Review Article

Role of Biomarkers, Scoring Systems and Platelet Indices in the Diagnosis of Acute Appendicitis — evidence based approach

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Acute Appendicitis is one of the most common causes of acute abdomen. A systematic approach beginning with history followed by examination and investigations which include blood parameters and imaging studies, is carried out for the conventional diagnosis of Acute Appendicitis. Conditions like mesenteric adenitis in children, diverticulitis in elderly and Pelvic Inflammatory Diseases (PID) in women can mimic appendicitis. Although radiological investigations such as Ultrasound (USG), Computed Tomography (CT), and Magnetic Resonance Imaging (MRI) of the abdomen have good efficacy in the diagnosis, continuing research is being carried out to devise algorithms using other investigations to avoid radiation exposure and cost. There are several novel biomarkers for appendicitis reported such as Interleukin 6 (IL-6), Serum Amyloid A (SAA), leucocyte gene expression (riboleukograms), Granulocyte Colony-stimulating Factors (G-CSF), Urine Leucine-rich Alpha-2-glycoprotein (LRG), Calprotectin or S100A8/A9, procalcitonin (PCT) and Pentraxin-3 (PTX-3).Multiple scoring systems including the Alvarado score, appendicitis Inflammatory Response (AIR) score, Adult Appendicitis Score (AAS), Raja Isteri Pengiran Anak Saleha Appendicitis (RIPASA) score and the Pediatric Appendicitis Score (PAS) are also being used. These scoring systems guide the clinician in risk stratification of the patient with acute appendicitis and decide upon the need for admission and surgical intervention. The various platelet indices such as Mean Platelet Volume (MPV), Platelet Distribution Width (PDW) and platelet count have been reported to be an indicator of disease severity in Appendicitis.

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Key words **: MPV, PDW, Negative appendicectomy, Alvarado score.**

When it comes to the possibility of considering appendicitis as a differential for acute abdomen – "appendicitis should never be lower than second"
— Sir Alexander Cope

The vermiform Appendix, once considered to be a vestigial organ, is thought to play an important role in the maintenance of normal colonic flora and may have a protective function against Clostridium difficile infection and prostate cancer[1]. Acute Appendicitis is one of the most common cause of acute abdomen and is usually the first major operation carried out by a surgery trainee in emergency. Shah *et al* reported that the prevalence, mortality and Disability Adjusted Life Years (DALY) of Appendicitis in India from the year 1990 to 2016 has decreased by 4.7%, 10.8% and 21.5% respectively[2]. A systematic approach beginning with History followed by examination and investigations which include blood parameters and imaging studies, is carried out for the conventional diagnosis of acute appendicitis (Fig 1). Various physical signs like Rovsing sign, Psoas sign and the obturator sign has been described in the literature which aids the diagnosis of acute appendicitis (Fig 2). Atypical presentations are not uncommon in appendicitis. Diagnostic dilemma arises as other conditions like Mesenteric Adenitis in children, Diverticulitis in Elderly and Pelvic Inflammatory Diseases (PID) in women can mimic appendicitis. Thus, supporting laboratory and radiological investigations are routinely carried out as part of evaluation to arrive at a definitive diagnosis.

The various imaging modalities used for the

Editor's Comment :

- A systematic approach is required to diagnose acute appendicitis in order to reduce the negative appendicectomy rates, complications and hospital costs.
- Although computed tomography is most sensitive and specific for the diagnosis of acute appendicitis, issues in its wide use are due to high cost and feasibility in basic health facilities.
- Platelet indices as well as biomarkers are most researched for its role in appendicitis and are cost-effective and widely available.
- A combined approach in the use scoring system with appropriate biomarkers and blood parameters can aid in the early diagnosis and treatment of acute appendicitis.

