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DIAGNOSIS OF ACUTE APPENDICITIS: DIAGNOSTIC SCORING AND SIGNIFICANCE OF PREOPERATIVE DELAY

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ACADEMIC DISSERTATION

To be presented, with the permission of the Faculty of Medicine of the University of Helsinki, for public examination in lecture room 1, Meilahti Hospital, on 28th of April 2017, at 12 noon.

Helsinki 2017

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TABLE OF CONTENTS

LIST OF ORIGINAL PUBLICATIONS

The present study is based on the following articles, which are hereafter referred to in the text by their Roman numerals.

I.   Sammalkorpi HE, Mentula P, Leppäniemi A. A new Adult Appendicitis Score improves diagnostic accuracy of acute appendicitis – a prospective study. BMC Gastroenterology (2014) 14:114

II.   Sammalkorpi HE, Mentula P, Savolainen H, Leppäniemi A. Introduction of Adult Appendicitis Score reduced negative appendectomy rate. Scand J Surg. Epub ahead of print, 2017.

III. Sammalkorpi HE, Leppäniemi A, Lantto E, Mentula P. Performance of imaging studies in patients with suspected appendicitis after stratification with Adult Appendicitis Score. World Journal of Emergency Surgery (2017) 12:6

IV.   Sammalkorpi HE, Leppäniemi A, Mentula P. High admission C-reactive protein level and longer in-hospital delay to surgery are associated with increased risk of complicated appendicitis. Langenbeck's Archives of Surgery (2015) 400:221-228

ABBREVIATIONS

AAS	Adult Appendicitis Score
AIR	Score Appendicitis Inflammatory Response Score
AUC	Area under curve
CRP	C-reactive protein
CT	Computed tomography
DOR	Diagnostic odds ratio
EAES	European Association of Endoscopic Surgery
ICD	International Classification of Diseases
IQR	Inter-Quartile Range
LR$^-$	Negative likelihood ratio
LR$^+$	Positive likelihood ratio
MRI	Magnetic Resonance Imaging
NSAP	Non-specific Abdominal Pain
NOTES	Natural Orifice Trans-luminal Endoscopic Surgery
r	Correlation coefficient
RLQ	Right Lower Quadrant of the Abdomen
ROC	Receiver Operating Characteristics
US	Ultrasound
USA	United States of America
WSES	World Society of Emergency Surgery

ABSTRACT

Background and aims: Acute appendicitis is a common cause of acute abdominal pain. Its typical symptoms and signs were described already in the 1880s. However, the diagnostic work-up for patients with suspected acute appendicitis has dramatically changed over the last decades, especially after computed tomography was introduced in the 1990s. Diagnostic scoring provides an accurate method for stratifying patients according to the probability of appendicitis, and therefore works as an excellent basis for a diagnostic algorithm. This study aimed at developing a new diagnostic score, the Adult Appendicitis Score (AAS), and validating its routine use as an integral part of a new diagnostic algorithm.

It is known that the diagnostic accuracy of the imaging studies in suspected appendicitis depends on the pre-test probability of the disease. One of the main goals in this study was to assess how accurate the imaging was in various AAS-stratified pre-test probability groups.

The longer is the overall duration of symptoms, the higher is the perforation risk in acute appendicitis. However the effect of in-hospital delay on the risk of perforation is controversial. The research in this thesis aimed to further clarify the matter.

Patients and methods: The two prospective data collections included 1737 patients with acute right lower quadrant abdominal pain. The first data collection of 829 patients was used to develop the AAS. Subsequently, the AAS was compared with two previously published scores as well as with the clinical assessment.

The AAS was incorporated into a novel diagnostic algorithm for patients with suspected appendicitis. A validation study on the diagnostic accuracy for the AAS was performed shortly after the diagnostic system was adopted and implemented. The validation study enrolled 908 patients in two university hospitals. The negative appendectomy rate was compared between the first and second patient cohort.

Patients that had diagnostic imaging were stratified into three probability-of-appendicitis groups according to the AAS score, and the diagnostic accuracy of ultrasound and computed tomography were compared between the three score groups.

In order to find the best marker to detect pre-hospital perforations, laboratory results and two previously published and validated diagnostic scores were analyzed in the first data set. Based on this analysis patients with appendicitis

8

were divided to those with and without likely to have pre-hospital perforation, which was subsequently used to study the effect of in-hospital delay on the perforation risk. The effects of total duration of symptoms, pre-hospital delay, and in-hospital delay on the risk of perforation were then analyzed.

Results: The new diagnostic score, AAS, was developed and incorporated into a novel diagnostic algorithm for routine clinical use. After the new algorithm was implemented in the Meilahti Hospital, the negative appendectomy rate decreased from 18.2% to 8.2%. With a specificity of 93%, the AAS stratified half of all patients with appendicitis into the high-probability group. In contrast, the probability of appendicitis was only 7% for the low-probability group. In addition no patient stratified to this group was found to have peritonitis. The new score had superior diagnostic accuracy compared both to the clinical assessment and to two previously published scores.

The diagnostic accuracy of imaging depended on the pre-test probability of appendicitis. When compared to the two other groups allocated by the AAS, in the low-probability group a positive computed tomography findings yielded lower post-test probability for appendicitis. This finding was also present when analyzing the ultrasound imaging data, where more false positive than true positive ultrasound imaging results were found in the low-probability group.

C-reactive protein (CRP) was the best marker for pre-hospital perforation. The total duration of symptoms was a significant risk factor for perforation in all patients with appendicitis. Nevertheless, the duration of pre-hospital delay between patients with uncomplicated and complicated appendicitis showed no difference for the subgroup of patients with the CRP values less than 99 mg/l. The in-hospital delay, however, was significantly different in this subgroup. For patients with CRP values 99 mg/l or more, the in-hospital delay did not significantly increase the perforation risk.

Conclusions: The AAS provides an accurate method to stratify patients according to their probability of appendicitis. After the score was implemented into clinical routine as an integral part of the diagnostic algorithm, it led to a dramatic reduction in the negative appendectomy rates.

When the AAS system stratifies the patient to have a low probability of appendicitis, the benefits of imaging are questionable. False positive imaging results can even induce negative appendectomies.

Most perforations in acute appendicitis occur as pre-hospital events. However, some of the perforations can be avoided by minimizing the in-hospital delay.

TIIVISTELMÄ

Taustat ja tavoitteet: Akuutti umpilisäketulehdus on tavallinen äkillisen vatsakivun syy. Vaikka umpilisäketulehdus tautitilana kuvattiin jo 1800-luvulla, sen diagnostiikka muuttuu yhä.

Umpilisäketulehduksen diagnostiikassa käytetään kliinisien oireiden ja löydösten lisäksi tulehdusreaktiota mittaavia laboratoriokokeita sekä kuvantamista. Oireita, löydöksiä ja laboratoriotuloksia voidaan yhdistää diagnostisen pisteytyksen avulla. Diagnostisella pisteytyksellä potilaat luokitellaan umpilisäketulehduksen todennäköisyyden mukaan kolmiportaisella asteikolla: todennäköinen, mahdollinen ja epätodennäköinen. Tällainen luokittelu on nopea ja tarkka apukeino jatkotutkimuksen, kuten tietokonetomografian, tarpeesta päätettäessä ennen mahdollista kotiutusta tai leikkaushoitoa. Useita eri pisteytyksiä on kehitetty, mutta yksikään niistä ei tähän mennessä ole osoittautunut riittävän tarkaksi soveltuakseen rutiininomaiseen käyttöön.

Diagnostisen kuvantamisen tarkkuuden ajatellaan riippuvan umpilisäketulehduksen todennäköisyydestä kuvannetussa potilasryhmässä. Kuvantamisen tarkkuutta ei kuitenkaan aiemmin ole tutkittu vertailemalla diagnostisella pisteytyksellä luokiteltuja potilasryhmiä.

Umpilisäkkeen puhkeaman riskin tiedetään kasvavan kun oireiden kesto pitenee. Sairaalan sisällä ennen leikkaushoitoa tapahtuvan viiveen merkityksestä puhkeaman riskiin on kuitenkin ristiriitaista tutkimustietoa.

Tämän väitöskirjatutkimuksen tavoitteena oli kehittää uusi diagnostinen pisteytys, ottaa tämä pisteytys käyttöön päivystyspoliklinikalla, ja varmistaa sen toimivuus rutiinikäytössä.

Tutkimme myös miten ultraäänikuvauksen ja tietokonetomografian diagnostinen tarkkuus vaihtelee uudella pisteytyksellä muodostetuissa potilasryhmissä, joissa umpilisäketulehduksen todennäköisyys on erilainen.

Tässä tutkimuksessa selvitimme lisäksi sairaalan sisäisen viiveen vaikutusta umpilisäkkeen puhkeaman riskiin.

Potilaat ja menetelmät: Tutkimusta varten kerättiin prospektiivisesti kaksi aineistoa, joissa oli yhteensä 1737 akuutista oikeanpuoleisesta alavatsakivusta kärsivää potilasta. Uusi pisteytys kehitettiin ensimmäisessä, Meilahden sairaalassa kerätyssä, 829 potilaan aineistossa. Uuden pisteytyksen diagnostista tarkkuutta verrattiin päivystävien kirurgien tekemän kliinisen arvion tarkkuuteen ja kahden aiemmin julkaistun pisteytyksen tuloksiin.

Pisteytys otettiin rutiinikäyttöön Meilahden sairaalassa ja Kuopion yliopistollisessa sairaalassa osana uutta ohjeistusta umpilisäketulehduksen diagnostiikasta. Uuden pisteytyksen käyttöönoton jälkeen näissä kahdessa sairaalassa kerätyssä 908 potilaan aineistossa tutkittiin pisteytyksen käytön vaikutusta diagnostiikan tarkkuuteen ja kuvantamisen käyttöön verrattuna ensimmäiseen potilasaineistoon.

Ultraäänikuvauksen ja tietokonetomografian diagnostista tarkkuutta verrattiin pisteytyksellä muodostettujen ryhmien välillä.

Jotta sairaalan sisäisen viiveen merkitystä voitaisiin luotettavasti analysoida, etsittiin ensin tarkin keino tunnistaa potilaat, joilla umpilisäke oli puhjennut jo ennen sairaalaan hakeutumista. Tätä varten analysoitiin tulehdusreaktiosta kertovia laboratoriotuloksia sekä kahden aikaisemmin kehitetyn diagnostisen pisteytyksen tulokset tutkimuspotilailla. Oireiden kokonaiskeston, oireiden keston ennen sairaalaan hakeutumista, ja sairaalan sisäisen viiveen pituuden merkitys umpilisäkkeen puhkeaman riskiin analysoitiin.

Tulokset: Uusi diagnostinen pisteytys, Adult Appendicitis Score, kehitettiin ja otettiin rutiinikäyttöön osana uutta diagnostista ohjeistusta. Uusi pisteytys oli tarkempi kuin päivystävien kirurgien arvio tai kumpikaan vertailussa mukana olleista aiemmin julkaistusta pisteytyksistä.

Uuden ohjeistuksen käyttöönoton jälkeen turhien umpilisäkepoistojen osuus väheni merkittävästi, 18,2 %:sta 8,2 %:iin.

Kuvantamistutkimusten diagnostinen tarkkuus riippui umpilisäketulehduksen todennäköisyydestä. Potilailla, joilla umpilisäketulehdus oli epätodennäköisin, ultraäänikuvauksen umpilisäketulehduslöydöksistä jopa useampi oli virheellinen kuin todellinen. Myös tietokonetomografiassa tarkkuus riippui umpilisäketulehduksen todennäköisyydestä kuvatussa ryhmässä.

C-reaktiivinen proteiini (CRP) oli tutkituista muuttujista paras tunnistamaan puhjenneen umpilisäkkeen. Oireiden kokonaiskeston pituus oli kaikilla potilailla riskitekijä umpilisäkkeen puhkeamiselle. Potilailla, joiden CRP oli 99 mg/l tai yli, viive ennen sairaalaan hakeutumista oli merkittävä puhkeaman riskitekijä, mutta sairaalan sisäisellä viiveellä ei ollut merkitystä puhkeaman riskiin. Sen sijaan potilailla, joiden CRP oli alle 99 mg/l sairaalaan tullessa, lisääntyi puhkeaman riski kun sairaalan sisäinen viive kasvoi.

Johtopäätökset: Adult Appendicitis Score on tarkka pisteytysjärjestelmä umpilisäketulehduksen todennäköisyyden arviointiin. Sen käyttö osana diagnostista ohjeistusta auttaa tarkentamaan diagnostiikkaa ja vähentämään turhien umpilisäkepoistojen osuutta merkittävästi.

Potilailla, joilla pisteytyksen mukaan umpilisäketulehdus on epätodennäköinen, on kuvantamistutkimusten hyöty pienin. Näillä potilailla kuvantaminen voi jopa lisätä turhien leikkausten osuutta.

Vaikka monilla potilailla umpilisäke on puhjennut jo ennen sairaalaan hakeutumista, osalla potilaista puhkeama voidaan välttää tarjoamalla potilaille viivytyksetöntä diagnostiikkaa ja hoitoa.

1. INTRODUCTION

Acute abdominal pain is a common complaint among emergency department patients. Diagnostics of one of the most common pathologies behind acute abdominal pain, acute appendicitis, has radically changed over the last decades.

Traditionally, the diagnosis of appendicitis was made solely based on clinical symptoms and signs, and later diagnosis included results of inflammatory laboratory variables such as leukocytes, neutrophils, and CRP. This practice in diagnostics led to a false positive diagnosis (negative appendectomy) rates in the range of 15-30% (1-3).

The development of imaging modalities, especially that of computed tomography (CT), has enabled more accurate diagnostics with a significant decrease in false positive diagnoses, which has led to lower rates of negative appendectomies (4, 5). This improvement in diagnostic accuracy has been achieved at the cost of exponentially increased use of imaging studies (5). Although in some institutions and countries imaging is considered mandatory for suspected acute appendicitis, in other institutions diagnostic imaging is still underused (6). This kind of difference in diagnostic pathways has led to varying rates of negative appendectomies. For example, a multicenter observational study in Great Britain reported negative appendectomy rates ranging from 3.3% to 37% (7).

Negative appendectomies cause an overuse of hospital resources such as operation theatre capacity and hospital beds. In addition to financial and logistical considerations, negative appendectomy is associated with similar or increased morbidity compared to appendectomy for uncomplicated appendicitis (8, 9).

Although negative exploration for suspected appendicitis is far from harmless, imaging is associated with some risks as well. In the absence of diagnostic guidelines, imaging is often either over- or underused. Mandatory imaging highlights the harms caused by imaging, whereas unacceptably high rate of negative appendectomies can follow highly selective imaging.

CT is the most accurate imaging method for the diagnostics of appendicitis but overuse of CT involves increased costs and increased risks of associated ionizing radiation and contrast medium, and a potential increased delay to treatment. Abdominal organs are sensitive to ionizing radiation, and suspected appendicitis is most frequent in young patients for whom the considerations of radiation-induced risks are most important (10-13).

After an initial uncontrolled increase in imaging, surgeons have successfully started to find ways of limiting the potentially harmful unselective CT imaging without compromising diagnostic accuracy (14-17). There is evidence that using a diagnostic algorithm or electronic decision support in suspected appendicitis is associated with a decreased need of CT imaging studies without any loss of diagnostic accuracy (14, 15).

Ultrasound (US) is often used as a primary imaging method to avoid radiation induced by CT. If US is diagnostic for appendicitis, then the patient avoids the use of CT. If US is negative or non-diagnostic for appendicitis, then the patient undergoes additional CT. US involves no ionizing radiation but its ability to recognize or rule out appendicitis is inferior to that of CT, and it is dependent on the skills of the radiologists and the pre-test probability of appendicitis. Furthermore, US is often inconclusive (18-20).

Diagnostic scoring was originally invented before the era of modern imaging technologies as an independent diagnostic tool. Scoring has therefore often been simply investigated in the surgical literature as an alternative to imaging (21). However, scoring and imaging should optimally be used as complementary methods in a diagnostic algorithm. The aim is to achieve accurate diagnosis with minimal risks, delays, and costs in a standardized manner independent of the experience level of the clinician. Lately, diagnostic scoring has been included in consensus guidelines of diagnosis of appendicitis (22, 23).

Diagnostic scoring is a method for stratifying patients according to the probability of the patient having appendicitis. Typically patients are stratified into three groups: high, intermediate, and low risk for appendicitis. Ideally, the patients in the low-risk group can be discharged, and patients in the high-risk group can be directly scheduled for surgery. The patients in the intermediate-risk group benefit most from further investigations such as imaging.

There are several different diagnostic scores for suspected acute appendicitis. The Alvarado score is the most widely known of these scores. The Alvarado score was originally developed for both pediatric and adult patients, and includes eight clinical and laboratory variables (24). The Appendicitis Inflammatory Response Score (AIR) was published in 2008 and is similar to the Alvarado score in many aspects but emphasizes the inflammatory response laboratory results, and seems to perform better compared to the Alvarado score (25, 26). None of the existing scores has gained prevailing popularity in everyday clinical practice. There are probably a few reasons for this. The results of scoring systems are often compared to imaging results and are therefore mistakenly understood as being competitive and not complementary to

imaging (21). The discriminating capacity *per se* of the existing scoring systems has not been reliable enough. There are some possible factors that impair the accuracy of these scoring systems. First, the diagnostics of acute appendicitis is different in children of varying ages compared to adults, and many of the previous scores are developed for patients of all ages. The reference values of inflammatory laboratory variables and possible differential diagnoses depend on the patient's age (27). The precise time of onset of symptoms, pain relocation, and other details of patient history are perhaps not known in the youngest patients. Second, the delay in presentation to hospital influences the results of inflammatory laboratory variables (28, 29). Third, the diagnosis of appendicitis is more equivocal in female patients (2). These three important confounding aspects have not been taken into account in previously described scoring systems.

