Aim: The aim is to compare the diagnostic accuracy of laboratory investigations and ultrasonography (USG) in distinguishing complicated appendicitis (C-AA) from uncomplicated appendicitis (UC-AA).

Materials and Methods: Forty-six children who underwent appendicectomy at our center between November 2018 and July 2020 were included. Based on intraoperative findings, they were divided into two groups – complicated (perforated, gangrenous, or associated with fecal peritonitis; \(n = 18\)) and UC-AA (\(n = 28\)). USG findings and inflammatory markers were compared in both groups at admission.

Results: At admission, the mean values for total leukocyte count (TLC) (16090.56 vs. 11739.29 per mm\(^3\)), high sensitivity C-reactive protein (hsCRP) (35.8 vs. 31.62 mg/L), and procalcitonin (PCT) (3.83 vs. 1.41 ng/mL) were significantly higher in C-AA. Visualization of a blind tubular aperistaltic structure was the only sonographic sign showing statistical significance – significantly lower in C-AA (50% vs. 90%). Independent predictors of C-AA were – duration of symptoms >48 h (odds ratio [OR] 6.3), free fluid/loculated collection in right iliac fossa (OR 3.75), TLC >11000/mm\(^3\) (OR 3.6), hsCRP >35 mg/L (OR 6.0), PCT >0.6 ng/mL (OR 4.02), and nonvisualization of appendix on USG (OR 8.33). Biochemical factors were sensitive (89%) and specific (55%) in differentiating C-AA from UC-AA but the addition of sonological parameters significantly improved the specificity of predicting complicated AA to 61% \((P = 0.0036)\).

Conclusion: Combining laboratory data with sonological findings significantly improves the predictive value for differentiating C-AA from UC-AA and can help decide operative approach and prognosticating.

Keywords: Appendicitis, complicated appendicitis, complicated versus uncomplicated appendicitis, inflammatory markers in appendicitis, perforated appendicitis
infection, and postoperative ileus. Therefore, in these patients, the aim should be to plan an optimal surgical strategy for minimizing the morbidity, length of hospital stay, and risk of readmission to the hospital due to a complication.

In recent years, studies on the antibiotic treatment of pediatric patients with simple appendicitis without surgery have been published. Even in C-AA patients, there has been a paradigm shift and early appendectomy and antibiotic treatment protocol are now recommended as it is associated with lesser hospital stay, cost, complications, and frequency of hospital readmission after discharge compared to those in patients undergoing delayed appendectomy after antibiotic treatment. Hence, early and accurate detection of C-AA in the emergency room itself is important in determining the appropriate antibiotic therapy and also the timing of surgery.

The aim of our study was to determine the predictive value of simple blood tests, such as total leukocyte count (TLC), serum bilirubin, amylase, procalcitonin (PCT), and high sensitivity C-reactive protein (hsCRP), in addition to sonological criteria, to increase the diagnostic accuracy in differentiating C-AA from UC-AA in children in the emergency room setting.

**Aim**
This study aims to compare the diagnostic accuracy of laboratory investigations and USG findings in distinguishing uncomplicated from complicated cases of AA based on operative findings and histopathology.

**Materials and Methods**
This is a prospective observational study that was held in the Department of Pediatric Surgery, Maulana Azad Medical College and Assoc. Lok Nayak Hospital, New Delhi. All patients clinically suspected of having AA and undergoing appendicectomy between November 2018 and July 2020 (21 months) with histopathology reports confirming the diagnosis of AA were enrolled. The following USG findings were noted: Visualization of the appendix as a blind, tubular, noncompressible, aperistaltic structure in right iliac fossa (RIF), probe tenderness in RIF, peri-appendiceal fat stranding, presence of free fluid/loculated collection in RIF, appendicular diameter and any other findings such as lymphadenopathy, localized bowel wall thickening or dilated bowel. The biochemical markers studied were TLC, serum bilirubin, serum amylase, hsCRP, and PCT.

**Results**
The mean age of patients in our study was 8.54 ± 2.4 years. The age of children with C-AA (7.67 ± 2.52 years) was significantly lower than those with UC-AA (9.11 ± 2.1 years); P = 0.0416.

Out of 6 patients in the age group of 0–5 years, 5 (80%) had C-AA. 5/18 (27.8%) patients with C-AA were ≤5 years of age while only 1/28 (3.57%) of UC-AA were ≤5 years age; P = 0.0185 [Table 1]. Overall, appendicitis was 3.6 times more common in boys (78.26%) than in girls (21.74%).

The average symptom duration in our study was 3.22 ± 2.53 days (4.28 ± 2.99 days in C-AA and 2.54 ± 1.88 days in UC-AA); P = 0.0193. Overall, the signs and symptoms were comparable between the two groups [Table 2].