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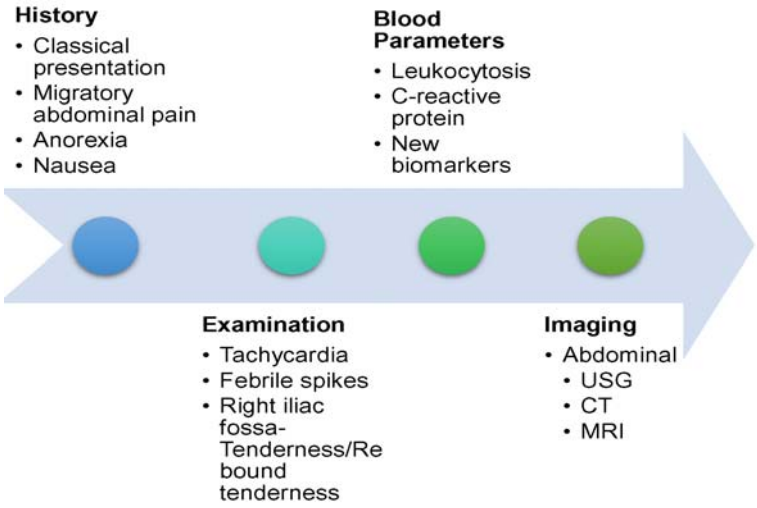

Fig 1 — Systematic approach to the diagnosis of acute appendicitis
USG- Ultrasound; CT- Computed tomography; MRI-Magnetic resonant imaging

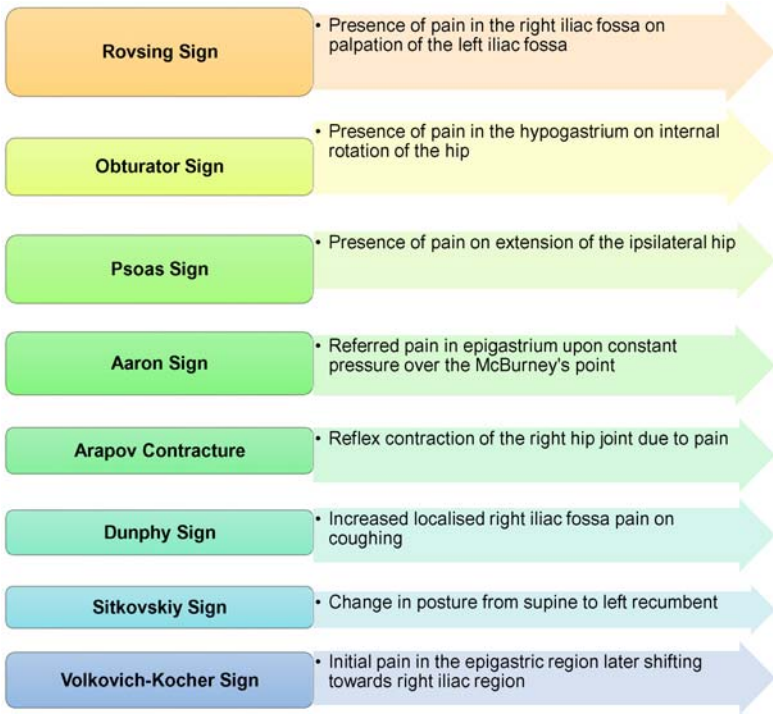

Fig 2 — Physical signs in acute appendicitis

diagnosis are ultrasound (USG), computed tomography (CT), and magnetic resonance imaging (MRI) of the abdomen. USG abdomen is a commonly used investigation for the diagnosis with a sensitivity and specificity of 83.1% and 90.9% respectively[3]. In USG there is no risk of radiation and is time-efficient, making it a screening investigation of choice and well suitable for paediatric population and pregnant patients. CT scan of the abdomen is the most effective, accurate and the gold-standard imaging modality to diagnose acute appendicitis with a sensitivity of 89.9% and a specificity 93.6%[3].Though MRI has a high sensitivity and specificity of 89.9% and 93.6% respectively for diagnosing acute appendicitis, it has a very limited role inthe clinical practice and is reserved for pregnant patients with diagnostic dilemma. The details of various radiological investigation is summarised in Table 1. Anelevation of Total Leukocyte Count (TLC) with neutrophilic leucocytosis is seen in 90% of the patients with acute appendicitis. The most commonly used score in the clinical practice is “Alvarado score” which includes components from symptoms, signs and laboratory tests.The use of single blood parameter such as elevated TLC may not be reliable in the diagnosis of acute appendicitis. A combination of markers such as elevated TLC, C- reactive Protein (CRP) and the proportion of polymorphonuclear cells (PMN) are more accurate in the diagnosis of acute appendicitis. However, these are non-specific inflammatory markers and they need to be correlated clinically.