In this thesis, a new diagnostic score for diagnosis of adult (≥16 years) patients with suspected acute appendicitis, the Adult Appendicitis Score (AAS), was constructed (study I). The new score was incorporated into a diagnostic algorithm, and subsequently validated (study II).

According to the results of meta-analyses the accuracy of imaging studies in suspected acute appendicitis seems to be dependent on the pre-test prevalence of appendicitis (20, 30). However, the impact of pre-test probability, as evaluated by diagnostic scoring, on the diagnostic performance of imaging studies has not been investigated before. This aspect is particularly important when scoring is implemented into routine management of patients with suspected appendicitis. In this thesis the diagnostic accuracy of imaging was investigated and compared with different pre-test probabilities for appendicitis that had been determined by AAS (study III).

The time interval between the onset of symptoms and treatment is associated with the severity of acute appendicitis (31-36). Hence, a delay in presentation to the hospital (pre-hospital delay or patient delay) is a risk factor for complicated appendicitis. However, there are controversial results regarding the effect of in-hospital delay on the risk of complicated appendicitis and perioperative morbidity. Several studies show that longer in-hospital delay increases the risk of complicated appendicitis and adverse outcomes (33, 37-42), but many other studies conclude that in-hospital delay is insignificant (43-46). Most of the studies that concluded that in-hospital delay does not affect the perforation rate and outcome of appendicitis were retrospective, and hence pre-hospital perforations were not recognized and excluded from the analyses. Patients with pre-hospital perforations are usually treated faster because of the more severe symptoms (36). This faster treatment may result in significant bias in the analysis of the effect of in-hospital delay. Moreover, no explanation was

given in those studies to results that suggested that the time interval from symptoms onset to hospitalization would affect the risk of perforation and other adverse events in a different way compared to the in-hospital diagnosis to treatment interval.

In this thesis, an accurate marker for pre-hospital perforations was searched, and the effect of in-hospital delay on the risk of complicated appendicitis was studied (study IV).

2. REVIEW OF THE LITERATURE

2.1 HISTORY OF ACUTE APPENDICITIS

In the 1800s, the disease that is now known as appendicitis went by with several names including "peri-caecal inflammation", "typhlitis", "perityphlitis", and "paratyphlitis". Dr. Reginald Fitz first described appendicitis and suggested its treatment by early appendectomy in his article "Perforating inflammation of vermiform appendix" in 1886 (47). At that time, patients with generalized peritonitis usually died, whereas abdominal abscesses could be drained. Non-operative treatment as we know today was practically non-existent with no intravenous fluids, antibiotics or vasopressors being available (48). In 1891, Charles McBurney published his article "The indications for early laparotomy in appendicitis", where he described typical symptoms and findings of appendicitis. The important clinical symptoms and signs in McBurney's article were the acute onset of abdominal pain, relocation of pain from the whole abdomen to the right iliac fossa, the maximal pain localization over the base of appendix, fever, tachycardia, and guarding. He described a focal point, later known as the "McBurney point", where the pain from appendicitis is localized. He described the location of this point: "This point is very accurately in the adult from 1.5 to 2 inches inside of the right anterior superior spinous process of the ileus on a line drawn to the umbilicus". When the etiology of abdominal pain was unclear, McBurney recommended observation and application of cold onto the abdomen (49). Before McBurney published his article entitled: "The incision made in the abdominal wall in cases of appendicitis, with a description of a new method of operating" in 1894, the surgery for appendicitis was performed through a midline incision or paramedian incision over the linea semilunaris (50). The oblique incision used in open surgery for appendicitis through decades became known as the McBurney incision after the article although it was not originally invented by McBurney (51).

Mortality from appendicitis and appendectomy was high. After the era of McBurney and Fitz, the surgery for appendicitis remained technically closely similar to modern open surgery, but development of hospitals and non-operative treatment including antibiotics and anesthesia, together with better access to health care have made appendicitis a benign disease with a low mortality.

In the early 1980s, Semm described appendectomy that was carried out using an endoscopic method previously used by gynecologists during surgical

pelviscopy (52). Laparoscopic appendectomy slowly became more common, and is today the standard operation for appendicitis (53).

Clinical symptoms and signs already referred to by McBurney remained the cornerstone of diagnostics for decades. Blood leukocytosis and increased proportion of neutrophils were later found to be associated with appendicitis (54). Immediate surgery in order to prevent perforation was the gold standard, and false positive diagnosis of 15-30% was considered normal (1).

In 1986, Alfredo Alvarado published the Alvarado Score, a diagnostic score for the early diagnosis of acute appendicitis. The score comprises 8 variables: migration of pain, anorexia, nausea, tenderness in the right lower quadrant of abdomen, rebound pain, elevated temperature, blood leukocytosis and shift to the left. The score stratified patients with suspected appendicitis into three groups according to the probability of appendicitis, thereby helping in the decision-making (24). Since the publication of the Alvarado score, several different scoring systems have been developed (Table 1).

The technological development of imaging modalities followed, which improved diagnostic accuracy and thus the use of diagnostic imaging became popular in suspected acute appendicitis. In some institutions, diagnostic imaging is now considered mandatory (6). Today, the typical rate of false positive diagnosis is around 10% but great variation in this rate still exists (6, 7, 55).

2.2 EPIDEMIOLOGY OF ACUTE APPENDICITIS

Acute appendicitis is the most frequent indication for emergency general surgery. The incidence of appendicitis is highest between the ages of 10 and 19 years, and men are more likely to develop appendicitis than women. The incidence of appendicitis was decreasing in USA between 1970 and 1984, but the incidence has been increasing since then. The annual rate of appendicitis increased from 7.62 to 9.38 per 10000 from 1992 to 2008. Appendicitis has become more common in older patients, whereas its incidence for the most susceptible ages has continued to decrease. The mean age of patients at diagnosis has risen from 29.6 to 32.7 years. The lifetime risk for appendicitis for males is 8.6% and for females 6.7% (56-58).

The reason for the increase of incidence is unknown, but there has been an association between the more accurate diagnosis especially with the frequent use of CT and the increase in the incidence of uncomplicated appendicitis (56). However, a large American (USA) epidemiological study reported, that the ratio of simple to complicated appendicitis of 3:1 remained the same during 1993-

2008, which does not support this theory (56). There are also studies that show a correlation between the exploration rate and incidence of uncomplicated appendicitis, whereas incidence of complicated appendicitis was unaffected. Studies on the epidemiology of perforated and non-perforated appendicitis showed these conditions followed different epidemiological trends (59, 60).

An epidemiological study conducted in Finland showed that the incidence of appendicitis decreased from 14.5 to 9.8 per 10000 between 1987 and 2008, which is contrary to the results from the USA (61).

There is a seasonal variation in admissions due to acute appendicitis, with summer being the highest and winter the lowest admission seasons (58, 61-63). The reason behind the seasonal variation is unknown. Epidemiological studies from United States show differences in incidence of appendicitis between ethnic groups (57, 63). The frequency of appendicitis rose during 1993-2008 among Hispanics, Asians, and Native Americans, whereas the frequencies in Caucasians and African Americans decreased. Any possible etiological factor for racial differences in incidence is unknown (56).

2.3 ETIOLOGY, PATHOGENESIS, AND CLASSIFICATIONS

2.3.1 Etiology and pathogenesis of acute appendicitis

Surgical textbooks teach that the main etiology of appendicitis is obstruction of the lumen of the appendix caused by fecolith, lymphoid hyperplasia or tumor, followed by secondary bacterial invasion of the appendiceal wall that eventually leads to necrosis and perforation when not treated promptly (64). Historical experimental studies that were first conducted in animal models and later also in humans, found that obstruction of the lumen of the appendix led to increased intraluminal pressure, which threatened the viability of the appendix (65). However, modern studies on the etiology of appendicitis do not support this hypothesis. The prevalence of fecolith in adult patients in a study by Singh and Mariadason was 13.7% for appendicitis and 31.6% for negative appendectomy samples. The prevalence of fecolith was 27.5% in perforated appendicitis compared to 12.0% in non-perforated appendicitis (66). A study of 101 autopsy appendices and over 3000 surgically resected appendices found fecolith in 27% of autopsies, yet inflammation was detected in none of these samples (67). A study of the pathology of appendix from New Zealand reported lymphoid hyperplasia to be more common in normal than inflamed appendices, and occurred only in 6% of 1711 appendices in which acute inflammation was detected (68).

Viral infections have been suggested as an etiological factor because of seasonal variation in the incidence of appendicitis but this theory remains unconfirmed (69). Some bacterial infections can cause appendicitis with or without involvement of the bowel (70). Parasitic infections are a known possible etiological factor of acute appendicitis especially in developing countries. *Enterobius vermicularis* (pinworm) that is common also in developed countries is the most common worm found in the appendix (71, 72). In addition to rarely causing appendicitis, pinworm can also cause appendicitis-like symptoms that lead to appendectomy (73).

In rare cases, ingested foreign bodies such as shotgun pellets from wild game can migrate to the appendix and cause inflammation with or without perforation (74).

In summary, the precise etiology of appendicitis remains unknown, but many possible contributing factors have been recognized.

2.3.2   Uncomplicated appendicitis

Uncomplicated appendicitis (suppurative appendicitis, simple appendicitis) is defined as acute inflammation of either the entire or part of the appendix. The mucosa of the appendix is acutely inflamed and often ulcerated. Histopathological analysis shows neutrophilic infiltration in the submucosa and muscularis propria. Transmural inflammation, vascular thrombosis, and intramural abscesses are typical. Gangrenous acute appendicitis is sometimes included under the definition of uncomplicated, and sometimes it is included under complicated appendicitis, depending on the source. Transmural inflammation with areas of necrosis and extensive mucosal ulcerations are seen in histopathological analysis of gangrenous appendicitis. Untreated gangrenous appendicitis will lead to perforation of the appendix with peritonitis or appendiceal abscess (Figure 1, laparoscopic images of uncomplicated appendicitis) (75).
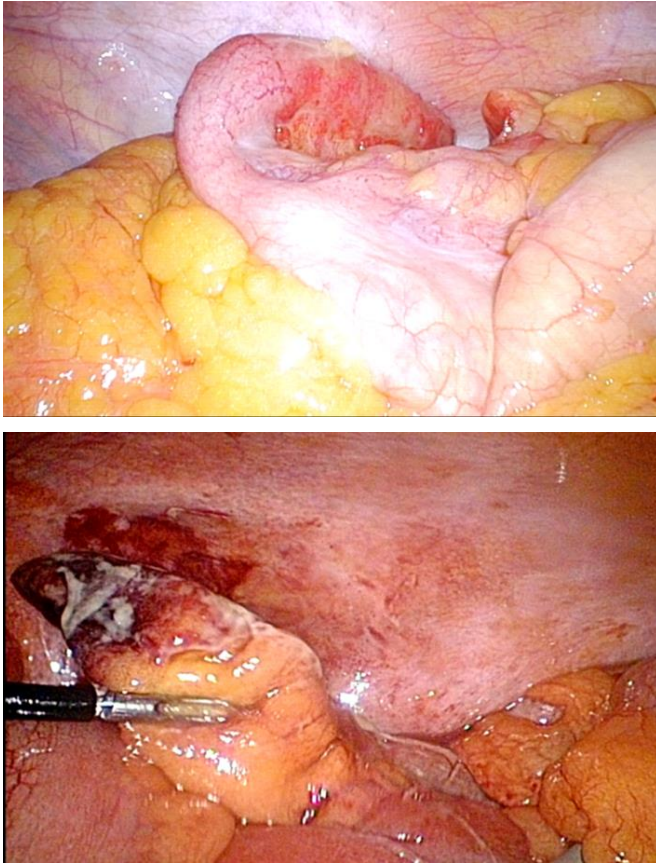
Figure 1 Laparoscopic images of uncomplicated appendicitis

2.3.3   Spontaneously resolving appendicitis

Spontaneous resolution of appendicitis has been described in the surgical and radiological literature (76-78). The histology of resolving appendicitis has also been described (79). The incidence of spontaneously resolving appendicitis is unknown, but is estimated to be at least 8% (78). There is epidemiological evidence that increased frequency of appendectomy is associated with increased rate of uncomplicated appendicitis, whereas the rate of complicated appendicitis is unaltered (59). The same phenomenon was reported by two randomized studies that compared early laparoscopy with observation conducted amongst patients with non-specific abdominal pain. Significantly more patients with acute appendicitis were found in the laparoscopy group, which suggests that spontaneous resolution occurred in the observation group (80, 81). There is also evidence that increased use of CT is associated with increased detection and therefore possible overtreatment of otherwise

spontaneously resolving appendicitis (82, 83). Spontaneously resolving appendicitis seems to recur frequently. No exact frequency can be stated, but a study by Barber et al. reported that 6.5% of all patients with acute appendicitis had previously presented to hospital due to a similar attack (76).

2.3.4   Complicated appendicitis

Complicated appendicitis can be defined in different ways. The conventional definition as used in this thesis is appendicitis with perforation and peritonitis or appendiceal abscess. However, the surgical literature is rather inconsistent because the term complicated appendicitis can include various degrees of disease severity from simple appendicitis with fecolith to perforated appendicitis with diffuse four-quadrant peritonitis. In some studies gangrenous, non-perforated appendicitis is also classified as complicated or advanced appendicitis. This classification is challenging for research purposes because gangrenous appendicitis without perforation has no specific diagnostic code in the ICD-classification system.

Disease severity grading systems based on intraoperative view of the appendix and peritoneal cavity have been developed for more accurate classification. The Sunshine Appendicitis Grading System score aims at predicting postoperative intra-abdominal collections and classifies appendicitis by scoring a range from 0 that indicates no appendicitis to 4 indicating perforated appendicitis with free fecolith, fecal staining, free feces or a visible hole in the appendix (84). A US-based study developed a disease severity score that enabled more accurate prediction of outcomes of patients with appendicitis. The score classifies Grade 0, normal appearance; Grade 1, inflamed without perforation; Grade 2, gangrenous without perforation; Grade 3, perforated with localized fluid; Grade 4, perforated with a regional abscess greater than 5 cm; and Grade 5, perforated with diffuse peritonitis (85).

Patients with complicated appendicitis have a longer duration of symptoms, more guarding and fever, and higher CRP values (31, 86-89). Radiological diagnosis of perforation is uncertain, and the most specific radiological findings to perforation include extraluminal gas, focal defect in appendiceal wall, abscess and small bowel ileus (88, 90, 91). One study analyzed clinical and radiological features of complicated appendicitis, and resulted in a scoring system that identified uncomplicated and complicated appendicitis that was more reliable than solely using imaging (92).

Appendicitis has conventionally been seen as a disease that invariably progresses from a simple uncomplicated malady to a complicated one. The association between the increase of delay from the onset of symptoms to

treatment with complicated appendicitis is described in the surgical literature (31-33, 93). An epidemiological study from the USA also showed that patients without private insurance and hence impaired access to healthcare have a higher rate of complicated appendicitis (63). This finding is supported by a study from South Africa that showed higher perforation rates in public than in private hospitals and also by a recent register study from the USA reporting that variations in perforated appendix admission rates were explained by variations in health insurance and personal incomes (93, 94).

A Swedish study found that the incidence of uncomplicated appendicitis was dependent on age, and also the rate of removal of a normal appendix, whereas the incidence of complicated appendicitis was not influenced by age and exploration rate. Hence uncomplicated and complicated appendicitis might be two different entities, and not all appendicitis would progress to perforation (95). See figure 2 for laparoscopic images of perforated appendicitis with peritonitis.
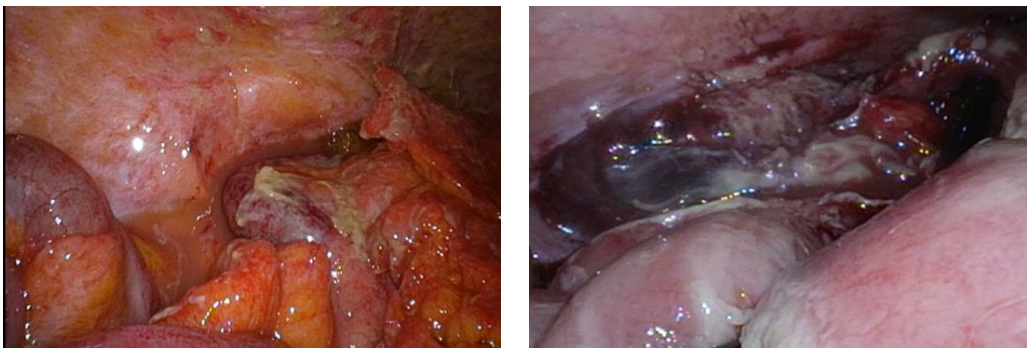
Figure 2 Laparoscopic images of perforated appendicitis with generalized peritonitis

2.3.5   Negative appendectomy

Negative appendectomy is defined as appendectomy performed for suspected appendicitis with no appendicitis detected, even when another necessary surgical treatment takes place during the same operation. Only the discharge diagnosis based on the intraoperative appearance of the appendix has been used by many studies. This practice results in lower reported rate of negative appendectomies compared to the studies that use histopathological analysis (55, 96).

