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Review Article

Unveiling the Role of Inflammatory Mediators and Gut Microbiome in Appendicitis: Types and Applications in Clinical Scoring

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Appendicitis is a common medical condition that affects millions of people worldwide. It is characterized by inflammation of the appendix. The exact mechanisms that trigger the inflammatory response in appendicitis are not well understood, but it is known that inflammatory mediators play a crucial role in the development and progression of the disease. In this review, we provide a comprehensive overview of the current understanding of the role of inflammatory mediators in the pathogenesis of appendicitis. This review article examines the various types of inflammatory mediators involved, including cytokines, chemokines, and prostaglandins, and discusses their interactions with other cells and molecules in the inflammatory cascade. Our review highlights the complex interplay between inflammatory mediators in the development of appendicitis and their potential implications for diagnosis and treatment of the disease. We discuss the potential for targeted therapies aimed at reducing the production or activity of specific inflammatory mediators, as well as the potential for new diagnostic approaches based on the detection of specific mediators in the blood or other bodily fluids. At the end, the role of inflammatory mediators in appendicitis is an active area of research, and continued investigation is necessary to fully elucidate the mechanisms involved. However, the growing understanding of the complex interactions between these molecules offers new opportunities for the development of targeted therapies and diagnostic tools for this common and potentially serious condition

1. Introduction

Acute appendicitis (AA) is a common surgical emergency that requires prompt diagnosis and intervention. It is the most common cause of acute abdominal pain, accounting for approximately 7% of emergency department visits in the United States alone [1]. Despite advancements in medical technology, diagnosing acute appendicitis remains difficult due to its nonspecific symptoms and varying clinical presentations. Additionally, controversies surrounding the optimal management of AA persist across different settings and practice patterns worldwide [2]. Appendicitis is caused by inflammation of the appendix. The exact mechanism of inflammation remains unclear, but it is thought to involve obstruction of the appendiceal lumen by fecaliths, lymphoid hyperplasia, or other factors, which leads to increased intraluminal pressure and compromised blood flow [3]. The diagnosis of acute appendicitis can be challenging, as the clinical presentation is often nonspecific and can mimic other acute abdominal pathologies [4]. In some patients, relying solely on clinical scores such as the Alvarado score, AIR score (appendicitis inflammatory response score), and

the new adult appendicitis score can effectively rule out acute appendicitis by accurately identifying low-risk patients. This approach can reduce the need for imaging and the negative appendectomy rates in such patients [2]. The classic presentation of appendicitis includes periumbilical pain that migrates to the right lower quadrant, accompanied by anorexia, nausea, vomiting, and fever. However, not all patients present with the classic symptoms, and some may have atypical presentations, especially in special populations, such as elderly or immunocompromised patients [5]. Several imaging modalities are used to aid in the diagnosis of acute appendicitis, including ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI) [6]. In addition, various laboratory markers, including C-reactive protein (CRP), procalcitonin (PCT), and interleukin-6 (IL-6), have been investigated as diagnostic aids [7].

2. Pathogenesis of Acute Appendicitis

The pathogenesis of acute appendicitis involves a complex interplay of inflammatory mediators, including proinflammatory cytokines, chemokines, and adhesion molecules, which lead to the recruitment and activation of immune cells, such as neutrophils and macrophages [8]. These inflammatory mediators are thought to be involved in the development of the clinical symptoms of appendicitis, as well as the associated complications, such as perforation and abscess formation [8]. Many studies have identified several potential biomarkers for the diagnosis and prediction of the severity of appendicitis, including IL-6, TNF-α, and CRP [9].

3. Biomarkers

Several potential biomarkers for the diagnosis and prediction of the severity of appendicitis have been identified in recent studies. These include the following:

(1) *C-reactive protein (CRP)*: a protein produced by the liver in response to inflammation. After an acute inflammatory stimulus, such as an infection or injury, the plasma levels of C-reactive protein (CRP) can rapidly and significantly increase in humans, by as much as 1000-fold or more. This rise primarily occurs due to the heightened synthesis of CRP by hepatocytes [10]. Elevated CRP levels have been associated with the diagnosis of acute appendicitis and can also be used to monitor response to treatment [11]. Also, C-reactive protein (CRP) are significant complementary inflammatory markers, and their simultaneous detection can safely reduce unnecessary antibiotic prescriptions in certain infectious syndromes [12]

(2) *Procalcitonin (PCT)*: a hormone that is released in response to bacterial infections. Elevated PCT levels have been shown to be a useful diagnostic tool for acute appendicitis and can also predict the severity of the disease [13, 14]

(3) *Interleukin-6 (IL-6)*: a proinflammatory cytokine that is involved in the pathogenesis of acute appendicitis. Elevated IL-6 levels have been associated with the severity of the disease and can be used to monitor response to treatment [15]

(4) *Tumor necrosis factor-alpha (TNF-α)*: another proinflammatory cytokine that is involved in the pathogenesis of acute appendicitis. Elevated TNF-α levels have been associated with the severity of the disease and can be used to predict the risk of complications [16]

4. The Role of Gut Microbiome

The gut microbiota, which refers to the trillions of microorganisms that live in the human gastrointestinal tract [17], mainly includes bacteria, fungi, protozoa, archaea, and viruses [18], among which bacteria are dominant that have been implicated in various aspects of human health and disease [19], including the development of appendicitis [20]. Appendicitis is an inflammatory condition of the appendix, and the exact mechanism by which the gut microbiota may contribute to appendicitis is not fully understood [8], but several theories have been proposed.