Acute appendicitis despite its common presentation, remains a disease with difficult diagnosis and most surgeons rely on their clinical skills in its diagnosis aided by laboratory parameters and radiological imaging. But still 55% of the patient presents with atypical clinical signs such as right flank pain in case of retrocaecal appendix, isolated periumbilical pain, absence of fever in elderly patients etc. or a negative laboratory parameter. The rate of negative appendectomy has been constant over the due course of time which ranges from 10-34%[4]. It not only affects the mental and physical health of the patients as there is a possibility of them contracting secondary infections, it also has a huge burden on the health care system. On the other hand, a mis-diagnosis can led to catastrophe of complications such as gangrene, perforation, intra-abdominal abscess formation, sepsis and adhesions. Therefore, it is important as a clinician to improve the diagnostic accuracy in order to avoid complications arising from unwanted surgery and delayed intervention. Studies have been conducted to validated and compare these scores such as Alvarado score described early in the literature to the most recent

Table 1 — *Details of radiological investigations in the diagnosis of acute appendicitis*

Radiological investigation	Findings (Main and Additional)	Sensitivity Adults (Children)	Specificity Adults (Children)	Utility
Ultrasound abdomen	Enlarged, immobile, non-compressible appendix Free fluid abdomen, hyperaemia of adjacent bowel loops, mesenteric fat stranding, regional lymphadenopathy	83.1% (91.3%)	90.9% (95.2%)	Routine investigation of choice
Computed tomography of the abdomen	Appendix more than 7 mm in diameter with thick inflamed wall associated with mural enhancement Mesenteric fat stranding Air specs and periappendiceal fluid - perforated appendix	89.9% (96.2%)	93.6% (94.6%)	Reliable and accurate Used in the presence of diagnostic dilemma
Magnetic resonance imaging of the abdomen	Enlarged appendix of size more than 7 mm with thickness of more than 2 mm Presence of surrounding inflammation	89.9% (97.4%)	93.6% (97.1%)	Reserved for pregnant patient

ones like Raja Isteri Pengiran Anak Saleha Appendicitis (RIPASA) score.

Although adequate evidence is available on the efficacy of radiological imaging such as CT and MRI, continuing research is being carried out to devise algorithms to avoid radiation exposure and cost expenditure. The various scoring systems, diagnostic tests and algorithms are predominantly devised towards the target population which includes children, pregnant patients and elderly where atypical presentations are common and performing these diagnostic tests might not be feasible in all possible situations. The focus of this review is on the role of various biomarkers, scoring systems and platelet indices in the diagnosis of acute appendicitis.

Biomarkers and Scoring Systems :

Acute appendicitis being a clinical diagnosis, a diagnostic dilemma arises in atypical presentations. No single parameter has high accuracy in the diagnosis of acute appendicitis thus, a combination of them is recommended. They predominantly help in ruling out the disease rather than diagnosing it. Therefore, there is need for devising scoring systems which includes all reliable parameters for an accurate diagnosis. This section will be dealing with the routine biomarkers used in clinical practice and the novel biomarkers which are under research. It will also be describing the various scoring systems used in the diagnosis of appendicitis.

Biomarkers for Acute Appendicitis :

TLC done on day-to-day basis for acute abdomen has a low sensitivity and specificity as it is a non-specific marker for appendicitis. It is generally elevated in all inflammatory conditions including appendicitis. However, a TLC count of > 10^9/L has a better sensitivity and can be complementary with a reliable history pointing towards appendicitis. An acute phase reactant used in the diagnosis of acute appendicitis is CRP which peaks at 24-48 hours of onset of inflammation[5]. Although it is non-specific and a poor predictor in an uncomplicated appendicitis, it is a strong predictor of complicated appendicitis. The granulocyte count and polymorphonuclear cell (PMN) ratio is another blood parameter commonly used in acute appendicitis. A count of >11 x 10^9 cells/L has a better likelihood ratio and is clinically significant when the value is >13 x 10^9 cells/L. The presence of immature PMN, or band forms, also known as left shift of >700/microliter has a higher sensitivity and specificity in comparison to elevated TLC in the diagnosis of acute appendicitis. This has been well demonstrated in paediatric patients. A combination of biomarkers increases the likelihood of a definitive diagnosis of appendicitis. Studies have reported that a combination of these markers such as TLC and PMN, TLC and CRP etc, when within normal limits rules out the possibility of appendicitis.More research is required in this field to device a multi-marker approach for the diagnosis of acute appendicitis.