The overall rate of negative appendectomies has declined since 1990s as a result of more accurate diagnosis that has mainly resulted from the development and wider utilization of imaging modalities (4, 6). A negative appendectomy rate of 20% or more was considered acceptable before the era of CT (97). Today, negative appendectomy rate of around 10% or less is

considered acceptable, but the rate still varies greatly. (6, 7, 55, 98). Despite the development of modern imaging, diagnostic methods are still not 100% accurate and hence the rate of negative appendectomy will remain above 0%.

Appendectomy is a relatively safe routine operation, but there is associated morbidity. Complications are at least as common in negative explorations as in therapeutic procedures; adverse events occur in approximately 10% of cases (7-9, 53).

2.3.6   Special types of acute appendicitis

When an appendix is incarcerated inside an inguinal hernia sac, the hernia is called Amyand's hernia after Claudius Amyand, the surgeon who described the condition, and performed the first successful appendectomy in 1735 (99). When the appendix is incarcerated in a femoral hernia sac, the diagnosis is de Garengeot hernia. These rare locations of an inflamed appendix, account for 0.1% of all appendicitis cases, most of them are Amyand's hernias (100-102).

2.4   DIAGNOSIS OF ACUTE APPENDICITIS

2.4.1   Clinical symptoms and physical examination

Clinical symptoms and signs of appendicitis have been familiar to physicians and surgeons for more than 120 years, and remain the most important part of the evaluation of patients with acute abdominal pain (47, 49). No symptom, sign or test is 100% accurate in diagnosing appendicitis, but a combination of various findings support the diagnosis. Before the era of CT, the decision to operate in suspected appendicitis was based on clinical signs and findings supported by laboratory examinations, and the reported negative appendectomy rate was commonly 15-30% (1, 5, 83, 103).

The most typical symptoms of acute appendicitis include acute right lower quadrant (RLQ) abdominal pain, relocation of pain from upper part of the abdomen to the RLQ, loss of appetite and nausea, and elevation of temperature. The pain can be aggravated by movement or cough as a sign of peritoneal inflammation, and the patient may have vomited (24, 25, 104, 105).

The most frequent finding in the physical examination is tenderness in the RLQ. However, even this sign is not positive in 100% of cases. Peritoneal inflammation caused by inflammation of the appendix can be tested in several different ways, of which the combination of guarding and rebound tenderness (also referred as Blomberg's sign) is the most accurate sign. Indirect tenderness

in Rovsing's test supports the diagnosis and so does the psoas sign, which when positive, indicates irritation to the iliopsoas muscle and that the inflamed appendix is in the retrocecal position. Patients often have elevated temperature. Rectal digital examination is not diagnostic of acute appendicitis. However, it might be valuable in diagnosing appendiceal abscess or diagnosing gastrointestinal malignancies behind the abdominal pain (24, 104, 106).

2.4.2   Laboratory examinations for suspected acute appendicitis

Several diagnostic laboratory values that measure inflammatory response are independently associated with appendicitis. This association is as strong as the association of typical clinical findings such as guarding and rebound tenderness. However, inflammatory laboratory examinations, as well as clinical symptoms and findings, have the strongest associations with appendicitis when they are combined with each other (104, 107-109). There are no laboratory examinations, independent or combined with each other that have 100% positive or negative predictive values for appendicitis (28). Blood leukocyte count, the proportion of polymorphonuclear cells, and CRP value are routinely used in clinical practice for suspected appendicitis, but many others have also been studied.

Leukocyte count

Elevation of the leukocyte count is an independent predictive factor of acute appendicitis, and takes place in the early phase of the disease (107, 110-112). The positive likelihood ratio (LR$^+$) for leukocyte count of ≥15 (x10^{-9}/l) in acute RLQ pain is comparable to the LR$^+$ associated with strong guarding, and superior to the LR$^+$ associated with pain relocation, both of which are commonly regarded as strong signs of appendicitis (107).

Polymorphonuclear cells

The increased proportion of polymorphonuclear cells (neutrophils, eosinophils and basophils), and increased proportion of neutrophils are known to be associated with appendicitis (24, 107, 113). Recent research suggests that elevated neutrophil-to-lymphocyte ratio is a predictor of severity of appendicitis (114, 115).

C-reactive protein

C-reactive protein (CRP) is synthesized in the liver by hepatocytes. Its production is stimulated by cytokines in response to inflammation or tissue destruction. CRP level rises in the first 6 to 8 hours in an acute inflammation, and reaches the peak level in 48 hours of disease activation (116). Elevated CRP

level is associated with appendicitis (107). However, the relatively slow activation of CRP limits its value in the diagnosis of acute appendicitis in the early phase of the disease, and even normal values of CRP do not therefore rule out possible appendicitis (29, 110). On the other hand, there is strong evidence that high CRP values are associated with more advanced appendicitis (31, 87, 88, 108, 109, 117, 118). Several studies have recognized high CRP level as a marker for complicated appendicitis (31, 86, 88, 117-119).

Research on other laboratory values

Bilirubin

Studies suggest that hyperbilirubinemia is a predictive factor for perforated or gangrenous appendicitis (120, 121). Other studies conclude that serum bilirubin level could be useful in the diagnosis of acute uncomplicated appendicitis (122, 123).

Urine analysis

Patients with acute appendicitis frequently have abnormalities in urine analysis, which can be misleading in primary diagnostics. A study assessed urological findings in acute appendicitis and reported that 48% of patients with appendicitis had abnormal urine findings (leukocytosis, hematuria or proteinuria of more than 0.5 g/l) preoperatively and 12% on the 6th postoperative day (124).

New inflammatory markers

Research on novel inflammatory markers aim at replacing conventional inflammatory parameters with more accurate and specific methods for appendicitis. Several cytokines, chemokines, leukocyte adhesion molecules, and matrix metalloproteinases have been analyzed. Chemokine C-C motif ligand 2 and interleukin-6 have had the strongest associations with appendicitis in these studies (125, 126). However, these new markers failed to improve the diagnosis of acute appendicitis compared to conventional diagnostic methods. High levels of two markers of acute inflammation, serum Amyloid A and procalcitonin, were associated with acute appendicitis and had higher predictive power compared to CRP in one study (127). In another observational study, procalcitonin had limited value as a marker to predict antibiotic response in conservative treatment of appendicitis compared to standard laboratory tests (128). Calprotectin level has been suggested as a method for distinction of uncomplicated and perforated appendicitis (129). Fecal calprotectin has also been studied in screening patients with RLQ abdominal pain, but is not in routine clinical use (130).

Abdominal cavity culture

Intraperitoneal culturing during appendectomy for perforated appendicitis is routine. However, bacterial cultures from the peritoneal cavity are often negative in perforated appendicitis, and when positive, show colonic flora. Common bacteria include *E. Coli* and other coliform bacteria, *Bacteroides Fragilis*, *Pseudomonas,* and *Streptococci*. Studies suggest that although routinely used, bacterial cultures are not necessarily clinically beneficial (131, 132).

Peritoneal aspiration cytology

Peritoneal aspiration cytology for the diagnosis of acute appendicitis was studied before the era of CT. Over 50% of neutrophils in the sample was suggested as being diagnostic for acute appendicitis in patients with RLQ abdominal pain. In one study, the sensitivity for this diagnostic test was 91% and the specificity 95% (133). This diagnostic method did not gain popularity, perhaps because it was invasive.

2.4.3 Diagnostic imaging for suspected acute appendicitis

The technological development of imaging modalities has enabled imaging to play an increasing and even essential role in diagnostics of acute appendicitis. Today, imaging for suspected appendicitis is even considered mandatory in many institutions (6).

Computed tomography

Computed tomography for suspected acute appendicitis was introduced in 1990s. Studies that compare negative appendectomy rates before and after the implementation of CT report an irrefutable association between increased use of CT and decreased rate of negative appendectomies (83, 134-136). However, the large-scale benefits of CT have been questioned in some studies (135, 137-139).

Commonly, intravenous contrast-enhancement is used with no oral contrast medium. Common signs of appendicitis in CT images include thickening of the appendiceal wall with peri-appendiceal fat infiltration, appendiceal enhancement and peri-appendiceal free fluid (140, 141). Figure 3 shows inflamed appendix in CT.

The diagnostic performance of CT has been analyzed in numerous studies. The reported specificity and sensitivity of CT in the 2010s have been 93-98.0% and 94-98.5%, respectively (142-144).

Contrary to the excellent diagnostic performance of CT in suspected appendicitis, the distinction between complicated and uncomplicated appendicitis by CT has not been reliable. The CT findings of focal defect in the appendiceal wall, abscess, extraluminal gas, ileus, periappendiceal fluid, and appendicolith have had the highest specificity, but the sensitivity of these findings has been low, 28-70% (88, 90-92). However, the fecolith's causal association to advanced pathology is controversial (33, 66). To increase accuracy in diagnosis of complicated appendicitis Atema et al. have suggested a scoring system based on clinical and imaging features in combination. (92).

In some institutions CT is performed on all patients suspected of acute appendicitis, but concerns about radiation-induced risks and increased costs have led to diagnostic strategies with a more selective use of CT and also low-dose CT protocols.
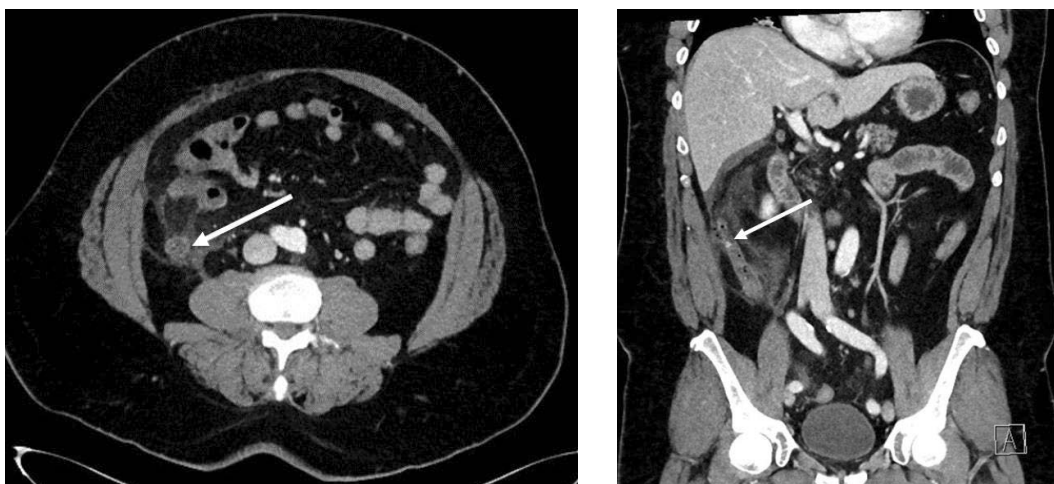
Figure 3 CT images of appendicitis. The arrows point at the inflamed appendix. After imaging this patient underwent laparoscopic surgery for perforated appendicitis with generalized peritonitis (Laparoscopic image of the same patient is shown in Figure 2.)

Ultrasound

Graded compression sonography (ultrasound, US) can be used in diagnostics of acute appendicitis. This technique was first described by Pulyaert in 1986 (145). Graded compression is used to displace gas-containing bowel loops to visualize the uncompressible inflamed appendix. Characteristic diagnostic features of appendicitis in graded compression US include local transducer tenderness, uncompressible thickened appendix and peri-appendiceal fat infiltration (140, 146). Figure 4 shows a typical US image of an inflamed appendix.

28

Lymphoid hyperplasia can be mistaken for appendicitis especially in children because it causes a thickening of the appendix. The presence of additional typical features of appendicitis makes diagnosis more reliable (147).

Comparisons between US and CT for diagnostic performance are equivocal. US has shown inferior diagnostic performance compared to CT in comparative studies, though equal diagnostic performance were reported in earlier studies (143, 148-150). However, US involves no ionizing radiation or contrast medium, and the cost of US examination is lower compared to CTs. The sensitivity and specificity of US have been 76-88% and 93-95%, respectively (143, 151).

The appendix is not always visible under US examination, and therefore negative US examination does not reliably rule out appendicitis. Nevertheless, the positive predictive value of US is good. This together with the aim of avoiding excess ionizing radiation has led to the use of US as a primary imaging modality in many institutions. However, in the case of inconclusive or negative US, imaging by CT is required. (18, 19, 150, 151).
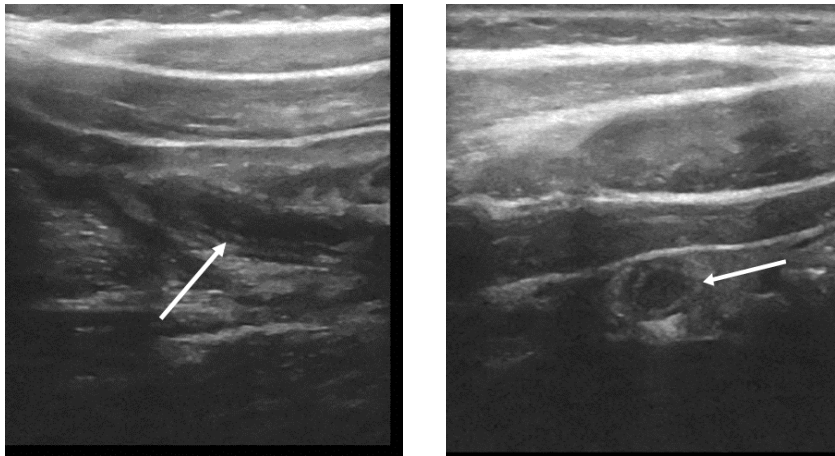
Figure 4 US images of appendicitis (the arrows point at the appendix)

Magnetic resonance imaging

Magnetic resonance imaging (MRI) features associated with acute appendicitis include appendiceal diameter >7 mm, peri-appendiceal fat infiltration and restricted diffusion of appendiceal wall (152). The diagnostic performance of MRI in suspected appendicitis is superior to US but inferior to CT. The MRI involves no ionizing radiation, and can be used even during pregnancy. MRI is often used to replace CT for pregnant patients after inconclusive or negative US. The reported sensitivity and specificity of MRI are 82-98% and 71-100%,

respectively, depending on the expertise of the MRI reader (153-157). However, MRI is not accurate at detecting appendiceal perforation (154).

Other imaging modalities

Before the era of CT, plain abdominal X-ray was frequently used in diagnostics of acute abdomen. The signs that were considered to support diagnosis of acute appendicitis by X-ray were appendicolith, RLQ soft tissue mass, extraluminal air, psoas margin obscuration, and levoconvex lumbar spine scoliosis (twist of the lower spine to the left). The diagnostic accuracy of plain abdominal X-ray is weak, and this imaging modality cannot be recommended in the diagnosis of acute appendicitis (158).

Leukoscintigraphy has been suggested as a possible diagnostic modality for acute appendicitis. The reported specificity and sensitivity are 82-89% and 90-98%, respectively. However, leukoscintigraphy is time-consuming and has not gained popularity in clinical practice (159, 160).

Risks of ionizing radiation

The precise risks of radiation from diagnostic imaging are unknown, but estimations based on research exist. The cancer risk associated with a CT examination is small but not non-existent. Abdominal organs are sensitive to ionizing radiation, and suspected appendicitis is most frequent in young patients with whom the considerations of radiation-induced risks are most important (10, 11). An analysis of radiation-induced cancer associated with suspected appendicitis by Rogers et al. pessimistically concluded that if all patients with suspected appendicitis undergo CT, one cancer death will occur as a cost for every 12 avoided negative appendectomies (161). Another estimation given by researchers was that approximately 2000 CT scans on young adults suspected of acute appendicitis would result in at least one cancer death (162).

Low-dose protocols for abdominal CT have been developed to reduce radiation dose of CT for suspected appendicitis. The common reported reference values for the effective radiation doses for standard abdominal CT range from 7 to 10 mSv, whereas the radiation doses of low-dose protocols can be as low as 2 mSv (144). Studies show equal diagnostic performance for low-dose CT compared to standard-dose CT in diagnostics of acute appendicitis, and diagnostic protocols including low-dose CT as a part of diagnostic work-up have been successfully adopted (18).

Many institutions have partly replaced CT by US in order to reduce risks of ionizing radiation. Consequently, US is used as the primary imaging method for

all patients in these settings, and CT is performed when US is negative or inconclusive (4, 6, 18). Equal or superior diagnostic performance has been reported in conditional versus immediate CT protocols using US as the primary imaging modality (19, 150). In addition to increased safety, conditional CT provides financial benefits (19, 151). A randomized study reported that selective CT imaging based on clinical assessment was cost-effective compared to routine CT (13).