One theory suggests that an imbalance or dysbiosis in the gut microbiota may trigger an inflammatory response in the appendix, leading to appendicitis [20]. Studies have shown that alterations in the composition and diversity of the gut microbiota, such as a decrease in beneficial bacteria and an increase in harmful bacteria, may be associated with an increased risk of appendicitis. For example, a decrease in the abundance of Bifidobacterium and Lactobacillus, which are known to have anti-inflammatory properties, and an increase in Enterobacteriaceae, which are known to produce inflammatory molecules, have been observed in the gut microbiota of patients with appendicitis [21].

Another theory suggests that the gut microbiota may influence the development of appendicitis through its role in regulating the immune system. The gut microbiota plays a crucial role in training and modulating the immune system, and alterations in the gut microbiota composition may result in an aberrant immune response in the appendix, leading to inflammation and appendicitis [22]. For example, certain bacteria in the gut microbiota have been shown to stimulate the production of immune cells and cytokines that can contribute to inflammation and tissue damage in the appendix [23].

Furthermore, recent research has also suggested that the gut microbiota may play a role in the formation of appendiceal biofilms, which are communities of microorganisms that adhere to the inner lining of the appendix. Biofilms have been implicated in the pathogenesis of various inflammatory conditions, including appendicitis. Studies have shown that certain bacteria in the gut microbiota have the ability to form biofilms in the appendix, which can trigger an inflammatory response and contribute to the development of appendicitis [24].

It is worth noting that the exact mechanism by which the gut microbiota may contribute to appendicitis is still an area

of ongoing research, and more studies are needed to fully understand the complex interactions between the gut microbiota and appendicitis.

The role of the gut microbiome in the pathogenesis of appendicitis has also been investigated, with evidence suggesting that alterations in the composition of the gut microbiota may play a role in the development of the disease [25]. The gut microbiome is the collection of microorganisms, including bacteria, viruses, fungi, and other microbes, that reside in the gastrointestinal tract. These microbes play a crucial role in human health by aiding in digestion, producing vitamins and other essential compounds, and regulating the immune system. The gut microbiome has also been implicated in various diseases, including inflammatory bowel disease, obesity, and even mental health conditions such as depression and anxiety [26]. Alterations in the composition and function of the gut microbiome have been associated with the development of certain diseases, including appendicitis [27]. Recent research has shown that the gut microbiota may play a role in the pathogenesis of appendicitis, possibly by affecting the immune response and inflammatory processes involved in the disease [28]. The use of probiotics as a potential treatment option for appendicitis has been explored, with some studies reporting favorable outcomes [29].

5. Effects of Probiotics

Probiotics are live microorganisms, usually bacteria or yeast, that are consumed to provide health benefits. They are commonly found in fermented foods such as yogurt, kefir, sauerkraut, and kimchi. Probiotics are believed to improve gut health by restoring or maintaining the natural balance of microorganisms in the gut. Some of the reported benefits of probiotics include improved digestion, stronger immune system, and reduced risk of certain diseases. Probiotics are also available in supplement form, often in the form of capsules, tablets, or powders [30] Probiotics are microorganisms that may be of net benefit to humans when consumed. The administration of sufficient doses of probiotics, which are defined as live microorganisms, primarily modifies the balance of the intestinal microflora of the host [31]. Their use has been studied in various gastrointestinal conditions, including inflammatory bowel disease, irritable bowel syndrome, and antibiotic-associated diarrhea [32, 33]. Probiotic effects are mediated by various and sometimes strain-specific mechanisms, including the strengthening of gut barrier structure and function; interactions with immune system components; production of short-chain fatty acids in the gut; and other direct and indirect influences on the stability, expression, and composition of host microbes [34].

6. Inflammatory Cascade and Cytokines, Chemokines, and Prostaglandins

Inflammatory cytokines (Table 1) are proteins produced by cells of the immune system in response to inflammation or infection, and they play a crucial role in regulating the immune response; almost every cell produces cytokines that are secreted and weighed less than 40 kDa. These proteins play a crucial role in regulating and influencing immune response.