Novel Biomarkers :

There are several novel biomarkers for appendicitis reported such as interleukin 6 (IL-6), Serum Amyloid A (SAA), leucocyte gene expression (riboleukograms), Granulocyte colony-stimulating factors (G-CSF), urine leucine-rich alpha-2-glycoprotein (LRG), calprotectin or S100A8/A9, procalcitonin (PCT) and pentraxin-3 (PTX-3). Most of these biomarkers are not routinely used in clinical practice as these are non- specific markers for appendicitis[5].

Interleukin 6 (IL-6) and Serum Amyloid A (SAA)

The activation of the immediate inflammatory response is predominantly mediated by a cytokine IL-6 which has been reported to be raised in the initial phase of appendicitis. It has a sensitivity of 73% and specificity of 72%. It is reported to havea better accuracy of 80% in comparison to TLC and CRP but is has not been put into clinical practice[6]. Serum Amyloid A (SAA) is a non-specific marker of

inflammation and is reported to have a dynamic response to inflammatory diseases in contrast to WBC and CRP. It has a sensitivity and specificity of 86% and 83% respectively[5]. This could aid in the early diagnosis of appendicitis but further studies are required.

Leukocyte gene expression (Riboleukograms) and Granulocyte colony-stimulating factor (G-CSF)

The sensitivity and specificity of riboleukogram is 89% and 66% respectively and is reported to be a highly sensitive marker for appendicitis[5]. But implementing this marker in clinical practice is difficult owing to its cost and technical difficulties. The sensitivity and specificity of G-CSF is 91% and 51% with an accuracy of 76%[5]. It has been reported that this marker aides not only in the diagnosis of acute appendicitis but also helps in predicting the severity of the diseases. This factor stimulates the bone marrow thereby leads to the production and release of neutrophils into the peripheral circulation and is a marker of inflammation.

Urine Leucine-rich alpha-2-glycoprotein (LRG) and Procalcitonin (PCT)

These are primarily the markers of infection. LRG is a novel marker with a variable accuracy of 99% with mass-spectrometry and 80% with the conventionally used LRG-ELISA. The sensitivity and specificity of 5-Hydroxy Indoleacetic Acid (HIAA) is reported to be 72% and 86% respectively. Studies have reported the presence of LRG much earlier than the release of neutrophils. But it has been reported to be raised in other bacterial infections as well such as pyelonephritis which makes it non-specific. The normal plasma levels of procalcitonin (PCT) is 0.1 to 0.5 ng/ml and is a prohormone of calcitonin which rises in response to bacterial and fungal infection. It also has an ability to predict the severity of the infection, which is detected based on its levels. A meta-analysis on procalcitonin as a marker for appendicitis in children reported a sensitivity of 62% and a specificity of 86%. The authors also reported a much higher sensitivity and specificity of PCT in cases of complicated appendicitis ie, 89% and 90% respectively indicating it has a better accuracy in the diagnosis of complicated appendicitis[7].

Calprotectin (S100A8/A9) and Pentraxin-3 (PTX-3)

Calprotectin is a calcium-binding protein which has been reported to be a gastrointestinal tract specific inflammatory marker with a sensitivity of 93-96% and a specificity of 16-54% according to various studies[5]. Although it has been reported to have high sensitivity, it is not a preferred biomarker due to its low specificity. Pentraxin 3 (PTX3) is one of the members of the superfamily of pentraxin which includes CRP and Serum Amyloid P. It is an acute phase reactant protein which was described in the year 1990, known to rise in response to inflammation. The normal value of PTX3 is reported to be < 2ng/ml. It is also known to have a role in humoral immunity and interact with components of complement pathways. PTX3 has a sensitivity of 95% and a specificity of 100% and when combined with IL-6 yields a better result[8]. The overall accuracy of PTX3 was reported to be 97.2% and IL-6 was 90.4%. Thus, it has been suggested that a combination of these two markers if added to Alvarado score may improve its diagnostic accuracy. The various biomarkers with their sensitivity and specificity has been summarised in Table 2.

Although the data is available on the utility of these markers in various research studies, none has been used in the day-to-day practice for the diagnosis of acute appendicitis. The major reason behind this is the cost of these markers, need for the specific laboratory set-up and testing kits. Many of these markers have limited data in the form of randomised controlled trails and meta-analysis. As CT is routinely available in most of the centre the utility of these markers are overlooked. These markers once established in clinical practice can reduce the amount of CT scans performed and reduce the risk of radiation and the hospital cost. Future studies should focus on the role of these novel biomarkers for the diagnosis of appendicitis in routine clinical practice.