2.4.4 Diagnostic scoring for suspected acute appendicitis

There is evidence that implementing a diagnostic algorithm or electronic clinical decision support into the diagnostics of appendicitis decreases the need for diagnostic imaging without impairing diagnostic accuracy (14-16). Several diagnostic scoring systems have been developed that aimed to facilitate and standardize diagnostic decision-making. The use of a diagnostic score enables patients with suspected appendicitis to be stratified into three groups according to the probability of appendicitis: low, intermediate, and high probability of appendicitis. When the first diagnostic score was published, there were no reliable imaging methods for suspected appendicitis. Today, with imaging widely available, scoring can be used to select patients in need of further examinations after initial physical examination and laboratory tests (163-165). The most accurate published scoring systems are developed for both adults and children. However, normal values of leucocyte count and neutrophil count vary in patients of different age, and this discrepancy can possibly impair the diagnostic accuracy of such scoring systems (27). In addition, common differential diagnoses are different in children of varying age and also when compared to adults.

Alvarado score

Alfredo Alvarado was the first to create a clinical diagnostic scoring system for improved diagnostics of acute appendicitis. For the construction of Alvarado Score he retrospectively reviewed patient records of 305 patients of 4-80 years of age whom had been hospitalized for acute abdominal pain that was suggestive of acute appendicitis. Patient data including various clinical symptoms and signs in addition to laboratory results were evaluated, comparing patients with acute appendicitis with patients with non-specific abdominal pain or acute mesenteric adenitis. The analysis of the symptoms and signs that were most strongly associated with acute appendicitis resulted in three symptoms (migration of pain, anorexia-acetone, and nausea-vomiting), three physical signs upon physical examination (tenderness in the RLQ, rebound pain, and elevation of temperature), and two laboratory findings

(leukocytosis and shift to the left). These 8 variables constituted the Alvarado score (Table 1).

The Alvarado score was constructed before the era of CT, when diagnosis of appendicitis relied on clinical symptoms and signs and laboratory examinations. The original publication by Alvarado suggested the following clinical cut-off values for the score: high probability of appendicitis, score 7 or more; intermediate probability of appendicitis, score 5 to 6; and low probability of appendicitis, score less than 5. Immediate surgery was suggested for patients with score 7 or more, and observation for patients with score 5 or 6 (24).

The Alvarado score has since its creation been validated in numerous patient populations, and has become the gold standard for the diagnostic scoring of suspected appendicitis. The Alvarado score is often used in research purposes in studies about diagnostic methods of appendicitis. Studies on the applicability of the Alvarado score as a screening method for imaging have also been published (25, 26, 163, 164, 166, 167).

Recent studies that evaluated the diagnostic performance of the Alvarado Score have reported a sensitivity range of 79-82% and specificity range of 75-76% in the high probability group (Alvarado score ≥7) (26, 168).

If the cut-off level of the high-probability group is limited to a score of 9 or more, then the specificity will improve, but with worsened sensitivity. At the same time this high score gives improved positive predictive value, and this entails fewer patients with appendicitis in the high-probability group, and more in the intermediate-probability group with equivocal diagnosis (164, 169).

Appendicitis Inflammatory Response Score

The Appendicitis Inflammatory Response Sore (AIR) was developed in Sweden and published in 2008 by Andersson and Andersson (25). The score is based on clinical symptoms and signs and common inflammatory laboratory variables (Table 1). The 316 patients analyzed for construction of AIR, and 229 patients analyzed for validation of the score were between 10-86 years of age, and were hospitalized in six hospitals in Sweden during 1992-1993 and 1997. The calculated sensitivity and specificity of the high-probability group in the original publication were 37% and 99%, respectively (25, 107).

The AIR score has been validated in external patient cohorts. Scott et al. reported that the AIR Score categorized 30 of 132 (23%) patients with appendicitis into the high-probability group, whereas Kollar et al. reported 22 of 67 (33%), and de Castro et al. reported 36 of 191 (19%). These same studies also reported sensitivities of 23%, 33%, 10% and specificities of 97%, 97%, 100% respectively for the high-probability group. (26, 170, 171). The study by

32

Scott et al. found that the negative predictive value of low-probability group was 94%, and that 63% of non-appendicitis patients were correctively classified into the low-probability group. The study by Kollar et al. also reported that 62% of non-appendicitis patients were correctly stratified into the low-probability group with a negative predictive value of 95%.

The AIR Score has had superior diagnostic performance in all published comparative studies compared to the Alvarado Score (25, 26, 171).

Other scoring systems previously described in the literature

There are several other diagnostic scores for suspected appendicitis. The Pediatric appendicitis score and the Lintula score were developed for pediatric patients, whereas the RIPASA score was developed and validated especially for Middle Eastern and Asian populations. On the other hand the Eskelinen Score was constructed for patients of all ages (166, 172-176). See Table 1 for comparison of the five previously published diagnostic scores.

Table 1. A comparison of the scoring variables and points of five previously published appendicitis scores

	Alvarado Score(24)	AIR Score*(25)	RIPASA Score(172)	Lintula Score(173)	Eskelinen Score(176)
Gender	-	-	Female=0.5 Male=1	Female=0 Male=2	-
Age	-	-	<39.9 years=1 >40 years=0.5	-	-
Intensity of pain	-	-	-	Severe=2 Mild or moderate=0	-
Location of pain: - In the RLQ - In any other location	-	1 -	0.5 -	4	22.82 11.41
Migration of pain	1	-	0.5	4	-
Anorexia	Anorexia-acetone 1	-	1	-	-
Nausea and vomiting	Nausea-vomiting 1	Vomiting 1	Nausea-vomiting 1	Vomiting 2	-
Duration of symptoms	-	-	<48 h=1 >48h =0.5	-	<48 h=4.26 ≥48 h=2.13
Location of tenderness: - in the RLQ - In any other location	2 -	- -	1 -	- -	7.02 3.51
Signs of peritoneal inflammation	Rebound tenderness 1	Rebound tenderness or guarding: Light=1 Medium=2 Strong=3	Rebound tenderness 1 Guarding 2	Rebound tenderness 7	Rebound tenderness Yes=8.5, No=4.25Y Rigidity Yes=13.24, No=6.62
Rovsing sign	-	-	2	-	-
Body temperature	≥37.3=1	≥38.5=1	>37<39°C=1	≥37.5°C=3 <37.5°C=0	-
Bowel sounds	-	-	-	Absent, tinkling, high-pitched=4	-
Leukocytosis	>10000=2	10.0-14.9 x 10^9/l=1 ≥15.0x10^9 /l=2	Raised 1	-	≥10000 g/l=11.76 <10000 g/l=5.88
Polymorphonuclear leukocytes	Neutrophils >75%=1	70-84%=1 ≥85%=2	-	-	-
CRP (g/l)	-	10-49=1 ≥50=2	-	-	-
Negative urine analysis	-	-	1	-	-
Foreign National Registration Identity Card (NRIC, Singapore)	-	-	1	-	-
Maximum points	10	12	17.5	32	67.6
Cut-off points for: - Probable appendicitis - Possible appendicitis - Improbable appendicitis	≥8 5-7 ≤4	≥9 5-8 ≤4	≥7.5 5-7 ≤4.5	≥21 16-20 ≤15	>57 50-5 <50

*AIR Score = Appendicitis Inflammatory Response Score

Differential diagnosis

Many different conditions mimic acute appendicitis. The diagnosis is most challenging in fertile-aged women with possible acute symptoms of gynecological origin. Other diagnoses that are often mistaken for appendicitis include mesenteric adenitis, acute diverticulitis and gastroenteritis (1, 2, 24).

2.5 TREATMENT OF ACUTE APPENDICITIS

2.5.1 Surgical treatment

For more than 100 years the gold standard in treatment of acute uncomplicated appendicitis has been prompt appendectomy to prevent perforation of the appendix. McBurney presented a transverse incision (McBurney incision, gridiron incision) in 1894 for appendectomy that later became the standard approach in the surgical treatment of appendicitis (50). In the early 1980s, Semm described appendectomy that was carried out using an endoscopic method that had been previously used by gynecologists during surgical pelviscopy (52). Laparoscopic appendectomy slowly became more common, and is today the standard operation in surgery for appendicitis (53).

2.5.2 Uncomplicated appendicitis

Laparoscopic versus open appendectomy

Laparoscopic appendectomy was introduced in 1980s and has now widely become the standard operation for acute appendicitis. Numerous studies that compared laparoscopic to the open approach have been conducted. The laparoscopic approach has been shown by these studies to have advantages for patients with non-complicated and complicated appendicitis, in the elderly, patients with comorbidities, and in obese patients (53, 177-182). There is less morbidity and shorter length of stay after laparoscopic operations for all patients (53, 182, 183). There were more intra-abdominal infections after laparoscopic appendectomy reported by some studies (184, 185) but this disadvantage is not reported by other studies and it seems to be related to the early years of laparoscopy use in appendectomy (53, 186). A Swedish national cohort study from 1998-2008 found that laparoscopy was associated with fewer wound complications but a higher rate of abdominal abscesses and intestinal injury (187). A Swiss analysis of 7446 patients that underwent laparoscopic appendectomy for acute appendicitis during 1995-2008 found there was a clear decrease in postoperative complications, reoperations, and

the length of hospital stay during the 12-year study period (186). A population-based analysis from Finland reported that open appendectomy was associated with six-fold mortality compared to laparoscopic appendectomy (188).

Laparoscopy with its associated faster postoperative recovery has also enabled outpatient care, with potential health care savings, for patients with uncomplicated appendicitis. Several studies report that outpatient laparoscopic appendectomy is a safe option (189-191). Laparoscopic appendectomy has a relatively short learning curve and is therefore also a feasible and safe way for surgical residents to start practicing laparoscopy (192). See Figure 5 for operation room image of laparoscopic appendectomy.

Figure 5 Operation room image of laparoscopic appendectomy

New minimally-invasive techniques

Studies that compared open with laparoscopic appendectomy have been followed by other studies that compared conventional laparoscopic appendectomy with single-incision laparoscopic appendectomy. The single-incision technique has not brought a clear advantage or disadvantage compared to conventional laparoscopy, and also operating times have been longer compared to conventional laparoscopic surgery. Moreover, one comparative study showed that the conversion risk was greater in complicated appendicitis for the single-port technique (193-195). The single-port approach is new and there is a paucity of published long-term results. However, the associated larger opening through the umbilicus seems to result in an increased rate of hernias for the single-port technique (196). Natural Orifice Trans-luminal Endoscopic Surgery (NOTES) appendectomies have been performed safely (197), but this

technique remains experimental and was not being performed in Finland at the time of writing this thesis.

Non-operative management of acute uncomplicated appendicitis

The practice of immediate surgery has been challenged lately by several studies that compared conservative treatment with antibiotics to appendectomy. These studies report that appendicitis has recurred within one year for between 26-32% of patients after conservative treatment (198, 199). A recent meta-analysis found that the evidence concerning complications and duration of sick leave between conservative or surgical treatment of appendicitis in randomized studies was of low or very low quality, and concluded that the choice of treatment for clearly uncomplicated appendicitis is "value- and preference dependent" (200). Some authors have expressed their concern over incidental appendiceal neoplasms that were undiagnosed in the case of non-operative treatment. Neoplasms are incidentally found in approximately 1% of appendectomy specimens in uncomplicated appendicitis. These neoplasms are usually unidentifiable by preoperative CT (201).

2.5.3   Complicated appendicitis

Perforation and peritonitis

The treatment for perforated appendicitis with peritonitis is immediate surgery combined with antibiotic therapy.

Studies that compared laparoscopic and open surgery in perforated appendicitis showed that laparoscopy had fewer surgical site infections, fewer overall postoperative complications, shorter length of hospital stay and similar rates of deep surgical site infections than open surgery (53, 202).

Traditionally, peritoneal irrigation has been used in the case of peritonitis in order to avoid postoperative intra-abdominal abscess formation. However, studies that compared peritoneal irrigation to suction alone found no difference in postoperative abscess formation (203, 204). Research suggests that placing a drain in the abdominal cavity is not beneficial and might even be harmful in perforated appendicitis (205).

Appendiceal abscess

The treatment of appendiceal abscess is controversial. Conservative treatment with or without interval appendectomy has been recommended by some studies due to lower complication and morbidity rates compared to immediate open surgery (206-209).

Laparoscopic appendectomy has become standard procedure in non-complicated appendicitis and for perforated appendicitis without abscess, but reported experience of immediate laparoscopic appendectomy for appendiceal abscess is scarce. One randomized controlled trial compared conservative treatment and immediate laparoscopic surgery and concluded that laparoscopic surgery is safe in experienced hands and associated with fewer readmissions and additional interventions (210).

2.5.4   The effect of delay of surgical treatment

Since appendicitis was first described in the surgical literature the underlying principle for the treatment of appendicitis has been prompt appendectomy in order to avoid perforation (47, 49). However, research has shown that not all cases of appendicitis proceed to perforation and some cases can even resolve spontaneously (78, 79, 95). This type of appendicitis with milder symptoms and no other treatment required than "medical treatment, rest, and intelligent nursing" was already described in the original publication by McBurney that recommended early laparotomy (49).

However, there is consensus that the interval of time between the onset of symptoms to the treatment is correlated with the severity of appendicitis, and that extended time to treatment leads to perioperative morbidity (31-35). Several studies found that the increasing in-hospital delay of treatment (time from hospital admission to surgery) has been associated with increased risk of perforation or other adverse events (33, 37-42). Some studies have controversially suggested that the in-hospital delay in treatment would not play a role in the risk of perforation or complications (43, 45, 211, 212). However, no explanation was given in these studies as to how the length of in-hospital time affects the risk of perforation in a different manner compared to that of the pre-hospital time (the interval of time from the onset of symptoms to hospitalization). Additionally, no elimination of pre-hospital perforations from the patient cohort was attempted in these studies to adjust for a comparison. Patients with complicated appendicitis have generally more symptoms and therefore shorter waiting times to surgery, which was not accounted for in these studies, and the omission of this factor can also create possible bias (36).

2.6 OUTCOMES OF ACUTE APPENDICITIS AND APPENDECTOMY

2.6.1 Mortality

Today, death following appendectomy is rare. The reported mortalities vary thus: 0.07% in one study from Germany (213), 0.11% in a study from USA (214), 0.21% in a study from Finland (188), 0.23-0.24% in studies from Sweden (215, 216), and 0.23% in a study from Denmark (217). The risk of mortality after appendectomy is related to the patients' age, comorbidities, and disease severity (188, 215, 216). There seems to be increased mortality after negative appendectomy (8, 188, 215, 218). The most frequent etiologies behind deaths following appendectomies are cardiovascular diseases (46%), appendicitis (18%), and non-appendicitis infections (14%) (216). A population-based analysis from Finland reported that open appendectomy had a six-fold mortality to that of laparoscopic appendectomy. The same study showed that overall mortality after appendectomy decreased in Finland, and this was possibly due to more accurate diagnostics and an increased proportion of laparoscopic appendectomies (188).

2.6.2 Morbidity

The risk of complications after appendectomy is related to comorbidities and the severity of appendicitis. Aiming at better prediction and prevention of postoperative complications, researchers have developed disease severity grading systems based on intraoperative view of the appendix and the peritoneal cavity (84, 85). However, one study found that there were no differences in the rate or severity of complications after laparoscopic appendectomy for either inflamed or non-inflamed appendix (9).

Laparoscopic appendectomy has been shown to cause less morbidity compared to open surgery in several studies (53, 186, 217). The overall outcomes of appendicitis also improved in Denmark during the same time period that laparoscopic appendectomy became more popular (217).

A Finnish register study used data obtained from the Patient Insurance Association, and found that complications following appendectomy that lead to a patient insurance claim were rare events (0.2%). The rates of compensated claims after open and laparoscopic surgery were equal, but the compensated complications related to laparoscopy were more severe. Only 57% of patients that received compensation had an inflamed appendix (219).

Morbidity in uncomplicated acute appendicitis

A study of 574 244 adult patients that underwent appendectomy in the USA during 2006-2008 showed that postoperative complications after either laparoscopic or open appendectomy for uncomplicated appendicitis were infrequent. The same study found that the overall complication rate after laparoscopic appendectomy for uncomplicated appendicitis was 4.13%. The specific complication rates for laparoscopic appendectomy were as follows: 0.26% for postoperative abdominal abscess 0.15% for wound infection and 1.92% for ileus. The median hospital stay was one day. After open appendectomy for uncomplicated appendicitis, the overall complication rate was 6.39%. The specific complication rates for open appendectomy were as follows: 0.76% for abdominal abscess 0.42% for wound infection and 3.11% for ileus. The median length of stay was 2 days. All complications except urinary tract infection and pulmonary embolism were significantly more frequent after open surgery. The rates of urinary tract infection and pulmonary embolism were equal after laparoscopy and open surgery (53). A national cohort study conducted in Sweden found that the rate of wound infections was equal (0.1%) for both operational modalities, but deep infections were more common for laparoscopic appendectomy (0.5%) compared to open appendectomy (0.3%). After adjustment for age, sex, co-morbidity and time interval, intestinal damage was found to be more common for operations with laparoscopic intention. Wound ruptures were extremely rare (<0.01%) after laparoscopic operations whereas after open surgery they were sometimes (0.1%) seen. In the beginning of this Swedish study in 1992, 3.8% of appendectomies were performed laparoscopically, and 16 years later in 2008, the last year of the study, 32.9% (187).