The presence of a blind tubular aperistaltic structure was the most common USG finding, seen in a significantly higher proportion of patients with UC-AA (89%) compared to C-AA patients (50%); P = 0.004. Other features such as per-appendiceal fat stranding (39% vs. 46%), probe tenderness in RIF (50% vs. 54%), and fluid collection (56% vs. 25%) were comparable between the two groups [Table 3]. The appendix could not be visualized in half of the patients with C-AA compared to only 10.7% of patients with UC-AA (P = 0.0034). Among these patients, 83.3% patients had at least one of the secondary signs such as free fluid/loculated collection in RIF, bowel wall...
thickening (5.6% vs. 10.7%), or dilated bowel (16.7% vs. 3.6%). Appendicolith was seen in only 1 patient, a case of C-AA [Table 3].

The average appendicular diameter in our study was 8.78 ± 2.65 mm and was comparable in the two groups (9.29 ± 1.92 mm in C-AA vs. 8.96 ± 2.95 in UC-AA; \( P = 0.57 \)).

Among the biochemical parameters that we studied, at the time of admission, the TLC, hsCRP, and PCT were significantly higher in the C-AA group. Bilirubin was higher and amylase was lower in the C-AA group but these were not statistically significant [Table 4].

The clinical parameters, taken together, had 71% sensitivity, 50% specificity, 69% positive predictive value (PPV), and a 53% negative predictive value (NPV) in the diagnosis of C-AA. The biochemical parameters were more sensitive (89%) and specific (56%) with a 76% PPV and 77% NPV. On addition to USG findings to the laboratory parameters, the diagnostic accuracy increased to 76% (86% sensitivity, 61% specificity, 77% PPV, 73% NPV) [Table 5].

The average hospital stay in our study was 5.25 ± 3.88 days. The duration of hospital stay in children with C-AA (7.39 ± 4.92 days) was significantly higher than those with UC-AA (3.93 ± 2.12 days); \( P = 0.01 \).

**Discussion**

Appendicitis, being one of the most common emergency surgical conditions, has been studied extensively. Identifying children with a C-AA is important since it decides further workup and surgical planning. Moreover, in the face of growing evidence for nonsurgical treatment of uncomplicated AA, the search for clinically useful markers to establish the severity of AA seems obligatory.

| Table 3: Ultrasoundography features in our study population |
|------------------------------------------------------------|
| **USG findings**                                           | **C-AA (n=18)** | **UC-AA (n=28)** | **Total (n=46)** | **P (C-AA vs. UC-AA)** |
| Prescence of a blind tubular aperistaltic structure in RIF | 9 (50)          | 25 (89)          | 34 (74)          | 0.004                   |
| Peri-appendiceal fat stranding                             | 7 (39)          | 13 (46)          | 20 (43)          | 0.64                    |
| Probe tenderness in RIF                                   | 9 (50)          | 15 (54)          | 24 (52)          | 0.79                    |
| Fluid collection in RIF                                   | 10 (56)         | 7 (25)           | 17 (37)          | 0.036                   |
| Appendicolith                                             | 1 (6)           | -                | 1 (2)            | -                       |
| Local bowel wall thickening                               | 1 (6)           | 3 (11)           | 4 (9)            | 0.554                   |
| Dilated bowel                                             | 3 (17)          | 1 (4)            | 4 (9)            | 0.129                   |

RIF: Right iliac fossa, C-AA: Complicated appendicitis, UC-AA: Uncomplicated appendicitis, USG: Ultrasonography

| Table 4: Biochemical markers at admission and comparison between the two groups |
|-------------------------------------------------------------------------------|
| **Biochemical markers**                                                      | **C-AA** Mean±SD | **UC-AA** Mean±SD | **Significance of mean (P)** |
| TLC (per mm^3)                                                               | 16,090.56±7451.68 | 11,739.29±4404.4  | 0.034                        |
| Bilirubin (mg/dL)                                                           | 0.77±0.33          | 0.63±0.31          | 0.141                        |
| Amylase (mg/dL)                                                             | 49.11±36.08        | 75.14±117.4        | 0.281                        |
| hsCRP (mg/dL)                                                               | 35.8±1.3           | 31.62±8.88         | 0.021                        |
| PCT (ng/mL)                                                                 | 3.83±4.17          | 1.41±2.77          | 0.039                        |