Scoring Systems and Acute Appendicitis :

Clinical scoring system also known as screening tool, prediction algorithm, clinical decision rule, risk score etc. are algorithms designed to diagnose, predict risks and outcomes, and aid in the management of any condition. These scores improve the clinical efficiency and reduces the medico-social burden in terms of unnecessary admissions, imaging, and intervention. A good scoring system should reduce the uncertainty in the diagnosis, guide through the

Table 2 — *The sensitivity and specificity of biomarkers for acute appendicitis*

Biomarker	Sensitivity	Specificity
Total leukocyte count >11,000 cells/mm^3	79%	55%
C-reactive protein	76%	50%
Granulocyte count/	29-89%	48-94%
Polymorphonuclear ratio	32-93%	46-90%
Interleukin 6 (IL-6)	73%	72%
Serum Amyloid A (SAA)	86%	83%
Riboleukograms	80%	66%
Calprotectin	93-96%	16-54%
Pentraxin-3 (PTX 3)	75-95%	100%
Procalcitonin (PCT)	36%	88%
Urinary 5-HIAA	72%	86%

management and give an idea on the outcomes[9]. It should be user friendly, patient-centred and individualized. The main drawback of these scoring systems are their complexity, which limits its use in basic centres like primary health care center where the junior trainees are employed.

Acute appendicitis is one such surgical condition with multiple scoring systems including the Alvarado score, appendicitis inflammatory response (AIR) score, Adult Appendicitis Score (AAS), Raja Isteri Pengiran Anak Saleha Appendicitis (RIPASA) score and the Pediatric Appendicitis Score (PAS). The various parameters used in these scoring systems are described in Fig.3. These scoring systems guide the clinician in risk stratification of the patient, decide upon the need for admission and surgical intervention. They also guide in predicting the prognosis or outcome of patients and reduce the medical burden. Although the utility, validity and accuracy of these scoring systems have been studied by researchers, the choice of scoring system used is left to surgeon's discretion.

The Alvarado score was described in the year 1986 and is one of the commonly used scores in clinical practice. The various parameters in Alvarado score is described in Fig 3. The tenderness in the right iliac fossa and elevated counts are given two points each and rest all are given one point each. A score of less than 4 rules out appendicitis but a higher score may not be very specific for the diagnosis of acute appendicitis with a sensitivity of 93.5% and a specificity of 80.6%. Employing Alvarado score in emergency situations reduces prolonged hospitalisation and radiation exposure. It is also the most simple scoring system and can be used at the level of primary care physician. The disadvantage of Alvarado score is that it cannot really differentiate between complicated and uncomplicated appendicitis in elderly and retro-positive patients. It also has low accuracy in pregnant patients especially in first trimester as confounding symptoms such as nausea and vomiting and elevated leucocytes counts are commonly seen in these patients. In the year 2008 two other scores were reported, the AIR and RIPASA score, both of which have been reported to have better sensitivity and specificity in comparison to Alvarado score. The AIR score is more objective and also incorporates the CRP as one of the parameter, which was studied for a long time as an independent factor for acute appendicitis. The AIR score is the most efficient and most pragmatic score with a sensitivity of 92% and specificity of 63%. The use of AIR score in a study showed lesser number of imaging, admission and negative laparotomy in low-risk patients. The RIPASA score has been reported to have better sensitivity and specificity, and is exclusively designed for the Asian population with various parameters including age, gender, and duration of symptoms. However, a study evaluating its use in Western population reported a sensitivity, specificity and diagnostic accuracy of 85.39%, 69.86% and 80% respectively at the cut-off point of 7.5. At this cut-off point it also has a specificity of 96% in pregnant population but larger studies are