Morbidity in complicated acute appendicitis

Postoperative complications are more frequent in perforated appendicitis. A register study by Masoomi et al. (53) reported that the overall complication rate after laparoscopic appendectomy for perforated appendicitis was 18.75% compared with 26.76% for open surgery. The rates of complications after laparoscopy were as follows: 1.65% for abdominal abscess, 0.58% for wound infection, and 13.34% for ileus. The median length of hospital stay was 3 days. The rates of complications after open surgery were as follows: 3.57% for abdominal abscess, 2.84% for wound infection, and 16.64% for ileus. The median length of hospital stay was 5 days. The rate of all complications except myocardial infarction and pulmonary embolism were more frequent after open surgery. The frequency of these two complications was equal for both modalities.

2.6.3 Long-term outcomes

The risk for small bowel obstruction after appendicitis was reported to be 2.8% in a Canadian study with a mean follow-up period of 4.1 years. The risk was higher after perforated appendicitis and midline incisions. There was no difference for the risk of bowel obstruction between open surgery and laparoscopy found in that study (220). A Swedish study found that the cumulative risk of small bowel obstruction was 1.4% for laparoscopic and 1.5% for open surgery at 15 years follow-up (187).

The risk of incisional hernia after the McBurney incision is relatively low, 0.7%. Risk factors for incisional hernia include diabetes, complicated appendicitis, female gender, and postoperative seroma (221).

A rare late complication of appendectomy, stump appendicitis, is described in the surgical literature as case reports, and as far as the author is aware no epidemiological data exist. Stump appendicitis is defined as inflammation of the residual appendix after appendectomy. A study that was published in 2012 reviewed 61 cases of stump appendicitis and reported that patients presented a mean 108 ± 20 months after the initial appendectomy. The type of initial appendectomy was reported In 58 cases. In 38 (65.5%) cases surgery was performed by open technique, and in 20 (34.5%) cases laparoscopically (222).

Patients who undergo appendectomy for acute appendicitis in childhood seem to have a lower risk for ulcerative colitis as adults. The reason for this is unknown. Appendectomy without appendicitis does not seem to have the same effect (223, 224).

The effect of appendicitis, especially perforated appendicitis, and appendectomy on subsequent infertility in female patients has been studied, but no firm evidence exists. Traditionally, perforated appendicitis has been considered to be a possible etiology for infertility. A cohort study controversially reported an association between appendectomy and increased pregnancy rate (225). A Canadian epidemiologic study found no evidence of perforated appendicitis being a risk factor for tubal infertility (226). A recent meta-analysis concluded that appendectomy is associated with ectopic pregnancy but not with infertility (227).

3. AIMS OF THE STUDY

The aims of the studies presented in this thesis were:

1) To develop and validate a new, accurate diagnostic score for adult (≥16 years) patients with suspected acute appendicitis, and implement it into routine clinical use as a part of a new diagnostic algorithm (Original publications I and II).

2) To investigate whether pre-test probability of appendicitis determined by the new diagnostic score influences the diagnostic performance of imaging studies. (Original publication III)

3) To investigate whether in-hospital delay of diagnosis and treatment plays a role in the risk of complicated appendicitis (Original publication IV).

4. METHODS

4.1 STUDY HOSPITALS

The studies presented in this thesis were conducted in two university hospitals in Finland. The main study hospital, Meilahti Hospital, is a part of Helsinki University Central Hospital that is the biggest university hospital in Finland. Meilahti Hospital is a care facility that provides both secondary and tertiary level of emergency general surgical care for adult (16 years or more) patients. Approximately 10 000 patients visit Meilahti emergency department because of abdominal emergencies annually, and approximately 2100 operations are performed for abdominal emergencies every year, acute appendicitis being the most common indication. The second study hospital, Kuopio University Hospital is the smallest University Hospital in Finland with approximately 2200 patient visits for abdominal emergencies per year.

4.2 DATA COLLECTION

The first prospective data collection took place in Meilahti Hospital's emergency department during 2011. All patients admitted because of RLQ abdominal pain or suspected acute appendicitis were enrolled in the study. The surgeons on duty collected the necessary data and recorded them on paper data-collection forms. The surgeons were unaware of the aims of the study, and there were no diagnostic guidelines given for suspected acute appendicitis during the first data collection.

The requested data in the case report form included symptoms and clinical findings along with inflammatory laboratory results (C-reactive protein count, leukocyte count, proportion of neutrophils). The surgeons were also requested in the study form to evaluate the probability of appendicitis on a clinical basis by using a three-step scale: probable, possible or improbable. The time points of the onset of symptoms and the first physical examination were recorded on the case report forms. The remaining relevant information was later retrieved from the patient databases.

4.3 PATIENTS

Information of patient data analyzed in each study is shown in Table 2. The first research data were obtained from 829 patients of whom 103 lacked neutrophil count data, and one lacked CRP data. Neutrophil counts were not determined in

suspected appendicitis at the study hospital before the first data collection period, and therefore some of the values that correspond with this time period are missing.

The patient data from the first data collection were analyzed in studies I, III, and IV as study patients, and in study II as reference patients. All patient data from the first data collection were used in study I. In study II the patients with lacking neutrophil count or CRP data were excluded, which left 726 reference patients for the study II. In study III, the data of patients who underwent imaging and had complete information for scoring (288 patients) were analyzed together with all patients from the second data collection who had undergone imaging. The data of 389 patients with appendicitis were analyzed in study IV (Table 2).

Total of 820 patients were enrolled in Meilahti Hospital, and 88 patients in Kuopio University Hospital during the second data collection period from September 2014 to May 2015. Inclusion criteria were adult (≥16 years) patients with RLQ abdominal pain or suspected acute appendicitis.

Shortly before the beginning of the second data collection, the AAS with the associated diagnostic algorithm was introduced into everyday clinical practice (Figure 6). Surgeons on duty performed the second prospective data collection by using a web-based case report form that collected the data necessary for scoring. The form calculated the score, and then according to the scoring result gave appropriate recommendations to the surgeons for further action. The remaining data were retrieved from local patient databases in Helsinki and Kuopio.

Scoring was mandatory during the second data collection period, but adherence to investigations and treatment protocols was not monitored.

The data from the second data collection in Meilahti and Kuopio (908 patients) were used in study II. In study III, data of patients from Meilahti hospital who had undergone imaging (534 patients) were used.

Table 2. Patient data used in each original study

	Meilahti 2011	Meilahti 2014-1015	Kuopio 2014-2015
Original study I: Construction of the AAS	Development of the AAS: **829** patients Cut-off limits of the score and comparison with two other diagnostic scores and clinical diagnostics: **725** patients	-	-
Original study II: Validation of the AAS	Control material for comparison of diagnostic performance, patients with full data available for scoring: **725** patients	Validation of AAS: **820** patients	Validation of AAS: **88** patients
Original study III: Diagnostic performance of imaging studies	All patients with full data for scoring that underwent imaging: **288** patients	All patients that underwent imaging: **534** patients	-
Original study IV: Pre- and in-hospital delay's effect on the risk of perforation	All patients operated on for histologically confirmed appendicitis: **389** patients	-	-

AAS = Adult Appendicitis Score
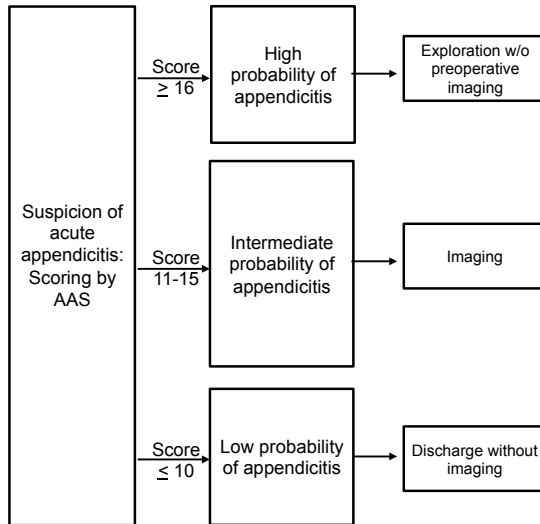
Figure 6 The new diagnostic algorithm. US was recommended as the primary imaging modality for patients who were 35 years or younger, and for pregnant patients. In other patients, CT was recommended as the primary imaging modality. Negative or inconclusive US was followed by CT in non-pregnant patients. MRI was recommended instead of CT for the pregnant patients (AAS = Adult Appendicitis Score)

4.4 IMAGING STUDIES

Diagnostic imaging (CT, US, and MRI) was available at all times at each surgeon's discretion during both study periods. The guidelines of imaging were adopted together with the scoring system before the second data collection.

Radiology residents with a minimum experience of 2 years or attending radiologists with a possibility to consult a more experienced colleague performed US during both data collection periods. A general survey of the abdomen and pelvis was performed using the graded compression technique. The criteria for acute appendicitis in US imaging were the following: non-compressible appendix larger than 6 mm in diameter with or without appendicolith together with local transducer tenderness, and peri-appendiceal fat infiltration.

CT scans were performed by using a 128 multi-detector row scanner. Patients underwent an abdominopelvic CT protocol with intravenous contrast-enhancement. Patients with known renal insufficiency or hypersensitivity to contrast media underwent unenhanced CT. CT images were analyzed by a staff radiologist during working hours and by radiology residents with a minimum

experience of 2 years and the possibility to consult a more experienced colleague after hours. The original reports that contributed to the decision-making by the surgeons were used in the study analysis. Criteria for acute appendicitis in CT imaging were as follows: increased appendiceal diameter (greater than 6 mm), with or without appendicolith, together with appendiceal wall thickening, increased wall enhancement, and peri-appendiceal fat infiltration.

4.5 SURGICAL TREATMENT AND FINAL DIAGNOSIS OF APPENDICITIS

The surgical method for appendectomy (laparoscopic or open) was at each surgeon's discretion. The appendix was removed every time surgery was performed for suspected appendicitis, even when a macroscopically normal appendix was seen. The diagnosis of appendicitis was based on histopathological analysis that showed transmural infiltration by neutrophils with the exception of three patients during the first, and three patients during the second data collection periods. These six patients had appendiceal abscesses, the diagnosis of which was based on CT findings, and they were initially treated non-operatively. Thus histopathological analysis was not possible in these patients. Gangrenous appendicitis was defined as necrosis (in the histopathological analysis) or perforation of the appendiceal wall.

4.6 STUDY APPROVALS

The Institutional Review Board and the Ethics Committee of the Department of Surgery, Helsinki University Central Hospital, and Institutional review board of Kuopio University Hospital approved the study protocols. No written informed consent for participation in the studies was requested because the diagnostics and treatment of the patients were unaffected by the study protocol.

4.7 STATISTICAL ANALYSIS

Statistical analysis was performed using SPSS® versions 20 and 22 (IBM, Armonk, New York, USA).

4.7.1 Construction of the diagnostic score

The construction of the score was accomplished by a backward stepwise logistic regression analysis with multiple imputations of missing values (neutrophils, CRP). A backward logistic regression analysis included all clinical findings and symptoms (tenderness in the RLQ, guarding in the RLQ, elevated body

temperature, pain in the RLQ, migration of pain, vomiting, and anorexia), including the duration of symptoms and laboratory values. Receiver operating characteristics (ROC) analysis was used to categorize continuous laboratory values and to determine the cut-off point or abnormal body temperature. Cut-off values for CRP were determined separately for patients with symptoms either less than or more than 24 hours, because the distributions of the CRP values differed significantly in these subsets of patients.

The duration of symptoms was used as a variable and also as an interaction term with categorized CRP values. Being a fertile aged woman (16–49 years old) was included as a variable and an interaction term for all signs and symptoms. Final step of backward stepwise logistic regression with multiple imputed pooled data resulted in statistically significant factors for construction of the score. Points for the score were obtained from regression coefficients by multiplying by 2 and rounding to the nearest integer.

ROC analysis was used to determine cut-off values (high, intermediate, and low probability for appendicitis) of the constructed score. A cut-off point with high specificity was chosen for high probability, and a cut-off point with high sensitivity was chosen for low probability. The values between the two points defined the intermediate probability for appendicitis.

Regression coefficients and the resulting points of the score are shown in Table 3.

Table 3. Construction of Adult Appendicitis Score

Symptoms and findings		Regression coefficient	p-value	Score
Pain in RLQ		1.249	<0.001	2
Pain relocation		1.068	<0.001	2
RLQ tenderness		1.667	0.045	3
RLQ tenderness women, age 16-49		-1.312	<0.001	1[†]
Guarding	none	reference		
	mild	1.115	0.001	2
	Moderate or severe	1.768	0.001	4
Laboratory tests				
Blood leukocyte count (x10^9)	<7.2	reference		
	>=7.2 and <10.9	0.312	0.348	1
	>=10.9 and <14.0	0.822	0.021	2
	>=14.0	1.365	<0.001	3
Proportion of neutrophils (%)	<62	reference		
	>=62 and < 75	1.143	0.001	2
	>=75 and < 83	1.368	<0.001	3
	>=83	2.062	<0.001	4
CRP (mg/l), symptoms < 24h	<4	reference		
	>=4 and <11	1.052	0.009	2
	>=11and <25	1.626	<0.001	3
	>=25 and <83	2.533	<0.001	5
	>=83	0.385	0.456	1
CRP (mg/l), symptoms > 24h	<12	reference		
	>=12 and <53	1.228	<0.001	2
	>=53 and <152	1.202	<0.001	2
	>=152	0.748	0.074	1

RLQ - the right lower abdominal quadrant

[†]Score for RLQ tenderness for women, aged 16-49 is based on the sum of the regression coefficients of RLQ tenderness (1.667) and RLQ tenderness for women aged 16-49 (-1.312).

4.7.2 Diagnostic performance of the new score

In study I the specificity, sensitivity, LR^+, LR^-, and diagnostic odds ratio (DOR)) for the AAS were calculated. Two previously published scores (Alvarado Score and AIR) were calculated and compared with the AAS by ROC analysis. Cut-off values chosen by the original authors were used in the comparison. The diagnostic performance of the new score was then also compared with initial clinical diagnoses by surgeons using the McNemar' s test.

Patients with missing data were excluded from the ROC analysis comparing the scores and from the analysis of diagnostic performance.

In study II the diagnostic performance of the AAS (specificity, sensitivity, LR^+, LR^-, DOR) was calculated in the second patient dataset. The Chi-square test was used to compare the negative appendectomy rate, perforation rate, and utilization of imaging with the reference population.

4.7.3 Diagnostic performance of imaging studies

The AAS was calculated for all patients in the study that investigated diagnostic performance of imaging studies (study III). The pre- and post-test probabilities of acute appendicitis in addition to the specificity, sensitivity, LR^+, LR^-, and DOR for US and CT were calculated. The diagnostic performance of MRI was excluded from further analysis because of the small number of patients imaged by MRI.

The results were compared between patient groups that were stratified by AAS. The Chi-square test was used to analyze diagnostic performance of imaging studies between these groups.

4.7.4 Pre-hospital and in-hospital delay and their effect on the risk of
perforation

A ROC analysis including blood leukocyte count, the proportion of neutrophils, CRP, Alvarado score, and AIR score was used for identification of the best marker for pre-hospital perforations and its cut-off value.

The Mann-Whitney U test and the Jonkheere-Terpstra test were used to compare differences in delays between patient groups. A linear-by-linear association Chi-square test or Fisher's exact test was used when appropriate to analyze the risk of in-hospital delay or increasing CRP levels for complicated appendicitis.

Pearson correlation coefficients were calculated to analyze correlations between admission CRP levels and pre-hospital duration of symptoms.

Spearman's correlation was used for the analysis of the correlations between hospital stay and in-hospital and pre-hospital delay. Confidence intervals at 95% (95% CI) for proportions were calculated by using normal approximation intervals.

5. RESULTS

5.1 PATIENTS

A total of 1737 patients with suspected acute appendicitis were enrolled into the study. Data of 103 patients were excluded from the calculation of the new Adult Appendicitis Score (AAS) because of missing neutrophil values, and also for one other patient because of missing CRP values. The Median age was 32 years (range 16-97), and 1039 (60%) of patients were women. (Table 4)

Table 4. Patients

Data collection	All patients	Women (%)	Men	Age - median, interquartile range (range)	Complete data for scoring
Meilahti 2011	829	483 (58%)	346	32, 25–47 (16–97)	725
Meilahti 2014-2015	820	507 (62%)	313	31, 24-45 (16-86)	820
Kuopio 2014-2015	88	49 (56%)	39	36, 25-54 (16-83)	88
All	1737	1039 (60%)	698	32, 25-46 (16-97)	1633

Appendicitis was the final diagnosis for 825 (47%) patients. Complicated appendicitis was found in 184 (22%) of these patients, 62 of these had appendiceal abscess, and the remaining 122 a perforation with peritonitis. Non-specific abdominal pain (NSAP) was the discharge diagnosis for 527 (30%) patients (Table 5).

