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DIAGNOSTIC MARKERS IN ACUTE APPENDICITIS: A SYSTEMATIC REVIEW

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Abstract

Introduction: *Appendicitis is the most common emergency case of abdominal surgery and requires immediate surgical intervention to avoid serious complications. If appendicitis is treated late, it will increase patient morbidity and mortality. Despite the relatively high incidence of needless appendectomies, ranging from 20% to 30%, such occurrences are deemed tolerable given the substantial reliability of beneficial outcomes.*

The aim: *This article showed diagnostic markers in acute appendicitis.*

Methods: *This study demonstrated compliance with all requirements by comparing itself to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 standards. Therefore, the experts were able to ensure that the study was as current as feasible. For this search strategy, publications published between 2013 and 2023 were considered. Several online reference sources, including Pubmed and SagePub, were utilized for this purpose. It was determined not to consider review pieces, previously published works, or works that were only partially completed.*

Result: *The PubMed database yielded a total of 87 articles in response to our search query, while the search conducted on SagePub resulted in 69 articles. The search conducted for the last year of 2013 resulted in a total of 29 articles found in PubMed and 31 papers found in SagePub. Ultimately, a comprehensive compilation of 22 papers was achieved, with 15 sourced from PubMed and an additional seven obtained via SagePub. We incorporated seven studies that satisfied the established criteria.*

Conclusion: *Study shows that a shift in pain from the epigastrium to the Mc Burney point and heel drop test is a sign of appendicitis based on physical examination. Examination of white blood cells and CRP can be other reliable markers to confirm acute appendicitis.*

Keyword: *Acute appendicitis; Alvarado score; Diagnostic; Marker*

INTRODUCTION

Appendicitis is the most common emergency case of abdominal surgery and requires immediate surgical intervention to avoid serious complications. If appendicitis is treated late, it will increase patient morbidity and mortality.[1] Appendicitis refers to the inflammatory process or inflammation of the vermiform appendix, which is a distinct organ commonly referred to as the appendix. Acute appendicitis represents a critical medical condition that is commonly found in the context of acute abdominal presentations.[2]

Appendicitis most commonly occurs at the age of 10-20 years. The ratio of men to women is 1.4:1. Studies in the United States show the lifetime risk of developing appendicitis is 8.6% for men and 6.7% for women. Studies have shown an association between acute appendicitis and manifestations of colorectal cancer. It has been reported that 2.9% of patients who experienced appendicitis had colorectal cancer compared to 0.1% of patients who did not experience appendicitis. A report in the United Kingdom reported that between the beginning of 2007 and 2012, 42,000 to 47,000 surgical procedures were performed for the indication of appendicitis each year. Complicated appendicitis is reported in 16.5% to 24.4% of cases.[3,4]

National epidemiological data on appendicitis in Indonesia is still not available. A study conducted at South Tangerang City Hospital stated that of 111 cases of appendicitis, the highest age distribution was in the 17-25 year age group (34.2%). There are more female patients than male patients. Another study at Adam Malik Hospital in Medan stated that the prevalence of peritonitis in patients with appendicitis in 2017 was 62.8%. Appendiceal perforation increases the risk of morbidity and mortality. The mortality risk of non-gangrenous acute appendicitis is 0.1%, while gangrenous acute appendicitis is 0.6%.[5,6]

Appendicitis typically arises from the occurrence of an obstruction, subsequently leading to an infection. Several factors can potentially lead to obstructions, including hyperplasia of lymphoid tissue, fecaliths, foreign substances, strictures, kingking, and adhesions.[2] When there is an obstruction in the proximal region of the appendix, it leads to the accumulation of mucus secretion within the lumen of the appendix, causing an increase in intraluminary pressure. The application of pressure will cause a disturbance in the lymphatic flow, leading to the occurrence of edema and damage to the mucosal lining. This particular stage is referred to as mild acute appendicitis.[7]

The prompt and precise diagnosis of acute appendicitis is crucial in order to provide prompt and effective treatment of the condition. However, the postponement of diagnosis and treatment might lead to complications such as gangrene perforation and diffuse peritonitis. Despite the relatively high incidence of needless appendectomies, ranging from 20% to 30%, such occurrences are deemed tolerable given the substantial reliability of beneficial outcomes.[8,9] The current study unveiled the presence of diagnostic markers in acute appendicitis.

METHODS

The person in command of this study took steps to ensure strict adherence to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines. The purpose of this method is to ensure the accuracy of the investigation's findings. This study's primary objective was to identify diagnostic markers for acute appendicitis. The primary objective of this study is to demonstrate the significance of the aforementioned and book-discussed topics. To be eligible for inclusion in the study, researchers had to meet certain requirements.