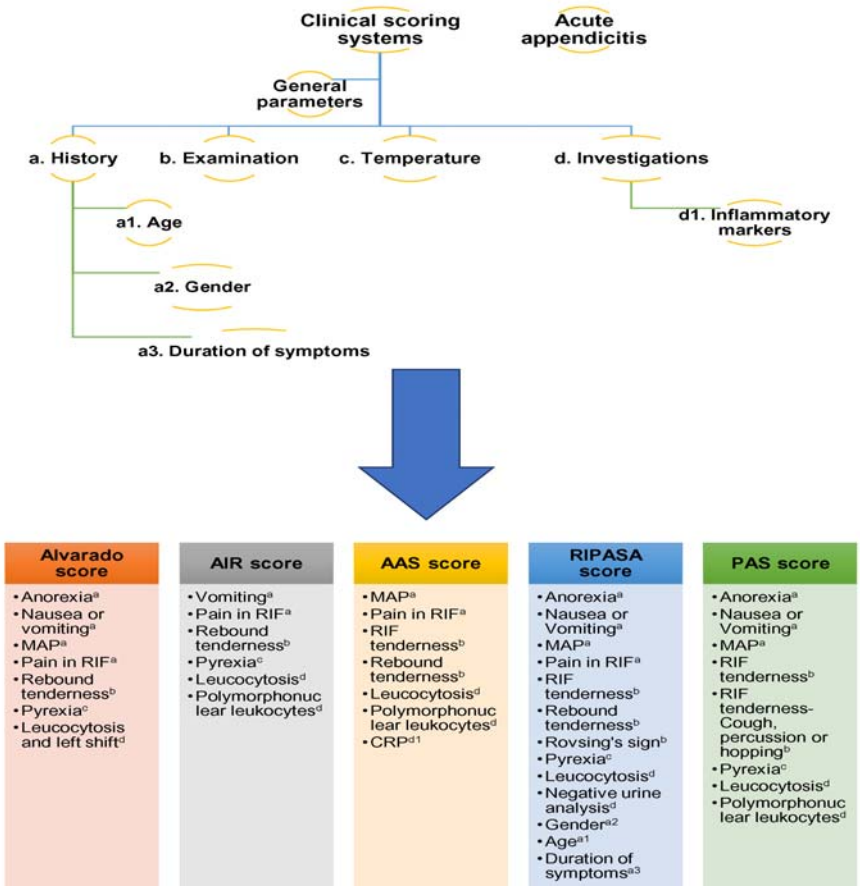

Fig 3 — Various parameters used in different scoring systems
MAP- Migratory Abdominal Pain; RIF- Right Iliac Fossa; CRP- C-Reactive Protein
AIR- Appendicitis Inflammatory Response Score; AAS- Adult Appendicitis Score; RIPASA- Raja Isteri Pengiran Anak Saleha Appendicitis Score; PAS- Pediatric Appendicitis Score

recommended for its validation. A reliable stratification is provided by the Adult Appendicitis Score (AAS), which stratifies patients as high, intermediate and low risk. A study on AAS score, reported 93% specificity in high risk patients for the diagnosis of acute appendicitis and its receiver operating curve (ROC) was significantly larger when compared to Alvarado score and AIR score[10]. In the recent World Society of Emergency Surgery (WSES) guidelines, the authors recommend an individualised approach for the diagnosis of acute appendicitis based on age, gender, clinical symptoms and signs. The authors also recommend the use of these scores for ruling out appendicitis rather than only diagnosis and also decide upon the need for imaging in patients with intermediate-risk.

The challenge in making the diagnosis in pediatric population is that a reliable history might not be possible in all circumstances, thus a scoring system should be more dependent on clinical signs. The PAS score is one such scoring system exclusively designed for pediatric population which includes the specific signs such as pain in right lower quadrant on coughing, hopping or percussion. Although several studies have validated its use in pediatric population it is also reported to over diagnose appendicitis in 35% of the patients. In preschool age group atypical presentations are common and is reported to have rapid progression and increase complication rates. A study on preschool age group population reported AIR score to have better efficiency in discriminating acute appendicitis in comparison to PAS score and Alvarado score. A recent score, the Pediatric Appendicitis Laboratory Score (PALabS), includes clinical signs, leucocyte counts, neutrophil counts, CRP and calprotectin, has sensitivity of 99.2% at a score of less than or equal to 6. The authors of WSES guidelines recommend a combined approach in children rather using only the clinical scoring systems.

These scoring systems when employed hasten the decision making process and guide if radiological imaging are necessary in the diagnosis and whether the patient needs an urgent surgical intervention. It also aids in reducing the number of negative laparotomies thereby reducing the morbidity and hospital cost. It is important to understand that a single scoring system may not be always accurate and each has its own advantages and disadvantages. Implementing them at lower trainee level in a busy emergency set-up is a challenge which needs to be addressed. Making the scores simpler with the least possible components might increase its wide-spread use. As a clinician it is important to individualize the diagnostic approach and the use of the scores based on presentation, patient-population and the resources available.