Table 5. Final diagnoses

Data collection	All patients	Uncomplicated appendicitis (%)	Complicated appendicitis (%)	Other specific diagnosis (%)	Non-specific abdominal pain (%)
Meilahti 2011	829	298 (36%)	94 (11%)	178 (21%)	259 (31%)
Meilahti 2014-2015	820	301 (37%)	80 (10%)	190 (23%)	249 (30%)
Kuopio 2014-2015	88	42 (48%)	10 (11%)	17 (19%)	19 (22%)
All	1737	641 (37%)	184 (11%)	385 (22%)	527 (30%)

Surgery for suspected appendicitis was performed on 946 patients, of whom 819 had appendicitis, and 18 had another disease that was diagnosed and treated during the same exploration, for example appendiceal or caecal tumor, perforated duodenal ulcer, and acute cholecystitis. Two cases of granulomatous inflammation of the appendix, and 24 neoplasias of the appendix or colon were also found in the histopathological analyses in the study. Thirteen neoplasias were found with simultaneous acute appendicitis and 11 without appendicitis. All patients with neoplasias were operated on for suspected appendicitis with the exception of one patient with mucinous neoplasia and ileocaecal invagination that were preoperatively detected by CT. This patient underwent open emergency right hemicolectomy. Neoplasias of the appendix or the colon were found in 2.4% of all operations for suspected appendicitis.

A total of 714 (75%) of all appendectomies were laparoscopic, and 232 open (including conversions from laparoscopy). Six patients were treated conservatively for appendiceal abscesses (Table 6).

There were 21 patients (3.3%) with minor (Clavien-Dindo I-II) and 3 (0.5%) with major (Clavien-Dindo III-IV) complications in 641 appendectomies for uncomplicated appendicitis (228). There were 22 (12.4%) patients with minor and 9 patients (5.1%) with major complications in 178 appendectomies for complicated appendicitis. There was no mortality (Table 7).

Table 6. Surgery for suspected appendicitis

Data collection	Surgery for suspected appendicitis	Laparoscopic appendectomy	Open surgery (including conversions from laparoscopy)	Appendicitis	Negative appendectomy*	Diagnostic exploration for suspected appendicitis**	Therapeutic operation, no appendicitis***
Meilahti 2011	477	302 (63%)	175 (37%)	389	88 (18%)	80 (17%)	8
Meilahti 2014-2015	415	380 (92%)	35 (8%)	381	34 (8%)	25 (6%)	9
Kuopio 2014-2015	54	32 (59%)	22 (41%)	47	7 (13%)	6 (11%)	1
All	946	714 (75%)	232 (25%)	817	129 (14%)	111 (12%)	18

*Surgery performed for suspected appendicitis, no appendicitis found (includes therapeutic operations for other diseases)
** Diagnostic exploration performed for suspected acute appendicitis, no surgical treatment required
*** Surgery performed for suspected appendicitis, other disease than appendicitis found and treated (e.g. appendiceal tumor, perforated duodenal ulcer, acute cholecystitis, pelvic inflammatory disease)

Table 7. Complications in patients who underwent surgery for suspected appendicitis. Classification by Clavien-Dindo Classification of surgical complications (228). There was no mortality.

	Meilahti 2011	Meilahti 2014-2015	Kuopio	All patients
Uncomplicated appendicitis				
Operations	298	301	42	641
Complications:				
Clavien-Dindo I-II*	9 (3.0%)	9 (3.0%)	3 (7.1%)	21 (3.3%)
Clavien-DIndo III-IV**	2 (0.7%)	1 (0.3%)	0	3 (0.5%)
All	11 (3.7%)	10 (3.3%)	3 (7.1%)	24 (3.7%)
Complicated appendicitis				
Operations	91	80	7	178
Complications:				
Clavien-Dindo I-II*	12 (13.2%)	7 (8.8%)	3 (42.9%)	22 (12.4%)
Clavien-Dindo III-IV**	3 (3.3%)	6 (7.5%)	0	9 (5.1%)
All	15 (16.5%)	13 (16.3%)	3 (42.9%)	31 (17.4%)
All				
Operations for appendicitis	389	381	49	819
Complications:				
Clavien-Dindo I-II*	21 (5.4%)	16 (4.2%)	6 (12.2%)	43 (5.3%)
Clavien-Dindo III-IV**	5 (1.3%)	7 (1.8%)	0	12 (1.5%)
All	26 (6.7%)	23 (6.0%)	6 (12.2%)	55 (6.7%)

*Requiring pharmacological treatment;
** Requiring surgical, endoscopic or radiological intervention

5.2 THE NEW SCORE

The AAS variables and the respective score points are presented in table 3 of the methods-section.

Full data for scoring was available for 725 patients in the first patient dataset. In the ROC-analysis, cut-off point for the high probability for appendicitis group

was ≥16 points, for the intermediate probability of appendicitis 11-15 points, and for the low probability of appendicitis ≤10 points.

More than half, 199 of 343 (58%) patients with appendicitis in the original study I were correctly stratified into the high-probability group together with 28 non-appendicitis patients. The specificity of the high-probability score, i.e. the probability that a patient without appendicitis had score under 16 was 92.7%.

A total of 277 patients were stratified into the intermediate-probability group (AAS 11-15). Of these patients 130 (47%) had appendicitis. The sensitivity of the AAS ≥11 i.e. the probability that a patient with appendicitis had score of 11 or more was 95.9%.

Of 382 non-appendicitis patients, 207 (54%) were in the low-probability group (AAS≤10). Only 14 patients of this group had appendicitis (Tables 8 and 9).

The specificity of the new score was significantly better compared to the clinical evaluation by surgeons that was based on the physical examination and laboratory results (Table 9).

Comparison of the AAS with the two previously published scores (Alvarado and AIR) by ROC- analysis revealed that AAS (AUC 0.882 [95% CI 0.858-0.906]) had better ability to recognize (high probability group) and exclude (low probability group) appendicitis compared to the Alvarado Score (AUC 0.790 [0.758-0.823]) and AIR score (AUC 0.810 [0.779-0.840]) (Table 9).

Table 8. Stratification of patients with and without appendicitis by AAS in studies I and II

	Low probability AAS ≤10	Intermediate probability AAS 11-15	High probability AAS ≥16	All patients
Meilahti 2011				
Appendicitis	14	130	199	343
No appendicitis	207	147	28	382
All patients	221	277	227	725
Probability of appendicitis	6.3%	46.9%	87.7%	47.3%
Meilahti and Kuopio 2014-15				
Appendicitis	23	196	213	432
No Appendicitis	286	157	33	476
All patients	309	353	246	908
Probability of appendicitis	7.4%	55.5%	86.6%	47.6%

Table 9. Comparison of the Adult Appendicitis Score (AAS), appendicitis inflammatory response (AIR) score, Alvarado-score, and clinical diagnosis in the diagnosis of acute appendicitis.

	Sensitivity (%)	Specificity (%)	LR+	LR-	DOR
AAS					
>=11	95.9	54.2	2.1	0.076	27.7
>=16	58.0	92.7	7.9	0.45	17.5
>=18	27.7	97.6	11.5	0.74	15.6
AIR-score					
>=5	83.1	63.1	2.3	0.27	8.4
>=9	14.6	97.1	5.0	0.88	5.7
Alvarado-score					
>=4	98.0	27.7	1.4	0.072	18.8
>=7	68.8	76.4	2.9	0.41	7.1
>=9	27.4	94.2	4.7	0.77	6.1
Clinical diagnosis[†]	54.8	86.1	3.9	0.52	7.5

LR+ = positive Likelihood ratio
LR- = negative Likelihood ratio
DOR = Diagnostic Odds ratio
[†] High probability of appendicitis estimated by surgeons on duty was based on clinical examination and laboratory results

## 5.3 Diagnostic performance of the AAS after its implementation into routine practice

The AAS was adopted and implemented into everyday clinical practice as an integral part of a new diagnostic algorithm for patients with suspected acute appendicitis shortly before the second data collection period commenced.

A total of 908 patients of whom 432 (48%) had appendicitis, were enrolled into study II in Meilahti and Kuopio Hospitals.

A total of 213 (49%) of all patients with appendicitis were correctly classified into the high probability group. Surgery was performed for suspected appendicitis on 225 patients in this group, including 12 negative appendectomies, which resulted in a negative appendectomy rate of 5.3% for the high probability group.

There were 286 (92.6%) non-appendicitis patients in the low probability group, which comprised 60% of all non-appendicitis patients. Appendicitis was the final diagnosis in 23 (7.4%) patients of the low probability group, and no patients of this subgroup had peritonitis. 196 out of 353 patients (55.5%) of the intermediate probably group had appendicitis.

The diagnostic algorithm and the flow of patients during the validation study are shown in Figure 7, and diagnostic performance of AAS is shown in Table 10.
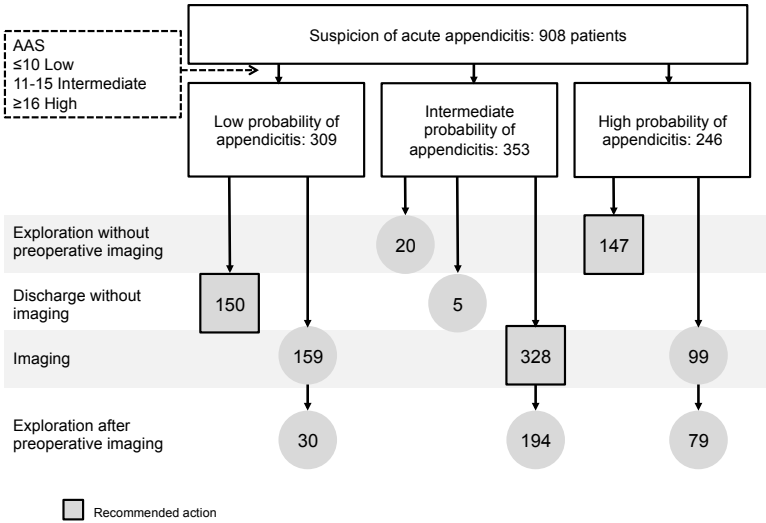
Figure 7 Flowchart of the validation study (Study II). Numbers in boxes and circles show number of patients

Table 10. Diagnostic performance of AAS in the validation study

	Sensitivity (%)	Specificity (%)	LR⁺	LR⁻	DOR
AAS ≥11	94.7	60.2%	2.38	0.09	27.03
AAS ≥16	49.4	93.3	7.37	0.54	13.60

LR⁺ = positive Likelihood ratio
LR⁻ = negative Likelihood ratio
DOR = Diagnostic Odds ratio

5.4 NEGATIVE APPENDECTOMIES

The negative appendectomy rate in Meilahti Hospital before the adoption of the new diagnostic algorithm was 87 of 477 (18.2%), whereas after the

implementation of the algorithm the rate of negative appendectomy decreased to 34 of 415 (8.2%), (p<0.001, Chi-square test).

The negative appendectomy rate for the high probability group in the study II was 12 (5.3%) of 225. Of these 12 operations, three were necessary for other reasons than appendicitis (one patient with acute cholecystitis, one with omental torsion and necrosis, and one with post-operative deep infection after laparoscopic hysterectomy). The remaining 9 of 225 (4.0%) operations were unnecessary explorations.

The negative appendectomy rate for the low probability group was 8 out of 30 (26.7%). False positive imaging results were obtained for four (50%) of these negative appendectomies, and the other four were performed due to a clinical suspicion of appendicitis despite there being negative results for preoperative US.

Of 215 appendectomies in the intermediate probability group, 21 (9.8%) were negative. Of these negative appendectomies, nine were performed either without preoperative imaging or after inconclusive imaging results, and the remaining 12 were performed after false positive imaging results.

5.5 DIAGNOSTIC IMAGING

The study III enrolled a total of 1545 patients. Of these patients, 723 (including 356 patients with appendicitis) had no imaging and were thus excluded from further analysis. The remaining 822 patients were analyzed.

Moreover, 497 patients underwent US, and 489 patients underwent CT. A total of 167 patients underwent both US and CT. MRI was only performed on 14 patients, therefore diagnostic performance of MRI was left outside further analyses.

5.6 DIAGNOSTIC PERFORMANCE OF US

Of 497 patients that underwent US 182 had appendicitis (pre-test probability of appendicitis 36.6%). The overall specificity and sensitivity of US were 94.4% and 48.6%, respectively. Post-test probability after positive US was 82.7%, whereas post-test probability after negative US was 23.2%.

US was performed on 187 patients with AAS ≤10 (low probability group), of whom 17 had appendicitis (pre-test probability of appendicitis 9.1%). The post-test probability of appendicitis for this group after positive US was 42.1%, which indicated that there were more false than true positive US results in this low probability group.
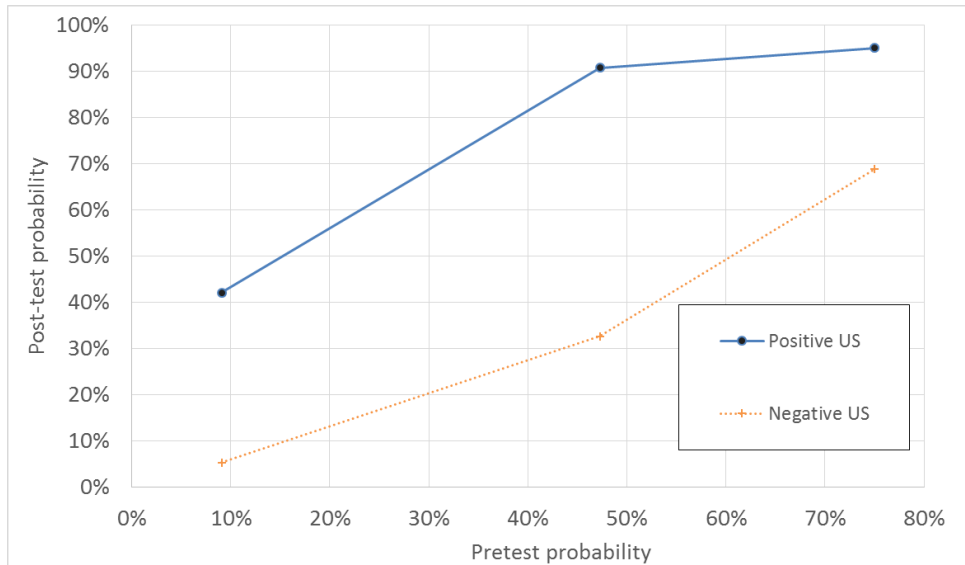
60

US was performed on 258 patients with AAS 10-15 (intermediate probability group), of whom 122 had appendicitis (pre-test probability of appendicitis 47.3%). The post-test probability of appendicitis after positive US findings for this group was 90.8%, whereas after negative US findings it was 32.6%.

US was performed on 52 patients with AAS ≥16 (high probability group), of whom 39 had appendicitis (pre-test probability of appendicitis 75.0%). The post-test probability after positive US for this group was 82.7%. The pre-test probability was lower in patients that underwent US compared to all the patients of the high-probability group (87.1%), which may be because imaging in this group was performed on patients with the most equivocal diagnoses after clinical examination.

There was a statistically significant difference in the post-test probability of appendicitis after a positive and after a negative US result between AAS groups of different pre-test probabilities (p<0.001, Chi-square test) (Table 11, Figure 8).

Table 11. Diagnostic performance of US, Patients diagnosed in Meilahti hospital

	Low probability (AAS ≤10)	Intermediate probability (AAS 11-15)	High probability (AAS ≥16)	All patients
Patients	187	258	52	497
Pre-test probability of appendicitis (%)	9.1%	47.3%	75.0%	36.6%
True positive	8	59	19	86
False positive	11	6	1	18
True negative	159	130	10	302
False negative	9	63	22	91
Specificity	93.5%	95.6%	90.9%	94.4%
Sensitivity	47.1%	48.4%	46.3%	48.6%
Post-test probability, positive test	42.1%	90.8%	95.0%	82.7%
Post-test probability, negative test	5.4%	32.6%	68.8%	23.2%

Figure 8 Pre- and post-test probabilities of appendicitis in patients imaged by US. The points in the figure refer to the three AAS score groups (low, intermediate, and high probability of appendicitis)

5.7 DIAGNOSTIC PERFORMANCE OF CT

Of the 489 patients that underwent CT, 257 had appendicitis (pre-test probability of appendicitis 52.6%). The overall specificity and sensitivity of CT were 92.2% and 98.4%, respectively. Post-test probability after positive CT was 92.7%, whereas post-test probability after negative CT was 1.74%.

CT was performed on 99 patients with AAS ≤10 (low probability group) of whom 16 had appendicitis. The pre-test probability of appendicitis was 16.2%. The post-test probability of appendicitis for this group after positive CT was 75.0%.

CT was performed on 276 patients with AAS 10-15 (intermediate probability group), including 138 patients with appendicitis. Pre-test probability of appendicitis for this group was 50.0%, and the post-test probability after positive CT was 91.2%.

CT was performed on 114 patients with AAS ≥16 (high probability group), of whom 90 had appendicitis. Pre-test probability of appendicitis was 78.9%. The post-test probability after positive CT for this group was 98.9%. The pre-test probability was lower in patients that underwent CT compared to all patients in the high-probability group (87.1%), this may have been because imaging in this group was performed on patients with the most equivocal diagnoses after clinical examination, and in some cases also after inconclusive US.

There was a statistically significant difference in the post-test probability of appendicitis after a positive CT result between the AAS groups of different pre-test probabilities (p<0.001, Chi-square test) (Table 12, Figure 9).

