you for participating in this study. Apart from taking a detailed history, you will undergo a blood test and if indicated additional ultrasonography of the abdomen and pelvis will be carried out. A total blood count and ultrasonography are commonly done investigations that carry minimal risk but which will be of benefit in your further management.

Participation in this study is out of your own free will. You will not be denied medical care in case you refuse to participate in the study. All information will be treated with confidentiality. Your identity will not be exposed to the public.

I, the undersigned have been explained to, understand the above, and voluntarily accept to participate in the study.

Signature/Thumb print:

Date _____

Telephone No (Patient)

For any enquiries or further clarification, you may contact

1. DR MBUTHIA MWANGI – PRINCIPAL RESEARCHER, TEL 0721380493
2. CHAIRMAN, UON/KENYATTA NATIONAL HOSPITAL ETHICS AND RESEARCH COMMITTEE

TEL 020-2726300 Ext 44355

APPENDIX V

CONSENT FORM FOR MINORS

DIAGNOSTIC ACCURACY IN ACUTE APPENDICITIS: A PROTOCOL BASED ON MODIFIED ALVARADO SCORE AND ULTRASONOGRAPHY AT KENYATTA NATIONAL HOSPITAL

This study is being carried out by Dr Mbutia Mwangi, a postgraduate student in the department of surgery; University of Nairobi. The purpose of this study is to investigate the diagnostic accuracy of a protocol based on the modified Alvarado score and ultrasonography in diagnosis of acute appendicitis at Kenyatta National Hospital. The information gathered will be useful both in the treatment of the patient and for other patients in future who will present in a similar manner and have suspected acute appendicitis.

There is no harm or risk to the patient for participating in this study. Apart from taking a detailed history, he/she will undergo a blood test and if indicated additional ultrasonography of the abdomen and pelvis will be carried out. A total blood count and ultrasonography are commonly done investigations that carry minimal risk but which will be of benefit in further management.

Participation in this study is out of own free will. Medical care will not be denied in case of refusal to participate in the study. All information will be treated with confidentiality. The identity of the patient will not be exposed to the public.

I Mr./Mrs./Ms _____ is the parent/guardian of

I consent for my child/ patient to participate in the study.

Signed _____ **[patient/parent/guardian]** **Date** _____

Witness signature _____ **Date** _____

ASSENT FORM FOR MINORS

I _____ hereby agree to participate in the study.

Date _____

For any enquiries or further clarification, you may contact

1. DR MBUTHIA MWANGI – PRINCIPAL RESEARCHER, TEL 07213804932. CHAIRMAN, UON/KNH ETHICS AND RESEARCH COMMITTEE, TEL 020-2726300 Ext 44355

APPENDIX VI

CONSOLIDATED FINDINGS FORM

Name _____ Study number _____

IP/Casualty number _____ Age _____

Sex _____

Modified Alvarado score _____

Ultrasonography diagnosis _____

Management decision _____

Intra-operative findings _____

Histopathological diagnosis _____