The paper had to be written in English and concentrate on diagnostic markers for acute appendicitis. To be published, the paper must satisfy both of these requirements. Several of the publications being evaluated were published in 2013 and within the predetermined timeframe deemed pertinent to the objectives of this systematic review. Editorials, submissions without a Digital Object Identifier (DOI), previously published review articles, and submissions that duplicate previously published journal articles are prohibited in the academic context.

We used “diagnostic markers” and “acute appendicitis” as keywords.The search for studies to be included in the systematic review was carried out from September, 7th 2023 using the PubMed and SagePub databases by inputting the words: *(("diagnosis"[MeSH Terms] OR "diagnosis"[All Fields] OR "diagnostic"[All Fields] OR "diagnostical"[All Fields] OR "diagnostically"[All Fields] OR "diagnostics"[All Fields]) AND ("marker"[All Fields] OR "markers"[All Fields]) AND ("appendicitis"[MeSH Terms] OR "appendicitis"[All Fields] OR ("acute"[All Fields] AND "appendicitis"[All Fields]) OR "acute appendicitis"[All Fields])) AND ((y_10[Filter]) AND (clinicaltrial[Filter]))* used in searching the literature.

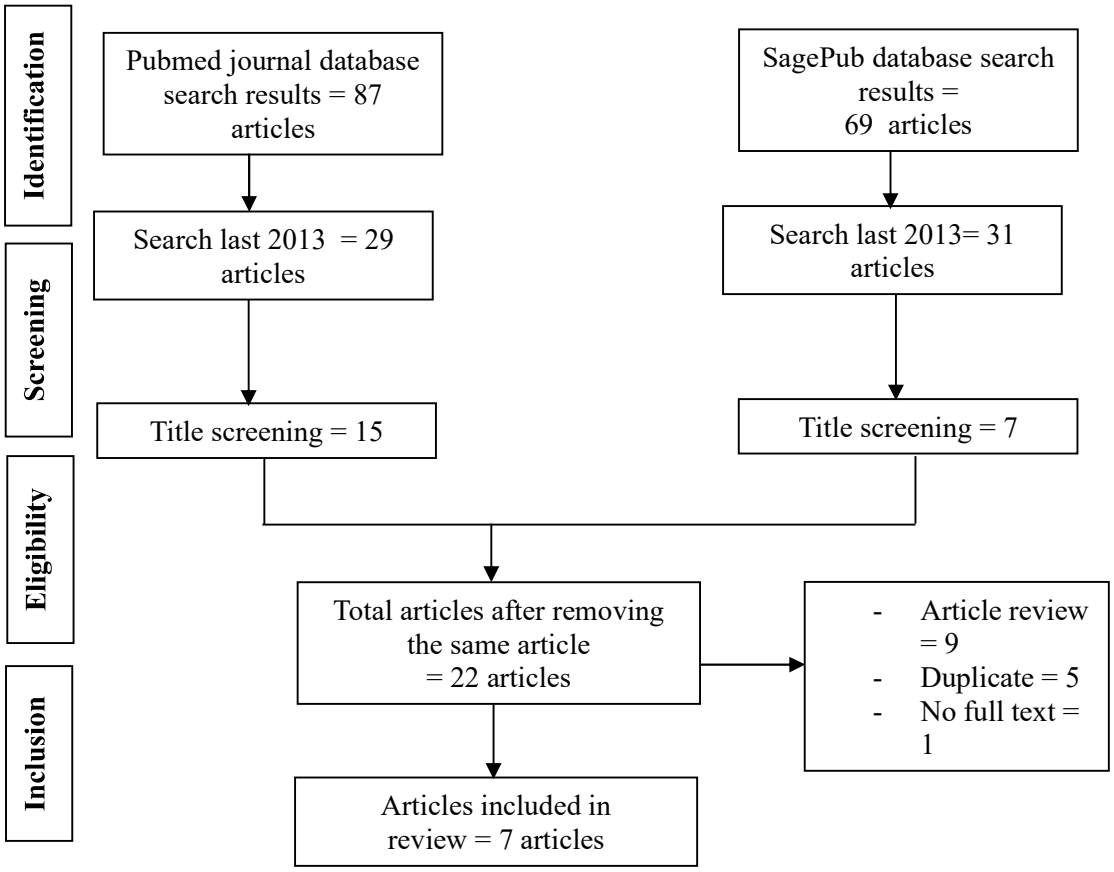

Figure 1. Article search flowchart

The researchers evaluated each paper's abstract and title for inclusion. The authors of the essay then chose germane research from the available literature. This result was the result of a thorough evaluation of multiple investigations revealing a consistent pattern. All submissions must be in English and unpublished previously. For the systematic review, only publications that met all inclusion criteria were considered. This narrows search results to only those that are pertinent to the user's search. Studies not meeting our criteria are discarded.