Cytokines are involved in appendicitis [35]. Activation of immune cells and the subsequent production and release of additional cytokines can occur as a result of the release of pro-inflammatory cytokines [36]. Recent research indicates that a simultaneous release of pro- and anti-inflammatory cytokines is mandatory in any immune response [37]. These cytokines are known as interleukins, chemokines, or growth factors [38]. Some cytokines can be redundant as they may have the same effect, but they can also act synergistically. Additionally, these cytokines have the potential to initiate signaling cascades, which means that even small amounts of these proteins can have significant consequences [39].

Note that this is some of the cytokines, and there are many other cytokines and chemokines that are involved in inflammation and immune responses. The functions and roles of cytokines can be complex and context-dependent, and their regulation is tightly controlled in the immune system.

Cytokines are a broad category of small proteins and glycoproteins that are produced by various cells, including immune cells, in response to an infection or injury. They act as chemical messengers that mediate communication between cells, modulating the immune response and initiating an inflammatory cascade. Cytokines can be proinflammatory, such as interleukin-1 (IL-1), tumor necrosis factor-alpha (TNF-alpha), and interleukin-6 (IL-6), or anti-inflammatory, such as interleukin-10 (IL-10) and transforming growth factor-beta (TGF-beta) [48].

Chemokines are a family of small cytokines that induce chemotaxis, the movement of cells towards a chemical signal. They are involved in recruiting immune cells to sites of infection or injury. Some examples of chemokines include interleukin-8 (IL-8), monocyte chemoattractant protein-1 (MCP-1), and regulated on activation, normal T cell expressed and secreted (RANTES) [49].

Prostaglandins are a group of lipid compounds synthesized by various cells, including immune cells, in response to inflammation. They are involved in the regulation of numerous physiological processes, including fever, pain, and inflammation. Prostaglandins are synthesized by the cyclooxygenase (COX) pathway, with COX-2 being the primary isoform involved in inflammation [50].

These molecules interact with other cells and molecules in the inflammatory cascade. For example, proinflammatory cytokines such as IL-1 and TNF-alpha can activate endothelial cells to express adhesion molecules, allowing immune cells to adhere and migrate into the tissue. Chemokines act as chemoattractants for immune cells, guiding them to the site of inflammation. Prostaglandins are involved in the production of pain and fever and can also stimulate the production of cytokines and chemokines [51]. In appendicitis, proinflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) are elevated in serum and peritoneal fluid, and their levels correlate with the severity of inflammation [51, 52]. A recent meta-analysis found that IL-6 had a pooled sensitivity of 85% and specificity of 82% for diagnosing acute appendicitis [53]. Chemokines such as interleukin-8 (IL-8) and monocyte

Table 1: Some of cytokines that are involved in appendicitis [40–47].

Cytokines	Origin	Major finding	Reference
Interleukin-6 (IL-6)	Immune cells, including macrophages, T cells, and fibroblasts	Involved in the regulation of immune responses, inflammation, and acute-phase reactions	[40]
Interleukin-10 (IL-10)	Various immune cells, including regulatory T cells, macrophages, and dendritic cells	An anti-inflammatory cytokine plays a role in dampening inflammation and immune responses, and it has immunosuppressive properties	[41, 42]
Interleukin-8 (IL-8)	Produced by various immune and nonimmune cells in response to inflammation	Proinflammatory chemokine plays a role in recruiting immune cells, such as neutrophils, to the site of inflammation	[43]
Interleukin-17 (IL-17)	Proinflammatory cytokine that is produced by a subset of T cells known as Th17 cells. Act as a key cytokine that links T cell activation to neutrophil mobilization and activation	Involved in inflammation and immune responses, particularly in defense against fungal and bacterial infections	[44]
Interleukin-12 (IL-12)	Cytokine that is produced by antigen-presenting cells, such as macrophages and dendritic cells	Is involved in promoting inflammation and regulating immune responses, particularly Th1 responses.	[45]
Tumor necrosis factor-alpha (TNF-α)	Proinflammatory cytokine that is produced primarily by macrophages	Plays a central role in inflammation, immune response regulation, and apoptosis and as a pathological component of autoimmune diseases	[46]
Interferon-gamma (IFN-γ)	A proinflammatory cytokine that is produced by several immune cells, including T cells and natural killer (NK) cells	Plays a role in immune responses against viral and intracellular bacterial infections	[47]

chemoattractant protein-1 (MCP-1) are increased in serum and peritoneal fluid [54]. A study by Sack et al. found that the combination of IL-8 and MCP-1 had a sensitivity of 85% and specificity of 92% for diagnosing acute appendicitis [55]. In appendicitis, prostaglandin E2 (PGE2) is increased in serum and peritoneal fluid, and its levels correlate with the severity of inflammation [56]. A study found that PGE2 had a sensitivity of 83% and specificity of 93% for diagnosing acute appendicitis [57].