Platelet Indices :

The clinical history, laboratory parameters and radiological imaging may not always yield a reliable result in patients with acute appendicitis in the day-to-day practice. Although the recent focus of research is towards biomarkers, the limitation is the cost and its difficulty in the implementation in the emergent settings. Thus, a need for markers which are cheap, easily available, and non-invasive. These markers should not only diagnose appendicitis reliably, but also should be able to differentiate between complicated and uncomplicated appendicitis. The platelet indices is one such marker which may fulfil these criteria and is now being studied.

Why platelets? Apart from their commonly known functions such as Hemostasis and Thrombosis, platelets play a vital role in the inflammatory response of the body to an invading infection. The activation of platelets lead to a cascade of inflammatory reactions leading to the release of various cytokines, chemokines which alter the cellular level functions. The various platelet indices include mean platelet volume (MPV), Platelet Distribution Width (PDW) and platelet count are the biomarkers of platelet activation. These parameters have been reported to be an indicator of disease severity not only in appendicitis but also in other inflammatory disorders and infectious diseases such as inflammatory bowel disease, rheumatoid arthritis, etc.

Platelet indices — A diagnostic and prognostic marker :

The Mean Platelet Volume (MPV) is a measure of thrombocyte volume and normally ranges from 7.2 to 11.2 femtoliter (fL)[11]. The platelets have different morphological structure based on their stages of maturity which correlates with their functions. This leads to a heterogenicity in the volume of platelets when compared at the different stages of a disease. The activation of platelets due to inflammation or infection leads to the change in their shape from biconcave to spherical with pseudopod formation and thus, increasing the MPV. The inflammatory cytokines such as thrombopoietin, interleukin 6 and interleukin 3 regulate the megakaryocyte pathway ie, increase their production and thus, play a major role in producing larger number of large platelets. In cases of bone marrow suppression, where production of megakaryocyte is affected, the existing platelets in circulation enlarge in size leading to the increase in

the MPV in response to inflammation. MPV can decrease or increase in response to inflammation thus can act as a negative and positive acute phase reactant. The release of megakaryocyte from the bone marrow in response to high-grade inflammation increases the MPV (increased production and release) whereas, at times the platelets can be sequestrated in the vessels where active inflammatory process is present and thereby reducing the MPV (consumption of platelets). Studies link MPV to acute as well as chronic inflammation, where it decreases with acute inflammation and increases in chronic inflammatory conditions. It is associated with sepsis, ankylosing spondylitis, myocardial infarction, unstable angina, pancreatitis, rheumatoid arthritis and Mediterranean fever[12,13]. It can also be used for evaluation of treatment response in chronic inflammatory conditions such as ankylosing spondylitis and rheumatoid arthritis where the MPV is low during the disease process (due to their consumption in inflammatory areas) and increases in response to the therapy. Sepsis leads to increased cytokine release, bone marrow suppression and endothelial damage leading to an imbalance between the immune and haemostatic pathways. Thus, an elevated MPV indicates poor prognosis in these patients. Platelet Distribution Width (PDW) is an indicator of morphological heterogenicity of plateletsize and ranges from 8.3 to 56.6%. It is a distribution curve which indicates the variability in volume in association with its size. The values increases with anisocytosis of platelets. The MPV and PDW in normal physiological conditions change in the same direction but reports from literature are conflicting and suggest that both have different mechanisms. Plateletcrit (PCT) is the measure of volume of platelet in the blood which ranges from 0.22-0.24% and is calculated using the formula platelet count x MPV/ 10,000. The other platelet indices which are not commonly used in routine practice are the Platelet Larger Cell Ratio (P-LCR), Mean Platelet Component (MPC), Mean Platelet Mass (MPM), Platelet Component Distribution Width (PCDW), and Immature Platelet Fraction (IPF).

P-LCR is the percentage of circulating large platelet ie, >12 fL in the blood which ranges from 15-35%. It is a marker of platelet activity[14]. MPC is the refractive index of platelets which is a marker of platelet activation. The other platelet activation parameters are PCDW and MPM. IPF is the percentage of circulating immature platelets in the blood in comparison to the total platelet population. The various platelet indices and their characteristics have been summarised in Table 3.