The investigation findings will be thoroughly analyzed. The investigation conducted for this study revealed the following: names, authors, publication dates, location, study activities, and parameters. Before choosing which publications to investigate further, each author independently analyzed the research contained in the titles and abstracts of all publications. Examining all of the articles that satisfy the review's criteria and deciding which ones to include is the next step. We will then select the articles for the review based on our findings. This criterion is used to select papers that necessitate closer examination. To simplify as much as possible the selection of works for evaluation. This section discusses the prior studies conducted and the rationale for their inclusion in the review.

RESULT

The PubMed database yielded a total of 87 articles in response to our search query, while the search conducted on SagePub resulted in 69 articles. The search conducted for the last year of 2013 resulted in a total of 29 articles found in PubMed and 31 papers found in SagePub. Ultimately, a comprehensive compilation of 22 papers was achieved, with 15 sourced from PubMed and an additional seven obtained via SagePub. We incorporated seven studies that satisfied the established criteria.

Table 1. The litelature include in this study

Author	Origin	Method	Sample Size	Result
Hakkoymaz, 2019[10]	Turkey	Cross sectional	51 patients with histologically confirmed appendicitis and 45 healthy controls	This study indicate that several biomarkers, including IMA (with a negative likelihood ratio [LR] of 0.1), CRP (with a positive LR of 7.2 and a negative LR of 0.2), NLR (with a negative LR of 0.1), and IMA/albumin ratio (with a negative LR of 0.1), hold significant diagnostic value for patients with AA.
Yardimci, 2016[11]	Turkey	Retrospective cohort study	413 consecutive patients with AA and 100 healthy controls	Both neutrophil-to-lymphocyte ratio (NLR) and mean platelet volume (MPV) have demonstrated utility in predicting the severity of acute appendicitis (AA).

Ahn, 2016[12]	Republic of Korea	Prospective cohort study	292 enrolled patients	The MESH (migration, high white blood cell count, shift to left, and heel drop test) is a straightforward clinical scoring system utilized to evaluate individuals with suspected appendicitis, with greater accuracy compared to the Alvarado score. Additional validation studies are required.
Sevinc, 2016[13]	Turkey	Retrospective cohort study	3,392 patients who underwent appendectomy in a 10-year period	Presence of at least 1 of the following findings in a patient suspected of having acute appendicitis was significantly associated with a definite diagnosis: WCC >11.900 mm3, serum bilirubin >1.0 mg/dl, NLR >3.0. In patients with acute appendicitis, serum bilirubin >1.0 mg/dl or NLR >4.8 were significantly associated with the presence of perforation. While WCC is a significant parameter for diagnosis of acute appendicitis, no significant association with perforated appendicitis was found. PLT and MPV were not useful parameters when diagnosing acute appendicitis.
Lietzen, 2016[14]	Finland	Randomized controlled trial	705 patients who had acute appendicitis on computed tomography	In clinical decision making, neither clinical findings nor laboratory markers are reliable enough to estimate the severity of the acute appendicitis accurately or to determine the presence of an appendicolith
Farooqui, 2015[15]	Denmark	Retrospective cohort study	1,008 patients were operated under suspicion of appendicitis	The utilization of blood markers in combination proved to be advantageous in the prediction of both appendicitis and perforated appendicitis. Furthermore, the inclusion of bilirubin and alanine transaminase blood levels alongside C-reactive protein and white cell count may prove to be valuable in clinical assessment.
Man, 2014[16]	Hungary	Randomized controlled trial	269 patients	The study results indicated that clinical judgment is a more dependable method for diagnosing acute appendicitis compared to the Alvarado score. However, it is worth noting that the score can still serve as a valuable diagnostic tool, particularly for less experienced medical professionals. The utilization of the novel scoring method has become more convenient.