7. Changes in the Blood Complete Blood Count (CBC) and White Blood Cell Count (WBC)

The complete blood count (CBC) is a widely utilized laboratory test in the diagnosis of acute appendicitis (AA). Numerous studies have investigated the significance of various blood components such as white blood cell (WBC) count, neutrophil-to-lymphocyte ratio (NLR), mean platelet volume (MPV), platelet distribution width (PDW), red cell distribution width (RDW), platelet count (PLT), lymphocyte (L) count, neutrophil (N) count, C-reactive protein (CRP) level, and the ratio of lymphocyte to C-reactive protein (LCR) in the diagnosis of AA [58–60]. The complete blood count (CBC) and white blood cell count (WBC) are commonly used to help diagnose acute appendicitis. Recent studies have further explored the role of changes in these markers in the diagnosis and management of appendicitis [61]. Complete blood count parameter evaluation with the clinical findings revealed that NLR is an important parameter that may help the diagnosis of acute appendicitis with an appendix diameter of >6 mm [58]. Also, leukocyte count and C-reactive protein along with raised ESR are the frequently used inflammatory markers for diagnosis of AA [14].

Another study published in 2021 in the Journal of Investigative Surgery looked at the role of red cell distribution width (RDW) in diagnosing AA. The study found that elevated RDW levels were associated with a higher likelihood of complicated appendicitis, as well as an increased risk of postoperative complications. The authors concluded that measuring RDW levels could help clinicians to identify patients who are at higher risk of complications and may require more aggressive treatment [62]. The NLR (neutrophil-to-lymphocyte ratio) can predict both the diagnosis and severity of appendicitis. The value of mean platelet volume (MPV) and platelet distribution width (PDW) levels in patients with acute appendicitis should be supported by new studies with larger patient groups. Therefore, in WBC, neutrophil levels are enough as they can guide the clinician about the presence of inflammation [63].This can have implications for prioritizing cases for surgery, monitoring patients treated conservatively, and patients who do not typically undergo CT scans, such as pregnant or pediatric patients [64].

8. Implications of Inflammatory Mediators for Diagnosis and Treatment of Appendicitis

In appendicitis, the interplay of inflammatory mediators plays a crucial role in the disease's development. Understanding these mediators and their implications for diagnosis and treatment is essential, and prioritizing specific markers depends on their relevance in the pathogenesis of appendicitis and their diagnostic or therapeutic potential;

commonly studied markers include C-reactive protein (CRP), white blood cell count (WBC), interleukin-6 (IL-6), and procalcitonin.

CRP and WBC are widely used in clinical practice for diagnosing appendicitis. Elevated levels of these markers indicate inflammation and can aid in decision-making for surgical intervention. The best performing single blood tests for ruling out pediatric appendicitis are WCC or absolute neutrophil count (ANC), with accuracy improved combining WCC and CRP. These tests could be used at the point of care in combination with clinical prediction rules [65]. However, their specificity and sensitivity may vary, necessitating further investigation.

IL-6 is a proinflammatory cytokine that plays a significant role in the pathophysiology of appendicitis. Targeting IL-6 or its receptors may hold promise for therapeutic interventions. WBC, IL-6, and hsCRP are useful laboratory parameters that can complete clinical examinations in the diagnosis of appendicitis in pediatric patients and the identification of complications that may develop postoperatively [66].

Procalcitonin, a precursor of calcitonin, has emerged as a potential marker for differentiating between uncomplicated and complicated appendicitis. The usefulness of PCT in aiding the diagnosis of AA depends on the severity of appendicitis. Patients who experience complicated appendicitis (CAA) such as perforation, gangrene, or necrosis have a significantly raised PCT level ($p < 0.05$) compared to those with uncomplicated appendicitis (UAA) [67].

Implementing targeted therapies for appendicitis in clinical settings requires careful consideration. Clinical trials are needed to evaluate the safety, efficacy, and long-term outcomes of specific therapies. Factors such as patient selection, timing of intervention, and optimal dosing need to be addressed. Understanding the complex interplay between inflammatory mediators in appendicitis is vital for improving diagnosis and treatment. Prioritizing specific markers, such as CRP, WBC, IL-6, and procalcitonin, can guide targeted therapies.

9. Emerging Diagnostic Approaches for Acute Appendicitis: Current State, Feasibility, and Cost-Effectiveness

The development of new diagnostic approaches for acute appendicitis based on the detection of specific mediators in blood or other bodily fluids presents exciting possibilities. This comprehensive analysis examines the current state of these diagnostic approaches, their feasibility in clinical settings, and their cost-effectiveness compared to traditional diagnostic methods.

9.1. Diagnostic Approaches Based on Specific Mediators

9.1.1. C-Reactive Protein (CRP). Elevated levels of CRP indicate inflammation and have shown promise as a diagnostic marker for appendicitis. However, its standalone diagnostic accuracy may vary due to sensitivity and specificity limitations [65].

9.1.2. White Blood Cell Count (WBC). Increased WBC count is a common indicator of inflammation but lacks specificity and can be influenced by various factors.