Table 12. Diagnostic performance of CT for patients diagnosed in Meilahti hospital

	Low probability (AAS ≤10)	Intermediate probability (AAS 11-15)	High probability (AAS ≥16)	All patients
Patients	99	276	114	489
Pre-test probability of appendicitis (%)	16.2%	50.0%	78.9%	52.6%
True positive	15	135	90	240
False positive	5	13	1	19
True negative	78	125	23	226
False negative	1	3	0	4
Specificity	94.0%	90.6%	95.8%	92.2%
Sensitivity	93.8%	97.8%	100%	98.4%
Post-test probability, positive test	75.0%	91.2%	98.9%	92.7%
Post-test probability, negative test	1.3%	2.3%	0%	1.74%
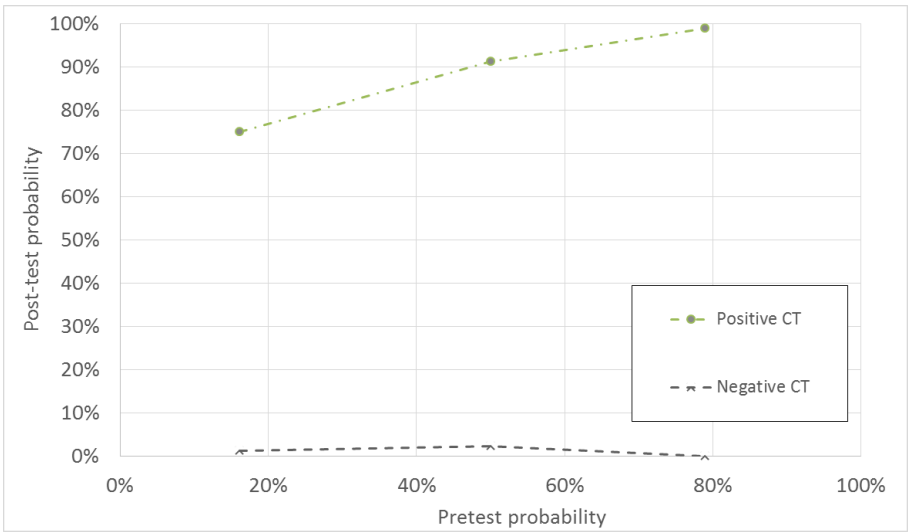
Figure 9 Pre- and post-test probabilities of appendicitis in patients imaged by CT. The points in the figure refer to the three AAS score groups (low, intermediate, and high probability of appendicitis)

63

5.8 DIFFERENTIAL DIAGNOSES IN IMAGING STUDIES OF LOW- AND HIGH-PROBABILITY PATIENTS

There were 18 patients that were diagnosed with other disease than appendicitis by US among the 187 patients of the low probability group that underwent US. Three of these patients underwent additional CT. The US findings led to two patients undergoing laparoscopic cholecystectomy for acute cholecystitis, one incarcerated umbilical hernia was operated on, and two patients underwent laparoscopy by gynecologists for suspected ovarian torsion (one of these was a negative exploration). Among the 99 patients of the AAS ≤10 group that underwent CT, 35 patients had other diagnoses than appendicitis in the CT reports.

Four patients of the AAS ≥16 group had other diagnoses than appendicitis by US, and two of them were operated on for acute cholecystitis. CT examinations were performed on 114 patients in this group, which resulted in other diagnoses than appendicitis for 18 patients.

5.9 DETECTING PRE-HOSPITAL PERFORATIONS BY CT

Of 489 patients that underwent CT, 81 had complicated appendicitis. Of these cases, 39 (48%) were correctly preoperatively identified as complicated appendicitis, 41 as uncomplicated appendicitis, and one as NSAP by CT. There were 14 false positives for complicated appendicitis in the CT findings. The sensitivity of CT for complicated appendicitis was 48.1%, and the specificity was 88.2%.

5.10 DETECTING PRE-HOSPITAL PERFORATIONS

In the original study IV ROC-analysis based on clinical findings and laboratory results obtained for the initial examination at the emergency department was carried out to find the best indicator for pre-hospital perforations. A total of 389 patients with appendicitis were included in this analysis. CRP had the highest AUC value compared to the proportion of neutrophils, blood leukocytes, Alvarado Score and AIR Score. The optimal cut-off value for CRP as a marker for perforation was 99 mg/l. The AUC-values of different variables are shown in Table 13.

A total of 78 patients had a CRP value of 99 mg/l or more, and 49 (62.8%) of them had complicated appendicitis. Of 311 patients with CRP values less than 99 mg/l, 42 (13.5%) had complicated appendicitis. The sensitivity of the CRP value of 99 mg/l or more for complicated appendicitis was 53.8%, and the specificity was 90.3%.

Table 13. Area under the curve (AUC) of potential markers for pre-hospital perforation

Variable	AUC
C-reactive protein	0.803
Blood leukocyte count	0.517
Proportion of neutrophils	0.603
Alvarado Score	0.611
Appendicitis Inflammatory Response Score	0.745

5.11 PRE-HOSPITAL DELAY

Patients with complicated appendicitis had a significantly longer median delay from the onset of symptoms to entry to the emergency department (pre-hospital delay) compared to the patients with uncomplicated appendicitis. The median pre-hospital delay of patients with complicated appendicitis was 36 hours (IQR 21-75), and for patients with uncomplicated appendicitis 22 hours (IQR 13-35), $p < 0.001$.

Pre-hospital delay correlated with the length of the total hospital stay for all patients with appendicitis (correlation coefficient $r = 0.313$, $p < 0.001$). Within the first 72 h from the onset of symptoms, there was a difference between patients with complicated ($r = 0.600$, $p < 0.001$) and uncomplicated ($r = 0.467$, $p < 0.001$) appendicitis in the correlation between admission CRP values and the duration of symptoms. When the CRP concentration was below 37 mg/l, and the patient had been symptomatic for at least 24 h, the risk of perforation was 2.0%.

Patient groups with admission CRP values of 99 mg/l or more, and less than 99 mg/l were analyzed separately. The difference in pre-hospital delay between patients with complicated and uncomplicated appendicitis was significant only for the patient group with CRP concentrations of 99 mg/l or more. The median pre-hospital delay in patients with complicated appendicitis in this high-CRP group was 59 h, and for patients with uncomplicated appendicitis 33 h ($p = 0.005$, Mann-Whitney U test). The median pre-hospital delay for the low-CRP group was shorter, and similar in patients with complicated and

uncomplicated appendicitis (median delay 21 h and 21.5 h, respectively, p=0.265) (Figure 10).
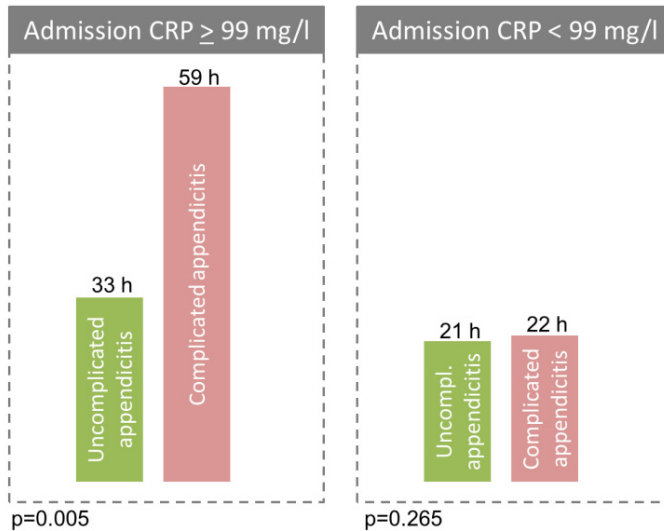
Figure 10 Median pre-hospital delay in patients with admission CRP ≥99 mg/l and patients with admission CRP <99 mg/l.

5.12 IN-HOSPITAL DELAY

In-hospital delay was defined as the time interval between the initial examination of the patient in the emergency department and that patient having surgery. The median in-hospital delay was 8.5 h (Inter-quartile range (IQR) 4.9-13.4 h). For the low-CRP group the in-hospital delay was longer in patients with complicated appendicitis (median 12 h, IQR 6-16 h) compared to patients with uncomplicated appendicitis (median 8 h, IQR 5-13 h) (Figure 11). The risk of perforation rose from 9.5% to 18.9% when the in-hospital delay increased from less than six hours to more than 12 hours (p=0.047). A longer in-hospital delay was also correlated with longer overall hospital stay (r=0.466, p<0.001).

A longer in-hospital delay for patients with an admission CRP concentration of 99 mg/l or more correlated with longer overall hospital stay (r=0.263, p=0.02) but was not associated with the risk of perforation.

The median diagnostic delay (time interval between the initial examination and diagnosis) was 2.9 h. The stronger the guarding in the RLQ was in the initial examination, the shorter the diagnostic delay was (p<0.001). Patients that underwent CT had longer diagnostic delays (p<0.001).
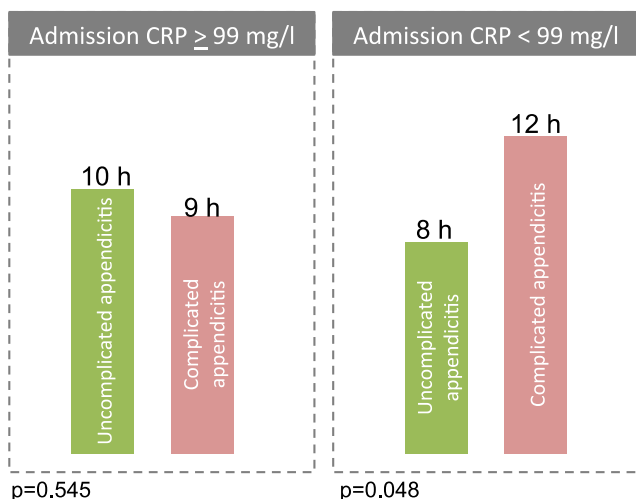
Figure 11 Median in-hospital delays in patients with admission CRP ≥99 mg/l and <99 mg/l

5.13 GANGRENOUS APPENDICITIS

Gangrenous appendicitis was for this study defined as perforated appendicitis or appendicitis with necrosis in histopathological analysis but without perforation (gangrenous uncomplicated appendicitis).

The effect of delay on the proportion of uncomplicated gangrenous appendicitis was investigated in the study IV. A total of 168 patients (43.2% of all appendicitis cases) had gangrenous appendicitis. This included 77 uncomplicated gangrenous and 91 perforated cases. 77 of 298 (25.8%) of patients with uncomplicated appendicitis had gangrenous appendicitis. The proportion of gangrenous appendicitis among all appendicitis patients and the proportion of perforated appendicitis increased along with the increased duration of symptoms (Figure 12).
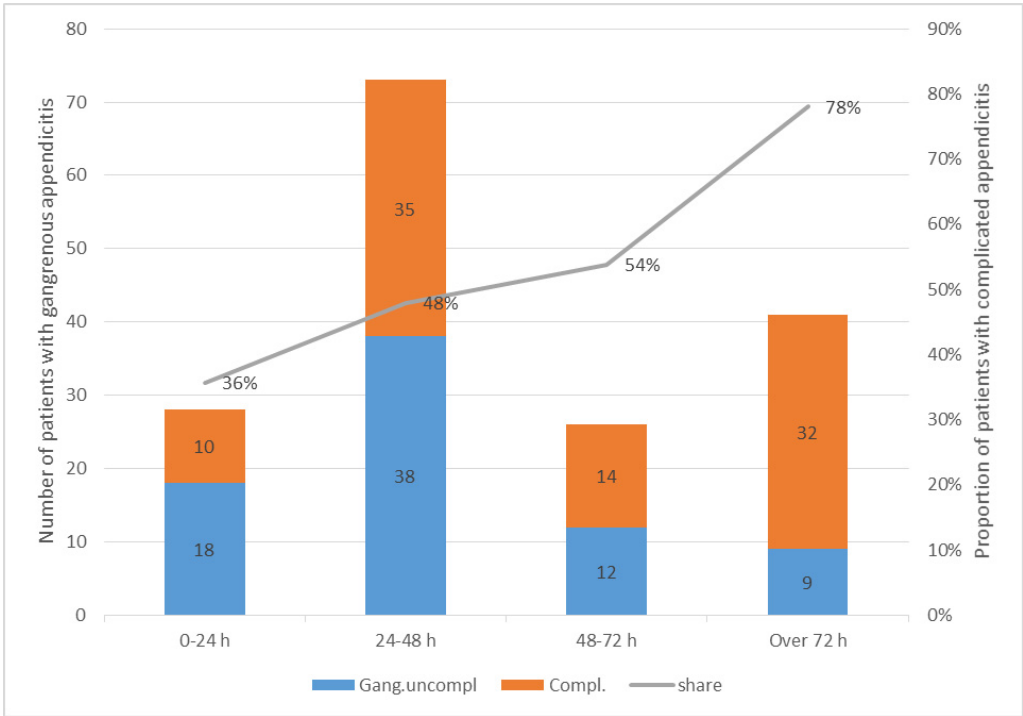
Figure 12 Proportions of complicated appendicitis after different total duration of symptoms, in all patients with gangrenous appendicitis (n=168)

6. DISCUSSION

6.1 THE NEW ADULT APPENDICITIS SCORE

In 2015, The European Association of Endoscopic Surgery (EAES) issued a consensus statement on the diagnosis and management of acute appendicitis. In their statement, they recommended the use of diagnostic scoring to categorize the patients into three classes with respect of their risk of appendicitis. This was intended to guide clinicians in their decision-making process when to use further imaging studies either to diagnose or rule out acute appendicitis (23).

The World Society of Emergency Surgery (WSES), in 2016, also assessed diagnostic scoring in their guidelines for the diagnosis and treatment of acute appendicitis. The first of eight main questions addressed by the expert panel was whether scoring could be used as the basis for the structured management of patients under suspicion of appendicitis. They stated that the current scoring systems may be able to exclude appendicitis, but not safely identify patients that warrant appendectomy. Hence, they concluded that "an ideal (high sensitivity and specificity), clinically applicable, diagnostic scoring system/clinical rule remains outstanding" (22).

Numerous studies have been performed to develop, validate and compare diagnostic scores for the diagnosis of acute appendicitis. The goal of these studies is clear: an optimal diagnostic score for appendicitis must recognize or exclude appendicitis fast and accurately. In order to reach this goal, a couple of prerequisites need to be fulfilled. First, the score must be developed and further validated in large, prospective patient populations with RLQ abdominal pain. Second, the score should be based on common and easily accessible variables known to have a strong association with appendicitis. However, no scoring system has gained wide acceptance in everyday clinical practice. This is probably due to their deficient ability to significantly improve diagnostic accuracy.

The implementations of diagnostic scoring, electronic clinical decision support, and diagnostic algorithms have been reported to be beneficial in decreasing the required rate of imaging for suspected acute appendicitis (14, 15). Prior to the commencement of the study the trial hospitals lacked a structured diagnostic approach. Additionally, the use of diagnostic imaging was recognized to be underutilized despite its sufficient availability. In addition, the principles of diagnostics were inconsistent among treating physicians. The existing scoring

systems did not seem to offer reliable methods to stratify the patients in an accurate manner. These considerations prompted us to develop the AAS diagnostic score.

In a recent review by Bhangu et al., scoring was included in the recommended diagnostic algorithm of patients with suspected appendicitis (229). In that review, they included two different scoring systems, named as the Alvarado Score and the Appendicitis Inflammatory Response (AIR) Score. The Alvarado score, published in 1986, is the best known and most cited scoring system. It is based on eight clinical and laboratory variables (24). The more recent AIR score, published in 2008, bears a lot of similarity to the Alvarado score, but it puts more emphasis on the inflammatory laboratory results (Review of the literature, Table 1) (25).

The study I on this thesis compared directly the diagnostic performance of these two former score systems and the AAS. The AAS was found to be superior to both the Alvarado and the AIR scores as well as to the physician's routine clinical assessment, supporting the routine use of the AAS.

In the study II of this thesis, the superiority of the AAS on the diagnostic accuracy was further reinforced as compared to previously published validation results both on the Alvarado and the AIR scores. Study II did not however include a direct comparison in between these scores.

Although the AIR score has excellent specificity in the high-probability group, only a minority of patients with appendicitis is stratified into that group. As a consequence, when this score is used, majority of the patients with appendicitis end up having preoperative imaging studies. The original report of the AIR Score stratified correctly 28 of 76 (36.8%) patients with appendicitis into the high-probability group, resulting in sensitivity and specificity of 37% and 99%, respectively (25). External validation studies of the AIR score have reported the sensitivity to range between 23 and 33% in the high-probability group (26, 170). In our study, the use of the AAS resulted in sensitivity of 49% within the high-probability group. That compares favorably to the above-mentioned AIR validation studies. The study I of this thesis found the sensitivity of the AAS and the AIR score in the high-probability group to be 58.0%, and 14.6%, respectively. In practice this means that the AAS is able to stratify roughly half of all patients with appendicitis into the high-probability group, whereas, the corresponding reported figure for the AIR score is from 23% to 37% (25, 26, 170). According to same studies, the negative predictive value, i.e. the likelihood of no appendicitis in the low-risk group, of the AIR was comparable to what we found for the AAS in the current study (93% compared to 94-96%).