Hakkoymaz, et al (2019)[10] showed 4% (n = 16) of all appendicitis cases were complicated, compared to 68.5% (n = 35) of non-complicated cases. A characteristic receiver operating characteristic (ROC) curve was used to assess the levels of the following in the appendicitis cases: IMA (positive LR = 3.0, negative LR = 0.1), GSH-Px (positive LR = 0.5, negative LR = 1.8), MDA (positive LR = 1.8, negative LR = 0.6), CRP (positive LR = 7.2, negative LR = 0.2), PCT (positive LR = 0.7, negative LR = 1.3), WBC (positive LR = 2.9, negative LR = 0.3), neutrophil-lymphocyte ratio (positive LR = 3.2, negative LR = 0.1), thrombocyte lymphocyte ratio (positive LR = 1.6, negative LR = 0.5), and IMA/albumin ratio (positive LR = 3.3, negative LR = 0.1). Furthermore, IMA levels in the complex instances (0.40 ± 0.05 AbsU) were substantially greater than in the non-complex cases (0.29 ± 0.04 AbsU) ($p < 0.01$).

Yardimci, et al (2016)[11] showed MPV means for the patient group were 9.3 ± 8 fL and 8.5 ± 0.9 fL for the healthy control group ($p = 0.05$). MPV was 8.8 ± 5.8 for phlegmonous appendicitis, 8.9 ± 5.8 for localized peritonitis, and 12.8 ± 9.7 for appendicitis with perforation and/or necrosis ($p=0.005$). The MPV cutoff value of 8.92 was established to distinguish AA with perforation and/or gangrene from other forms of AA. NLRs were 8.3 ± 5.6, 9.1 ± 6.2, and 10.6 ± 6.4 for patients with phlegmonous appendicitis, appendicitis with localized peritonitis, and appendicitis with perforation and/or necrosis, respectively; $p = 0.023$. To distinguish AA with perforation and/or gangrene from other varieties of AA, the NLR cutoff value was established at 7.95.

Ahn, et al (2016)[12] showed heel drop test had a higher predictive value than rebound tenderness. Variables and their points included in the new (MESH) score were pain migration (2), elevated white blood cell (WBC) >10,000/μL (3), shift to left (2), and positive heel drop test (3). The MESH score had a higher AUC than the Alvarado score (0.805 vs. 0.701). Scores of 5 and 11 were chosen as cut-off values; a MESH score ≥5 compared to an Alvarado score ≥5, and a MESH score ≥8 compared to an Alvarado score ≥7 showed better performance in diagnosing appendicitis.

Sevinc, et al (2016)[13] showed white cell count (WCC), bilirubin, and NLR were significant parameters for the diagnosis of acute appendicitis. Cut-off values were 11900/mm3 for WCC (sensitivity = 71.2%; specificity = 67.2%; odds ratio [OR] = 5.13), 1.0 mg/dl for bilirubin (sensitivity = 19.1%; specificity = 92.4%; OR = 2.96), and 3.0 for NLR (sensitivity = 81.2%; specificity = 53.1%; OR = 4.27). Serum bilirubin and NLR were independent variables for the diagnosis of perforated appendicitis. Cut-off values were 1.0 mg/dl for bilirubin (sensitivity = 78.4%; specificity = 41.7%; OR = 2.6) and 4.8 for NLR (sensitivity = 81.2%; specificity = 53.1%; OR = 2.6).

Lietzen, et al (2016)[14] showed uncomplicated acute appendicitis and perforation and / or abscess patients had significantly greater C-reactive protein levels (mean 122 and 47, respectively, P < .001) and longer duration of symptoms than uncomplicated acute appendicitis patients; 81% of uncomplicated acute appendicitis and perforation and / or abscess patients and 38% of uncomplicated acute appendicitis patients had symptoms >24 hours before admission (P <0.001). In receiver operating characteristic analysis, C-reactive protein and temperature were clinically significant only when compared to uncomplicated acute appendicitis and perforation and/or abscess (AUC >0.7), but no optimal cutoff points were found.

Farooqui, et al (2015)[15] showed a lot more white blood cells, bilirubin, CRP, and ALT in the blood of people with acute appendicitis than of people who did not have appendicitis. There were a lot more WBC, bilirubin, and CRP in people with perforated appendicitis than in people without ruptured appendicitis. The best way to tell the difference between acute appendicitis and other conditions was to use a linear regression model that combined bilirubin, ALT, and white blood cell count. These tests—a linear regression model with WBCC, bilirubin, and CRP amounts as variables—were the most accurate at telling the difference between appendicitis that has perforated and one that has not.

Man, et al (2014)[16] showed number of negative appendectomies was 12 (9.16%) in patients were treated on the basis of their Alvarado score versus 5 (3.6%) patients underwent treatment based on clinical judgment (p = 0.063). The clinical judgment had better specificity and sensitivity than the Alvarado score. For that reason, the specificity of the Alvarado score was refined using statistical methods, with weighting of certain clinical data and inclusion of new ones (e.g., ultrasound investigation). Consequently, the area under the curve by receiver operating characteristic analysis gradually increased, and the Alvarado score became more accurate.