TLC: Total leukocyte count, PCT: Procalcitonin, hsCRP: High sensitivity C-reactive protein, SD: Standard deviation, C-AA: Complicated appendicitis, UC-AA: Uncomplicated appendicitis

| Table 5: Diagnostic accuracy of the clinical, biochemical and radiological criteria |
|-----------------------------------------------------------------------------------|
| **Clinical**                                                                      | **Biochemical**    | **Clinical + biochemical** | **Clinical + USG** | **Biochemical + USG** | **Clinical + biochemical + USG** |
| Sensitivity                                                                      | 71.43              | 89.29                      | 75                  | 64.29                    | 85.71                      | 75          |
| Specificity                                                                      | 50                 | 55.56                      | 55.56               | 61.11                    | 61.11                      | 61          |
| PPV                                                                             | 68.97              | 75.76                      | 72.41               | 72                       | 77.42                      | 75          |
| NPV                                                                             | 52.94              | 76.92                      | 58.82               | 52.38                    | 73.33                      | 61.11       |
| PLR                                                                             | 1.43               | 2.01                       | 1.69                | 1.65                     | 2.2                        | 1.93        |
| NLR                                                                             | 0.57               | 0.19                       | 0.45                | 0.58                     | 0.23                       | 0.41        |
| Accuracy                                                                        | 63.04              | 76.09                      | 67.39               | 63.04                    | 76.09                      | 69.57       |
| \( P \)                                                                         | 0.141              | 0.0049                     | 0.0403              | 0.0888                   | 0.0036                     | 0.0179      |

NLR: Negative likelihood ratio, PLR: Positive likelihood ratio, NPV: Negative predictive value, PPV: Positive predictive value, USG: Ultrasonography
Studies similar to ours were done by other workers in pediatric patients[7-10] but none of them took into account the radiological criteria along with the laboratory markers. A few studies based solely on comparing sonological criteria between the two groups[11,12] studied the association of symptom duration, maximum diameter of appendix, peri-appendiceal fluid, fluid-filled lumen, and appendicolith with perforated appendicitis.

Hence, our study is unique in the way that we have combined clinical and laboratory findings along with sonological criteria to predict C-AA in children from UC-AA preoperatively so that the surgical management can be appropriately tailored.

In our study, the children with C-AA were significantly younger than those with UC-AA. The majority of the children under 5 years of age had C-AA. This higher incidence of C-AA in preschool children can be attributed to a multitude of factors including the inability of the young child to communicate properly to parents, nonspecific presentation, overlap of symptoms with other common childhood illnesses, and anatomic immaturity (lack of an adequate omental barrier) leading to rapid progression to perforation and peritonitis in this age group.[13]

Our findings, as those of Yang et al.,[7] highlighted no difference in various signs and symptoms between perforated and nonperforated groups. Anorexia, which is the third component of the Murphy’s triad (right lower quadrant pain, nausea/vomiting, and anorexia) in AA, was the least common symptom in their study too. The low incidence can be explained by the inability of younger children to vocalize about anorexia and also due to socio-cultural differences.[14] Furthermore, the dull periumbilical pain in early stages of appendicitis is confused as hunger by some children and hence, anorexia is not reported as such.

The average symptom duration in our study was significantly higher in C-AA patients. Pham et al.[8] did a retrospective review of 392 children and found that symptom duration ≥24 h was the most significant factor associated with perforated appendicitis (odds ratio [OR] 5.5, 95% confidence interval [CI] 3.5–8.9; P < 0.01). Symptom duration ≥48 h was one of the most significant factors associated with a diagnosis of C-AA (OR 6.3, 95% CI 1.6273–24.3908; P = 0.0077) in our study too.

Among the diagnostic modalities, USG has proven to be very accurate in skilled hands with a sensitivity ≈85% and specificity >90%.[15] The normal appendix is a compressible blind-ending tubular structure that lacks peristalsis and indicators of AA include visualizing a noncompressible appendix, with a diameter >6 mm and/or a wall thickness >2 mm,[16] lack of air in the appendiceal lumen, periappendiceal fat stranding, presence of appendicolith, complex right lower quadrant mass, enlarged mesenteric lymph nodes, presence of free fluid.[17] The presence of echogenic peri-appendiceal fat is the most important diagnostic criterion for AA in children and strict application of other criteria such as diameter should be avoided.[18] Dilated bowel with echogenic fat and abscess or loculated fluid in RIF is the most specific signs for perforated AA (specificity >99%) and echogenic fat around the appendix is the most sensitive sign (sensitivity 68%–75%).[19]