9.1.3. Cytokines and Chemokines. Specific cytokines and chemokines, such as interleukin-6 (IL-6), IL-8, and tumor necrosis factor-alpha (TNF-α), have shown potential as diagnostic markers for appendicitis [66]. Elevated levels of these mediators have been associated with inflammation in appendicitis. However, further studies are needed to establish their diagnostic accuracy and cutoff values.

9.1.4. MicroRNAs. MicroRNAs are small RNA molecules involved in the regulation of gene expression. Some studies have identified specific microRNAs, such as miR-29c-3p that was reported to increase in the acute period of AA [68], as potential biomarkers for appendicitis. These microRNAs can be detected in blood or other bodily fluids, and their altered expression patterns have shown promise in distinguishing appendicitis from other conditions. However, additional research is required to validate their diagnostic accuracy and clinical utility.

9.1.5. Procalcitonin (PCT). PCT is a promising biomarker for distinguishing between uncomplicated and complicated appendicitis. Elevated PCT levels can aid in early diagnosis and risk stratification, potentially guiding treatment decisions [67].

9.1.6. Urine Markers. Urinary biomarkers, such as urine interleukin-6 (IL-6) and urine neutrophil gelatinase-associated lipocalin (NGAL), have shown potential in diagnosing appendicitis [67]. These markers, when combined with clinical assessment, may improve diagnostic accuracy, but further validation is required.

9.1.7. Peritoneal Fluid Analysis. Peritoneal fluid analysis during laparoscopy can provide valuable information. Elevated levels of inflammatory markers, such as lactate, in peritoneal fluid may suggest appendicitis and guide the surgeon's decision-making. So, lactate estimation is sensitive, noninvasive, and time and cost-effective marker for acute abdominal disorders and could be useful tool for the surgeon in decisional process [69].

9.1.8. Imaging Techniques. Advanced imaging techniques, including ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI), continue to play a significant role in diagnosing appendicitis. These modalities provide detailed anatomical information and help identify inflamed or enlarged appendices. While these imaging approaches do not directly detect inflammatory mediators, they remain important tools in the diagnostic process:

(a) *Ultrasound*: ultrasonography is commonly used in pediatric populations due to its noninvasive nature. It provides visualization of the appendix and surrounding structures, but operator dependence and limitations in obese patients may affect accuracy

(b) *Computed tomography (CT)*: CT scan offers high sensitivity and specificity in diagnosing appendicitis. However, concerns about radiation exposure and cost-effectiveness have prompted efforts to minimize unnecessary CT scans

(c) *Magnetic resonance imaging (MRI)*: MRI shows promise as a radiation-free alternative to CT, especially in pregnant women and young patients. Although it has limitations in terms of availability and cost, it provides detailed anatomical information

Implementing these diagnostic approaches in clinical settings requires careful consideration. Factors influencing feasibility include availability of laboratory tests, cost, turnaround time, and ease of use. Some diagnostic tests, such as CRP and WBC count, are already routinely available in most healthcare settings. Others, such as specific urine or peritoneal fluid markers, may require further validation and standardization. While these novel diagnostic approaches hold promise for improving appendicitis diagnosis, their cost-effectiveness compared to traditional methods is still an area of ongoing investigation. The potential reduction in unnecessary surgeries and improved patient outcomes may offset the costs associated with additional testing. However, comprehensive cost-effectiveness analyses and studies comparing the diagnostic accuracy and outcomes of these approaches to traditional methods are necessary before widespread adoption.

9.2. Feasibility of Implementing Diagnostic Approaches

9.2.1. Laboratory Testing. Diagnostic approaches based on specific mediators often require laboratory testing, which may be available in hospital settings. Challenges such as turnaround time, sample collection, and cost need to be considered for efficient implementation.

9.2.2. Point-of-Care Testing (POCT). Some diagnostic tests can be performed at the bedside or in emergency departments, providing rapid results and facilitating timely decision-making. POCT approaches for CRP and PCT have shown promise, but further validation and standardization are necessary.

9.3. Cost-Effectiveness Considerations

9.3.1. Reduced Imaging Utilization. Accurate diagnostic approaches based on specific mediators may reduce the need for imaging studies, such as computed tomography (CT), leading to potential cost savings and minimizing radiation exposure.

9.3.2. Improved Resource Allocation. Implementing reliable diagnostic approaches can help streamline patient management, enabling appropriate allocation of healthcare resources and reducing unnecessary hospital admissions.

9.3.3. Cost of Testing. The cost-effectiveness of these diagnostic approaches depends on factors such as test availability, affordability, and reimbursement policies. Economic evaluations comparing the costs of specific mediator-based testing versus traditional methods are needed.

10. Clinical Scoring Systems (CSSs) for Diagnosis of Acute Appendicitis

Several scoring modalities have been developed to help clinicians make an accurate diagnosis. These include the following.