DISCUSSION

Acute appendicitis remains a commonly seen etiology of acute abdomen, with appendectomy being regarded as the preferred approach for managing this condition. Abdominal discomfort arises as a result of the contraction of the appendix, distension of the lumen of the appendix, or traction on the inflamed appendix wall. Initially, individuals may have a sensation of pain that is characterized by a vague, dull, and intermittent nature. This type of pain is classified as visceral pain and is localized in the epigastric region or in proximity to the umbilicus.[17]

The reason for this is because the appendix and small intestine share the same innervation. Following a duration of many hours, typically ranging from 4 to 6 hours, the pain relocates and endures in the lower right region of the abdomen, specifically at McBurney's point. When the duration of inflammation exceeds six hours, it results in the stimulation of the parietal peritoneum, leading to intensified and localized pain during activities such as coughing or walking. In addition to the fundamental symptoms, appendicitis can give rise to a range of other manifestations.[18]

These symptoms vary on where the appendix inflames. The following symptoms appear: Retroperitoneal retrocecal appendixes are shielded by the cecum and do not cause lower right abdominal pain or peritoneal stimulation. The stomach hurts on the right when walking, breathing hard, coughing, or straining. If the appendix is near or attached to the rectum, symptoms and stimulation of the sigmoid or rectum will increase peristalsis, making rectum emptying more rapid and repeated (diarrhea); if it is near or attached to the bladder, stimulation of the walls can increase urinary frequency.[19,20]

Visceral stimulation by the vagus nerve causes nausea and vomiting in the beginning. After pain, nausea and vomiting appear hours later. Vomiting occurs in 75% of patients, however most vomit once or twice. The pain can cause anorexia many hours later. Almost all acute appendicitis patients have anorexia; if not, the diagnosis should be questioned. Some acute appendicitis patients have diarrhea and constipation before pain. This frequently happens at the rectal-stimulating pelvic appendix. If the fever is higher than 37.5-38.5°C, a perforation is suspected.[19,20]

Man, et al (2014)[16] showed 12 (9.16%) patients who were treated based on their Alvarado score had negative appendectomies, compared to 5 (3.6%) patients who were treated based on clinical judgment (p = 0.063). The specificity and sensitivity of the clinical judgment were superior to those of the Alvarado score. Due to this, the specificity of the Alvarado score was improved through the use of statistical methods, including the weighting of certain clinical data and the addition of new ones (such as an ultrasound investigation).

Many research have examined the predictive value of inflammatory markers for AA diagnosis.[10,15] Most common are CBC parameters (WBC, NLR, PLT, MPV, PLR), CRP, and PCT. Studies on MPV levels in appendicitis patients yielded conflicting results. Study reported mean MPV values for appendicitis patients and the control group were 9.3 ± 8 fL and 8.5 ± 0.9 fL (p = 0.0005), respectively, and authors emphasized that elevated MPV values could aid in determining the severity of the disease during a clinical diagnosis.[11] Another study showed that MPV was not a useful parameter in the diagnosis of AA.[13] Lietzen, et al[14] showed CRP and temperature were clinically significant only when compared to uncomplicated acute appendicitis and perforation and/or abscess (AUC >0.7), but no optimal cutoff points were found.

Acute appendicitis elicits an inflammatory reaction. The existing body of literature has demonstrated that there is a notable elevation in white blood cell count during an inflammatory reaction, namely in cases where a bacterial infection has occurred in the appendix.[21] Previous research has indicated that there is a notable elevation in the levels of bilirubin and

C-reactive protein (CRP) at the initial detection of acute appendicitis. The etiology of sepsis-associated hyperbilirubinemia can be elucidated by the concurrent occurrence of heightened hemolysis and impaired hepatic bilirubin uptake and excretion.[22,23]

Previous research has demonstrated that bacterial endotoxins, such as those produced by Escherichia coli bacteria, have been found to reduce hepatic bile secretion, hence leading to the development of intrahepatic cholestasis and sinusoidal damage. The hepatocyte's absorption of bile salts was observed to decrease in animal models when exposed to endotoxins. The findings of our study indicate a statistically significant elevation in ALAT levels, particularly in those diagnosed with appendicitis. This phenomenon may arise due to an inflammatory response inside the hepatocytes or as a consequence of sinusoidal injury.[19,20]

CONCLUSION

Study shows that a shift in pain from the epigastrium to the Mc Burney point and heel drop test is a sign of appendicitis based on physical examination. Examination of white blood cells and CRP can be other reliable markers to confirm acute appendicitis.

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