Platelet Indices and Acute Appendicitis :

The role of platelet indices in the diagnosis of acute appendicitis is being studied similar to that of acute cholecystitis and mesenteric ischemia. Most of these data are from retrospective reports and the results of the studies were not uniform and conflicting in some aspects. The predominant parameter used was MPV in the diagnosis of acute appendicitis, and PDW in few studies.Varying results have been documented where most studies reported a decrease in MPV and an increase in PDW, with few reporting an increase in MPV. Few studies also reported no change in MPV in patients with acute appendicitis. Apart from the regular comparison of values of these platelet indices in patients with appendicitis with that of controls, studies have been carried out to find the significant cut-off of these markers for an accurate diagnosis. The sensitivity, specificity and accuracy of MPV with a cut of <7.6 fL was reported as 83.73%, 75% and 83.56% respectively. Boshnak et al reported that an increased TLC (neutrophils) with an increased PDW can be used in the diagnosis of acute appendicitis with a diagnostic accuracy of 77% and 69.5% respectively[15]. The authors however suggested that MPV and RDW (Red cell distribution width) levels may not be useful in the diagnosis of acute appendicitis. On the contrary, a systematic review and meta-analysis reported in the year 2017, included 88 studies with a total of 1416 patients of acute appendicitis and 685 controls[16]. The authors reported a significant low level of MPV in appendicitis patients in contrast to the controls. Similarly, in a recent systematic review and meta-analysis, the authors concluded that appendicitis patients have decreased MPV but the utility of other platelet indices such as PDW, platelet count needs further research to establish its role in acute appendicitis. Both the meta-analysis reported a high heterogenicity between the inflammatory markers and acute appendicitis, the later reported, sample size, patient age, appendicitis type, sample collection time and study quality to be the factors associated with inconsistent results among various studies. The authors emphasised on the need for further studies on prospective basis with large sample size and considering the association of these factors.

In a summary, although there are several advances in clinical practice in diagnosing appendicitis such as CT, MRI and diagnostic laparoscopy, there are several limitations in the routine use of these investigations particularly in paediatric and pregnant patients and also the in rural areas especially in developing countries owing to its cost and feasibility. It is also very difficult to implement them in routine clinical practice as they are time-consuming and there is a need for professionals for their interpretation. Hence, there is a

Table 3 — *Platelet indices and their characteristics*

Platelet indices	Definition	Units	Normal Value	Uses in clinical practice
Mean platelet volume (MPV)	Measure of the average size of platelets in circulation	Femtolitre(fL)	9.4-12.3 fL	High- ITP, myeloproliferative diseases, Bernard-Soulier syndrome Low- Aplastic anemia, inflammatory bowel disease
Platelet distribution width (PDW)	Measure of platelet anisocytosis	Percentage(%)	8.3-56.6%	High- Acute cholecystitis, ST elevation myocardial infarction Low- Non-malignant tumors
Plateletcrit (PCT)	Product of MPV and platelet count; Volume of circulating platelets	Percentage (%)	0.22-0.24%	High- Acute cholecystitis, Crohn's disease Low-ITP
Platelet large cell ratio (P-LCR)	Percentage of circulating large platelets measuring over 12 fL	Percentage (%)	15-35%	High- ITP Low- Myeloid insufficiency
Mean platelet component (MPC)	Measure of mean refractive index of the platelets- intrathrombocytic protein concentration	Gram per decilitre (g/dL)	21.5-30.5 g/dL	Myelodysplastic syndrome
Mean platelet mass (MPM)	Calculated from the histogram of platelet dry mass	Picogram (pg)	-	Platelet activation marker
Platelet component distribution width (PCDW)	Measure of platelet shape variability	Gram per decilitre (g/dL)	-	Platelet activation marker
Immature platelet fraction (IPF)	Percentage of immature platelets	Percentage (%)	1.1-6.1%	Low- Thrombopoiesis

need for simple, cost-effective, commonly used parameter which can be interpreted without the need of expertise. Considering the lack of evidence from prospective studies, there is a need for a large population-based cohort study or a well-structured and planned randomised control trial to establish the role of inflammatory markers in the diagnosis of acute appendicitis. It is also important to note that a single parameter may not be accurate for the diagnosis, a combination of commonly available markers proven to have a role in acute appendicitis can be used in order to increase the accuracy. The overall aim is to improvise the diagnosis of acute appendicitis and reduce the negative appendectomy rate even in primary health care facility and low-volume centres.

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