10.1. Alvarado Score (Figure 1). This is a clinical scoring system that includes eight clinical parameters, such as migration of pain, rebound tenderness, and elevated white blood cell count, to help differentiate between patients with and without appendicitis [70]. The Alvarado score is a clinical scoring system that combines clinical and laboratory parameters to diagnose appendicitis.

The original score included migration of pain, anorexia, nausea/vomiting, fever, right lower quadrant tenderness, rebound tenderness, leukocytosis, and left shift [70]. The Alvarado score lacks specificity when it comes to diagnosing acute appendicitis in adults and may not be reliable in differentiating between complicated and uncomplicated cases in elderly patients. Furthermore, its sensitivity is reduced in patients with HIV [2]. Several modifications of the score have been proposed, including the RIPASA score, which includes additional parameters such as C-reactive protein (CRP) and imaging findings [71]. A meta-analysis by Thirumallai et al. found that the Alvarado score had a sensitivity of 77% and specificity of 81% for diagnosing acute appendicitis [72]. Currently, the AIR score and AAS score exhibit the highest discriminating power as clinical prediction scores for adults with suspected acute appendicitis. They have shown to decrease negative appendectomy rates in low-risk groups and lower the need for imaging studies and hospital admissions in both low- and intermediate-risk groups [2]. However, scoring techniques and imaging techniques have only slightly decreased the percentage of negative appendectomies. This has generated a continued interest among the investigators and authors to focus on inflammatory process and search for better inflammatory markers in AA [14].

10.2. Appendicitis Inflammatory Response (AIR) Score (Table 2). This scoring system uses six parameters, including white blood cell count, C-reactive protein level, and body temperature, to diagnose acute appendicitis and predict its severity [73].

The scoring system may vary depending on the specific hospital or medical center that is using it, but generally, higher scores indicate a higher likelihood of appendicitis [74].

10.3. Pediatric Appendicitis Score (PAS) (Table 3). This score is used specifically for pediatric patients and includes clinical features, laboratory results, and imaging findings to determine the likelihood of acute appendicitis [75].

The PAS assigns points to different clinical criteria, such as right lower quadrant pain, vomiting, fever, rebound tenderness, migration of pain to the right lower quadrant, and elevated white blood cell count. The total score is calculated

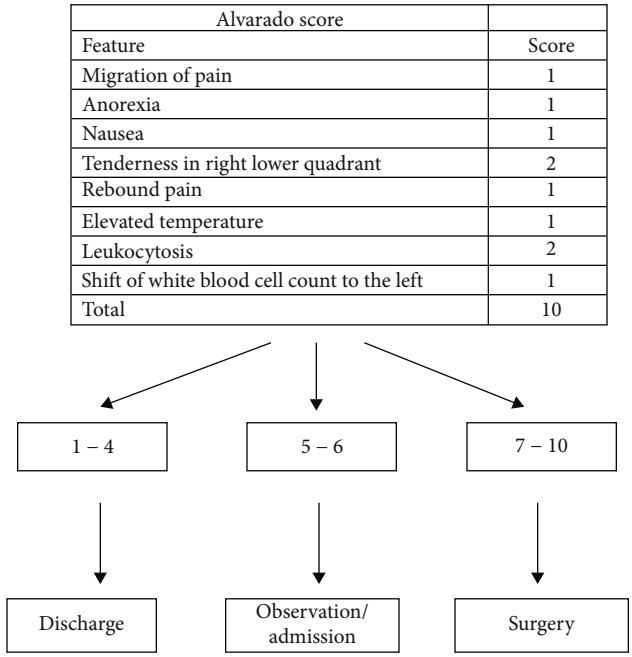

Figure 1: Probability of appendicitis by the Alvarado score, risk strata, and subsequent clinical management strategy [70].

Table 2: Appendicitis inflammatory response score [73].

Symptoms, signs, and laboratory tests	Score
Vomiting	1
Pain in the right iliac fossa	1
Rebound tenderness and rigidity in the right iliac fossa	
Mild	1
Moderate	2
Severe	3
Temperature > 38.5°C	1
C-reactive protein (CRP)	
10_14	1
≥50	2
White blood cell count (WBC) ($\times 10^9$)	
≥10 and <15	1
≥15	2
Neutrophil count %	
≥70 and <85	1

by adding up the points for each criterion, with a higher score indicating a higher probability of appendicitis [76].

PAS had a high accuracy in diagnosing appendicitis and distinguishing it from nonspecific abdominal pain (NSAP) and other types of abdominal pain not related to appendicitis. Additionally, the PAS system was found to significantly reduce cases of false negative appendicitis diagnoses [77].

Table 3: The pediatric appendicitis score [78].