The Alvarado score has better sensitivity compared to the AIR score for the high-probability group. However, the specificity has been insufficient and thus obviating its clinical use as a routine diagnostic method (21, 26, 170, 171). In the original publication of the development of the AIR score, the Alvarado score was also assessed. The study reported the Alvarado score stratifying correctly only 21 out of 76 (27.6%) patients with appendicitis into the high-probability group. The respective sensitivity and specificity rates were 28% and 99% (25). Kollar et al. reported that the Alvarado Score stratified 53 of 67 (79%) patients with appendicitis and 28 patients with no appendicitis into the high-risk group with a specificity of 76%. This resulted in negative and positive predictive values of 93%, and 65%, respectively (26). A comparative study between the Alvarado score and CT reported that the high-probability group had a sensitivity of 47.1%, a specificity of 81.7%, and a positive predictive value of 67.6% for the Alvarado score (169). Hence, the study concluded that the Alvarado score could recognize patients who have a low risk of appendicitis, whereas it discriminates insufficiently patients with higher probability of appendicitis. This leads to a need of additional imaging studies for this group. Due to frequent false positive diagnoses, in the clinical practice the Alvarado score seems to be inferior both to the AIR score and to the AAS.

The better discriminating capability of the AAS might be explained by the ways how this new score is constructed as compared to its counterparts. First, fertile aged women pose the biggest diagnostic challenge for appendicitis. This was highlighted in the study by Tan et al., where an Alvarado score of 9 or more in women resulted in a comparable positive likelihood ratio to that of 7 or more in men (169). Kalan et al. found equally the sensitivity of a modified Alvarado Score (Alvarado score without measurement of shift to the left) to be inferior in women (230). This important fact has been taken into consideration and included in the AAS score. Second, the duration of inflammation affects the CRP value, a fact that is taken into account in the AAS. Third, the AAS is limited to patients of 16 years or older, whereas the other two scores include also children.

6.2 THE NEW DIAGNOSTIC ALGORITHM

When designing a diagnostic algorithm for patients with suspected appendicitis, the ionizing radiation risks should be carefully considered. This is the case especially among adolescents and young adults, as they both represent the majority of patients and they are known to be more sensitive to radiation. According to the estimates, 2000 CT scans that are performed on young adults

for a suspected of acute appendicitis would result in at least one cancer death (161, 162).

US is commonly incorporated in the diagnostic algorithms. The goal is to reduce the number of CT studies and thereby decrease costs as well as radiation-associated patient harm. US as the first-line imaging modality is used to identify which patients can go directly to surgery or when further imaging with the CT is necessary (4, 6, 231). The Dutch national diagnostic appendicitis guidelines require imaging for all patients suspected to have an acute appendicitis (6). According to the guidelines, US is the primary imaging modality, followed by the CT in cases where the US remains either negative or inconclusive. The rate of negative appendectomies has been shown to decrease when using this protocol (6). However, some authors criticize these guidelines and debate over what actually the acceptable negative appendectomy rate should be (55). A Dutch study showed that mandatory imaging might lead to a higher than expected rate of negative appendectomies (232). Two studies that followed the guideline-based imaging protocol reported the rates of negative appendectomy to be 6.2% and 12% (6, 232). These published rates are close to the respective figure in the current study, achieved after the implementation of the AAS without mandatory imaging.

In our current study, the scoring and US were not directly compared. However, diagnostic scoring with the new AAS seems to be associated with fewer patients that require further imaging studies than the case is with the US-based stratification. This study found that 393 out of 497 (79%) US examinations were either negative or inconclusive. This implicates that at least more than half of patients would have had an additional CT study if an US-based stratification protocol had been used instead of the AAS. However, the above-mentioned Dutch studies found that only 30-35% of patients had both US and CT. After using the diagnostic score, only approximately half of all patients would require some sort of imaging for suspected appendicitis. Hence, it can be assumed that stratification by scoring, compared to the alternative, would save both time and costs.

The definition of negative appendectomy varies. Many retrospective studies defined negative appendectomy according to what was recorded at the hospital discharge. However, this approach involves factors that may render a less reliable diagnosis. First, there is evidence that, at the time of surgery, the surgeons do not necessarily recognize abnormal appendixes reliably, and at the time of hospital discharge, histopathological confirmation is typically not yet available (96, 233). Second, diagnostic laparoscopies with the appendix left in place are not invariably defined as negative operations. The same applies to

surgery performed for suspected appendicitis, when some other disease is diagnosed and treated in the same session.

Independent of the definition applied, negative appendectomies lead to an unbeneficial surgery and unnecessary hospital stay with associated morbidity. On rare occasions even severe complications occur (9). From the health economics perspective it also leads to ineffective resource utilization, meaning less operating room capacity and hospital beds available for those patients with an actual need of emergency surgical care.

On one hand, pre-hospital perforations are relatively common and, on the other, the appendicitis can at times resolve spontaneously. Thus, researchers have emphasized the correct diagnosis over an early diagnosis (95). This current study showed that these two important considerations are not in conflict with each other. When a diagnostic algorithm with integrated diagnostic scoring is used, a more accurate diagnostics is enabled without the need for time-consuming mandatory imaging studies.

After the new diagnostic algorithm was taken into everyday use at the Meilahti Hospital, the rate of negative appendectomies decreased from 18.2% to 8.2%. A further analysis on the negative appendectomies showed that only 6% of all operations performed were actually unnecessary because 2.2% of these explorations for suspected appendicitis found another pathology requiring prompt surgical treatment. Even without having performed a formal cost-benefit analysis, cost savings can be expected from using this new algorithm that includes the AAS, thanks to the dramatically diminished rate of negative explorations. This benefit still remains, despite an increase from 40% to 65% in the number of patients with diagnostic imaging studies.

Adherence to the new diagnostic algorithm was not strictly controlled. Examining physicians used their discretion, with respect of incorporating imaging studies as a part of their diagnostic work up, in cases of discrepancy in between the score and their own clinical assessment, or if an alternative diagnosis was suspected. Potentially one might conclude that too many imaging studies were ordered during the validation study. However, a lot of patients present themselves with an atypical history or clinical findings. In such cases, the importance of physicians' clinical assessments whether imaging studies are required or not is clear and evident. When combining the results of scoring with the clinical evaluation, the most accurate diagnosis is achieved.

The routine use of the AAS in everyday clinical practice is supported by the decrease in the negative appendectomy rate and by the superior diagnostic accuracy of the AAS, as compared both to the routine clinical assessment and to the Alvarado and the AIR scores. However, some patient groups with suspected

appendicitis most likely benefit from imaging studies, even though this aspect was not directly evaluated in the study protocol. First, pregnant women under suspicion of acute appendicitis are recommended to have US, as the clinical diagnosis of appendicitis for pregnant patients is especially equivocal. Furthermore, surgery increases the risk of miscarriage and prematurity. If the US is inconclusive, it mandates an emergency abdominal MRI (234-237). Second, immunosuppressed patients can have milder symptoms, and due to their vague inflammatory response, less pronounced leukocyte and CRP-elevations. This weakens the discriminating capability of the new score in this immunocompromised patient population. In addition, they have potentially a worse outcome when suffering from whichever acute emergent medical condition. Hence, this indicates an immediate imaging whenever appendicitis is suspected. Third, symptoms and findings of patients with suspected appendiceal abscess differ from those of other appendicitis patients. These patients have often experienced only vague symptoms for several days, have typically fever and high CRP values. In addition to an enhanced diagnostic accuracy, CT imaging aids substantially in the surgical management plan for his patient group.

6.3 IMAGING AND PRE-TEST PROBABILITY

To our knowledge, no previous publications of original studies exist that compared the diagnostic accuracy of CT and US between patient cohorts with different pre-test probabilities for appendicitis. Two meta-analyses by van Randen et al. and Terasawa et al. analyzed the results of imaging in patient cohorts who had different prevalences (pre-test probability) of appendicitis. They found that post-test probabilities after positive CT and US findings were significantly decreased when the appendicitis prevalence was lower. They also revealed that post-test probabilities after a negative imaging increased in case of a higher prevalence of appendicitis (20, 30). Imaging thus gave the least benefit for patients both with the highest and lowest probabilities for appendicitis. The results of this thesis partly corroborate these findings. False negative results of US were common for high-probability patients in both meta-analyses and in this present study. However, for the CT this was the case only in the meta-analyses and was not confirmed in the current study. These results suggest that CT should be chosen as the primary imaging modality if, despite the high scoring result symptoms are atypical for appendicitis or some other disease is suspected. Needless to say, in a clinical setting the choice of imaging modality depends on the differential diagnosis to what is primary suspected. For example, US examination is usually preferred in the case of suspected cholecystitis (238,239).

In the high-probability group, the pre-test probability of appendicitis was 79% and 75% for the patients imaged by the CT and US, respectively. The pre-test probability was lower in patients that underwent imaging compared to all patients in the high-probability group (87.1%). This was probably because patients that had imaging studies in this group were the ones with the most equivocal diagnoses after the clinical examination, and thereby leaving a lot of room for physician's discretion.

The prevalence of appendicitis was less than 10% for the low-probability group (AAS ≤10). For these patients, the false positive imaging results of US were even more commonly found than the true positive results both in the mentioned meta-analyses and in study III of this thesis. As these patients typically have mild symptoms and a weak inflammatory response, at least some of these patients probably represent cases of appendicitis that would resolve spontaneously (77, 78). Hence, patients of the low probability group that cannot be directly discharged would probably benefit most from follow-up and repeated scoring after, for example, six to eight hours.

Spontaneously resolving appendicitis and its histology has been described in the literature, but the incidence is unknown (77-79). Two studies, on which patients with non-specific abdominal pain were randomized either to follow-up or to immediate laparoscopy, reported in the latter group an increased prevalence of uncomplicated appendicitis. This suggests that spontaneously resolving appendicitis is a common phenomenon behind mild and non-specific abdominal complaints (80, 81).

6.4 IDENTIFYING PATIENTS WITH COMPLICATED APPENDICITIS

Comparing different studies with respect to the diagnostics of perforation is challenged by differences how complicated appendicitis is defined. CRP has been identified as a marker for complicated appendicitis in several previous studies as well as also in this present study (29, 87, 88, 117, 119). In the study IV, CRP cut-off value at 99 mg/l or more for complicated appendicitis had a sensitivity and specificity of 53.8% and 90.3%, respectively. This makes it a practical marker for perforation, especially in those hospitals that do not routinely perform CT on all patients under suspicion for appendicitis.

However, previous studies have shown that the distinction between uncomplicated and complicated appendicitis is challenging even when the CT is used (88, 90-92). The overall sensitivity of CT for perforated appendicitis has been reported to be less than 75% (90). Atema et al. suggested a scoring system

that combines clinical and imaging features, in order to better discriminate between complicated and uncomplicated appendicitis (92).

In this present study the sensitivity and specificity of CT for complicated appendicitis were 48.1% and 88.8%, respectively. These results are comparable to the sensitivity and specificity found for CRP level of 99 mg/l or more. However, our study did not directly compare these two methods. Some of the perforations that were detected intraoperatively might also have happened in the interim between the CT examination and the actual surgery. In summary, complicated appendicitis cannot be excluded solely by a negative CT report; the decision-making should be guided by the clinical picture together with the laboratory results, especially CRP values.

6.5 THE EFFECT OF DELAY ON THE RISK OF COMPLICATED APPENDICITIS

In the study IV of this thesis, the duration of symptoms was associated with the risk of complicated appendicitis. This finding is in agreement with that of numerous previous studies (32-34, 36, 37).

The surgeon is posed with challenges when trying to affect the delay in presentation to hospital (pre-hospital delay). To make an improvement, the public awareness about the potential dangers of delay needs to be influenced. The insurance status and income level in the USA and South Africa have been shown to affect the access to care, and thereby the rate of perforations and outcomes in acute appendicitis (93, 94). Because Finland has public health coverage to all citizens, in theory all patients have an equal access to the public health care. This means that the outcome results of appendicitis are not affected to same extent by above-mentioned factors.

In contrast, the delay in diagnosis and treatment can be minimized, once the patient has entered a health care facility (in-hospital delay). However, this speeding-up must not be done at the cost of more inaccurate diagnoses.

In-hospital delay in the treatment of acute appendicitis remains controversial. There is pressure towards avoiding nighttime surgery, although evidence shows that increasing delay in diagnosis and treatment is associated with an increased risk of perforation and impaired outcomes (34, 37, 38, 240, 241). The acute care surgery service model is an example of a method to reduce in-hospital delay (42). The use of this model enabled an earlier evaluation and treatment of patients with acute appendicitis, leading to better outcomes, shorter hospital stay, and cost savings.

Controversially, many studies have concluded that in-hospital delay plays any significant role neither to the perforation risk nor overall outcome (44, 45, 242).

Ingraham et al. did a large retrospective cohort study, concluding that a longer in-hospital delay in appendicitis did not adversely affect the 30-day outcomes (43). Patients were categorized in three comparative groups according to the length of the in-hospital delay, as follows: less than 6 h, 6-12 h, and more than 12 h. However, due to inherent limitations of a registry-based data, no data on pre-hospital delay, rate of pre-hospital perforations or other clinical information was included. Thus, results might have been confounded by earlier operations of patients with more severe symptoms and later operations of patients with milder symptoms (43). The same possible bias is included in other retrospective studies that assessed the same matter.

Our study showed that the perforation risk was associated with the length of in-hospital delay for those patients who had their CRP value less than 99 mg/l.

The longer duration of symptoms increased both the number of gangrenous appendicitis and the proportion of perforated appendicitis cases among them. This is in line with the old theory of appendicitis progressing from inflammation to necrosis and eventually to perforation.

However, not all patients with appendicitis are the same, as some patients reportedly experience even a spontaneous resolution of the symptoms (78, 95). Our study demonstrated the risk of complicated appendicitis to be low on patients with a low CRP level and long-lasting symptoms. CRP analysis could be useful when deciding which patients should be operated on during nighttime; this is borne out by our finding that all patients CRP levels under 10 mg/l at admission and in-hospital delay of less than 12 h had an uncomplicated appendicitis. Hence, nighttime patients with short duration of symptoms and normal CRP could safely wait until the next morning. The risk of complicated appendicitis increases if the CRP value is higher or waiting time gets longer. This study found that complicated appendicitis was very unlikely in patients with a total duration of symptoms of at least 24 h and with CRP 37 mg/l or less. These patients might therefore present a patient group on which appendicitis potentially resolves spontaneously. However, this is at the current stage hypothesis-generating only, and more research is thus needed in order to understand how to recognize such patients.

6.6 THE LIMITATIONS OF THE STUDY

This study is potentially limited by the fact that the new diagnostic score has not yet been validated in an external patient population that is large enough. Only 88 patients were stratified in Kuopio during the study II.

In the same study the proportion of patients having diagnostic imaging was higher than what the diagnostic algorithm required. On the other hand, some patients with low or intermediate scores were operated on without any preoperative imaging. This is typical for an observational study. However, in majority of patients the guidelines were followed (69%).

Equally in the study III, imaging was not performed on all patients. The use of imaging was at the discretion of the physician. These patients had probably more equivocal diagnosis than other patients with the same scoring result. The patient selection bias in imaging might therefore have influenced the results on the diagnostic accuracy.

6.7 FUTURE PROSPECTS

The clinical utility of the AAS needs to be externally validated in centers outside of the Meilahti Hospital to further strengthen the reliability of the new score, justifying its routine use.

A randomized study of the intermediate-probability patients is in progress at the Meilahti Hospital. Patients are randomized either to follow-up with repeated scoring or to immediate imaging (DIAgnostic iMaging or Observation in Early Equivocal appeNDicitis [DIAMOND] NCT02742402).

Finally, more research is warranted to find better means to recognize patients that, without prompt intervention, will eventually proceed to perforation. Likewise, additional research attempts should focus on identifying patients that are likely to experience spontaneous resolution. Still after over a century of research on acute appendicitis, this intriguing question remains unanswered.

7. CONCLUSIONS

1. The Adult Appendicitis Score was developed and validated as a new diagnostic scoring system for adult patients suspected of acute appendicitis. The score was implemented into a new diagnostic algorithm for patients with suspected acute appendicitis, and is now a routine part of patient management at the Helsinki University Central Hospital. The rate of negative appendectomies decreased from 18.2% to 8.2% after the adoption and implementation of the AAS and the associated diagnostic algorithm (Original publications I and II).
2. The diagnostic accuracies of CT and US were related to the pre-test probability of appendicitis as determined by the AAS. Imaging had a high frequency of false positive results for patients who had the smallest likelihood of the disease (Original publication III).
3. A CRP value of 99 mg/l or more, measured at hospital admission, is a practical marker for pre-hospital perforations. Although more than half of patients with complicated appendicitis experience perforation before they are admitted, some patients will develop perforation as a result of delay in diagnosis and treatment (Original publication IV).

ACKNOWLEDGEMENTS

lifetime. And of course for my nieces and nephews Emppu, Touko, Hilla, Aurora, Ohto, Tuisku, and soon-to-be born "Vauva" – the extra sunshines in my life.

I offer my warmest thanks to all my in-laws in the Juopperi-Ylihautala-Salo-Sammalkorpi-family. Kaija-Riitta and Aarre, my mother and father in-law deserve my warmest thanks. You have literally traveled thousands of kilometers to help with this project. Saara, Mika, Kaisla, Mikko, Kisu, Roosa, Ella, Elina, Eero, and Marja – it is such a fortune to have you all in my life!

I reserve my deepest gratitude for my beloved husband Sammeli. Nothing seems impossible when I have you beside me! Thank you for sharing your life with me.

And Peppi, Sisu, and Elo – for filling my life with purpose and joy.

Helsinki, March 2017

Henna Sammalkorpi

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