Pediatric appendicitis score (PAS) Low risk < 4; high risk ≥ 7	
Nausea/vomiting	1
Anorexia	1
Migration of pain to RLQ	1
Fever	1
Cough/percussion/hopping tenderness	2
RLQ tenderness	2
Leukocytosis (WBC > 10,000)	1
Neutrophilia (ANC > 7,500)	1
Low-risk PAS < 3; high-risk PAS > 7; indeterminate risk PAS 4-6	

10.4. Adult Appendicitis Score (AAS). This scoring system is similar to the PAS but is designed for use in adults. It includes clinical parameters, laboratory findings, and imaging results to help diagnose acute appendicitis [79].

The AAS assigns points to different clinical criteria, such as right lower quadrant pain, migration of pain to the right lower quadrant, rebound tenderness, fever, anorexia, nausea/vomiting, and elevated white blood cell count. The total score is calculated by adding up the points for each criterion, with a higher score indicating a higher probability of appendicitis [80].

Adult appendicitis score (AAS) example is shown as follows:

(1) Migration of pain to the right lower quadrant: +1 point

(2) Anorexia: +1 point

(3) Nausea or vomiting: +1 point

(4) Tenderness in the right lower quadrant: +1 point

(5) Rebound tenderness in the right lower quadrant: +2 points

(6) Elevated body temperature (>37.3°C or 99.1°F): +1 point

(7) Leukocytosis (>10,000/mm^3): +1 point

(8) Left shift on differential white blood cell count: +1 point

(9) Absence of cough or vomiting before pain onset: +1 point

(10) Pain in the right lower quadrant with coughing or percussion: +2 points

10.4.1. Calculation. The total points obtained from the individual items are added together to obtain the AAS score. The score can range from 0 to 12, with higher scores indicating a higher probability of appendicitis [80].

10.5. Eskelinen Score. This scoring system combines clinical, laboratory, and imaging parameters to help diagnose acute appendicitis and predict its severity [81].

The Eskelinen scoring system, also known as the Alvarado-Eskelinen scoring system or the modified Alvarado score, is a clinical scoring system used for assessing the probability of acute appendicitis in patients presenting with abdominal pain. It is a modification of the original Alvarado score [81].

The Eskelinen scoring system includes the following parameters; each assigned a certain point value:

(1) Right lower quadrant tenderness: 1 point

(2) Migration of pain to the right lower quadrant: 1 point

(3) Nausea or vomiting: 1 point

(4) Anorexia: 1 point

(5) Leukocyte count > 10,000/mm^3: 2 points

(6) Neutrophil percentage > 75%: 2 points

(7) Shift to the left (increase in immature neutrophils): 1 point

10.5.1. Calculation. The total points obtained from the individual parameters are added together to obtain the Eskelinen score. The score can range from 0 to 9, with higher scores indicating a higher probability of appendicitis.

10.6. The Karaman Score. The Karaman score is a clinical scoring system used for predicting the likelihood of acute appendicitis in patients presenting with abdominal pain. It was developed by Karaman et al. and published in the Turkish Journal of Surgery in 2018 [82]. The Karaman score includes various clinical parameters, and each parameter is assigned a certain point value. The total points obtained from the individual parameters are then used to calculate the overall Karaman score, which can help in determining the probability of appendicitis [82].

The Karaman score includes the following parameters with their associated point values (as reported in the original publication):

(1) Pain migration to the right lower quadrant: +2 points

(2) Nausea or vomiting: +1 point

(3) Anorexia: +1 point

(4) Rebound tenderness in the right lower quadrant: +2 points

(5) White blood cell count > 10,000/mm^3: +1 point

(6) Neutrophil percentage > 75%: +1 point

(7) C-reactive protein > 0.5 mg/dL: +1 point

(8) Maximum pain intensity ≥ 7/10: +1 point

(9) McBurney's point tenderness: +1 point

10.6.1. Calculation. The total points obtained from the individual parameters are added together to obtain the Karaman score. The score can range from 0 to 11, with higher scores indicating a higher probability of appendicitis.

Raja Isteri Pengiran Anak Saleha Appendicitis (RIPASA) is a scoring system for diagnosing acute appendicitis. It was developed in 2010 by researchers from Brunei Darussalam and has since been validated in multiple studies [71]. The RIPASA score includes clinical symptoms, signs, and laboratory findings such as leukocytosis and elevated C-reactive protein (CRP) levels. The score ranges from 0 to 10, with higher scores indicating a higher probability of acute appendicitis. A cutoff score of 7 or higher is often used to indicate the need for appendectomy. The RIPASA score has been shown to have higher sensitivity and specificity compared to other commonly used scoring systems such as the Alvarado score [83].

These scoring modalities can aid in the diagnosis of acute appendicitis and help clinicians determine the appropriate course of treatment.

10.7. Management Modalities. The management of acute appendicitis typically involves the following:

(i) *Surgery*: the primary treatment for acute appendicitis is the surgical removal of the inflamed appendix, known as an appendectomy. The surgery can be done either as an open surgery or as a laparoscopic procedure, which involves making small incisions in the abdomen and using a camera and specialized instruments to remove the appendix

(ii) *Antibiotics*: in some cases, antibiotics may be given before surgery to help reduce inflammation and prevent the spread of infection. However, antibiotics alone are not a reliable treatment for acute appendicitis, and surgery is still the recommended treatment [84]

(iii) In some rare cases, a nonsurgical approach called "antibiotic first" may be used for selected patients who meet specific criteria. This approach involves giving antibiotics first to treat the infection and then assessing if surgery is still necessary. [85]. According to a 2020 Cochrane review, the "antibiotic first" approach may be considered in carefully selected patients with uncomplicated acute appendicitis. However, the review also states that the quality of evidence is low, and more research is needed to determine the safety and effectiveness of this approach

(iv) *Fluids and nutrition*: patients with acute appendicitis may experience nausea and vomiting, which can lead to dehydration and malnutrition. It is important to maintain adequate hydration and provide adequate nutrition during the recovery period

(v) *Observation*: in some cases, patients with suspected appendicitis may be observed in the hospital for a period of time to monitor their symptoms and determine whether surgery is necessary

11. Targeted Therapies for Inflammatory Mediators in Appendicitis and Its Potential Drawbacks and Risks

Targeted therapies are aimed at reducing inflammatory mediators associated with appendicitis, and here are a few examples of targeted therapies that have shown promise in preclinical or early-stage studies:

(i) *Anti-inflammatory agents*: medications that target specific inflammatory pathways or mediators involved in appendicitis could potentially reduce inflammation and associated symptoms [86]

(ii) *Neutrophil-targeted therapies*: neutrophils are immune cells involved in the initial inflammatory response. Strategies that target neutrophil recruitment, activation, or migration could potentially limit the excessive inflammatory response in appendicitis [87]

While targeting specific inflammatory mediators in appendicitis that holds promise for improved diagnosis and treatment, it is important to consider the potential drawbacks and risks associated with reducing their production or activity. A thorough discussion of these risks includes the following:

(1) *Impaired immune response*: inflammatory mediators play a crucial role in the body's immune response to infections and tissue repair. Indiscriminate suppression of these mediators may compromise the immune system's ability to combat infections effectively. This could increase the risk of secondary infections, delayed wound healing, and overall susceptibility to infectious diseases [86]

(2) *Increased risk of infections*: targeted therapies that suppress or modulate inflammatory mediators may disrupt the delicate balance required for proper immune function. This disruption could create an environment more susceptible to infections, particularly opportunistic or latent infections. Patients undergoing targeted therapies should be closely monitored for signs of infections, and appropriate precautions should be taken [88]

(3) *Long-term effects*: the long-term effects of targeted therapies on the immune system, overall health, and potential disease recurrence require careful consideration. Comprehensive studies are needed to assess the safety and efficacy of these therapies over extended periods, including evaluating the potential for immune system dysregulation or the development of resistant strains of bacteria

(4) *Loss of protective effects*: inflammatory mediators serve important protective functions in the body, including initiating the inflammatory response to clear pathogens and promoting tissue repair. By suppressing or modulating these mediators, there is a risk of compromising these protective effects. This could lead to impaired healing, prolonged recovery, or inadequate clearance of infectious agents, potentially resulting in persistent or recurrent inflammation [86]

(5) *Unintended consequences on normal inflammation*: inflammatory mediators play a crucial role in initiating and regulating the body's natural inflammatory response. Indiscriminate suppression or modulation of these mediators may disrupt the normal inflammatory process, which is essential for tissue healing and protection against pathogens. This interference could lead to impaired wound healing, delayed recovery, or abnormal tissue repair

(6) *Impact on microbiome*: inflammatory mediators can influence the composition and function of the gut microbiome, which plays a critical role in maintaining overall health and immune function [89]. Targeted therapies that disrupt or alter the production of specific mediators may inadvertently affect the balance of the microbiome, potentially leading to dysbiosis and associated complications

It is important to seek medical attention promptly if you suspect that you have acute appendicitis. Delayed treatment can increase the risk of complications and make the recovery process longer and more difficult. In selected cases, acute appendicitis can be managed by nonoperative treatment taking into consideration patient assurance, proper observation, communication, and follow-up [84].

In conclusion, acute appendicitis remains a common surgical emergency with significant morbidity and mortality if not diagnosed and treated promptly. The diagnosis of appendicitis can be challenging, and several imaging modalities and laboratory markers are used to aid in the diagnosis. Surgical removal of the appendix remains the standard of care, although nonoperative management with antibiotics alone may be considered in selected cases. The pathogenesis of appendicitis involves a complex interplay of inflammatory mediators, and recent advances in our understanding of the role of these mediators may lead to improved diagnostic and treatment options in the future.

Data Availability

The datasets generated during and/or analysed during the current study are available in the PubMed repository (https://pubmed.ncbi.nlm.nih.gov).

Conflicts of Interest

All authors declare that they have no conflicts of interest.

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