In our study, the appendix could be identified in almost 90% of patients with UC-AA but in only half of the C-AA patients (P = 0.004) as the perforated appendix decompresses and may also slough out making identification difficult.[20] Other features such as periappendiceal fat stranding, probe tenderness in RIF, and fluid collection were comparable between the two groups. Blumfeld et al.[11] did a retrospective evaluation of USG findings in 161 children from two different centers who had undergone appendicectomy and noted that the findings of free fluid in RIF (P = 0.12) and the presence of echogenic fat around the appendix (P = 0.13) did not have a statistically significant association with appendiceal perforation. On the other hand, Boettcher et al.[21] reported a higher incidence of appendix visualization in perforated compared to simple appendicitis (95.7% vs. 81.8%; P = 0.02) but this can be attributed to the use of a high-frequency ultrasound with graded compression to identify the appendix with greater accuracy. Among the patients in our study in whom the appendix could not be visualized on USG, more than 80% of patients had at least one of the secondary signs such as free fluid/loculated collection in RIF, bowel wall thickening, or dilated bowel. In 212 children with AA, Wiersma et al.[22] found hyperechoic mesenteric fat in 97.3% of patients with nonvisualization of appendix, fluid collections in 16% and dilated bowel loops in 6.6%. They concluded that in case of nonvisualization of the appendix without secondary signs, appendicitis can be safely ruled out, and furthermore, secondary signs of appendicitis alone are a strong indicator of AA.

In our series, except for 1 patient, the MOD was greater than 6 mm in all the patients in whom appendix could be visualized, which conforms with the cutoff for a diagnosis of AA.[20] The average appendicular diameter in our study was comparable in the two groups. Similarly, Blumfeld et al.[11] also noted that the appendix diameter was comparable between the two groups (1.2 ± 0.36 cm vs. 1.1 ± 0.3 cm) and was not predictive of perforated appendicitis. This indicates that appendicular edema is
marked even at the beginning of the pathological process in UC-AA.

Various laboratory tests, like TLC, DLC, PCT, or CRP, can aid in the determination of AA severity.[23] Laboratory parameters, such as CRP level, white blood cell (WBC), and neutrophil/lymphocyte ratio have also been used to differentiate between complicated and uncomplicated C-AA.[24] Recently, a group of heterogeneous plasma proteins called acute phase reactants (APRs), which increase or decrease with inflammatory stimuli, have increasingly been used in diagnosis of AA and as possible predictors for C-AA in children.[8,25] At admission, the mean hsCRP (mg/L) in our study was significantly higher in C-AA patients and we also found that an hsCRP value >35 mg/dL was highly sensitive (100%) but not specific (21%) in predicting C-AA (PPV 100%, NPV 45%). Several authors have similarly found CRP as a predictor of perforated appendicitis.[7,9,26]

In our study, the PCT levels (ng/mL) at admission were significantly higher in the C-AA group and a PCT >0.6 ng/mL was 72% sensitive and 61% specific in the diagnosis of C-AA. Cui et al.[27] did a meta-analysis on the diagnostic accuracy of PCT in pediatric AA and found that the pooled sensitivity and specificity of PCT for the diagnosis of pediatric C-AA were 89% and 90%, respectively. Feng et al.[9] found that a serum PCT level >0.46 ng/mL is an independent predictor of perforated appendicitis in children (sensitivity 93%, specificity 92%, PPV 92%, and NPV 93%).

In our study, we found that the TLC (per mm³) was significantly higher in C-AA patients at admission and a TLC >11000/mm³ had a 72% sensitivity and 54% specificity of detecting C-AA. Similar findings related to higher WBC counts in C-AA were found by other workers too. For example, Yang et al.[7] and Feng et al.[9] noted a WBC >12000/mm³ while Miyauchi et al.[10] found WBC >15000/mm³ to increase the odds of a perforated appendicitis. Beltran et al. showed that WBC count and its sensitivity increased from the onset of symptoms to diagnosis.[28] Pham et al.[8] also noted leukocytosis as an independent predictor of perforated appendicitis (OR 1.9, 95% CI 1.0–3.5, P = 0.04).

In children with perforated appendicitis, there is an increase in Kupffer cell function and hepatocyte injury as a result of excessive bacterial endotoxin load on the liver through portal venous system and also suppression of hepatic bilirubin destruction as a result of increased APRs such as interleukin-6 and tumor necrosis factor which ultimately lead to an increase in the serum bilirubin levels.[29] However, in our study, we found serum total bilirubin levels (mg/dL) to be nonsignificantly higher in the C-AA group at admission. Serum bilirubin >0.6 mg/dL had 67% sensitivity and 50% specificity of detecting C-AA in our series. Similar to our results, Kilic et al.[30] also found, in their study on 118 children with AA, that the mean plasma TB level was higher in the perforated group (0.93 ± 0.43 mg/dL vs. 0.78 ± 0.44 mg/dL) but was not statistically significant (P = 0.77).

Serum amylase is neither sensitive nor accurate in the diagnosis of AA but has a high specificity and PPV. This means that if the amylase level is not elevated in a patient with suspected AA, it is of no significance, but when elevated it suggests a C-AA.[31] Although related to the reabsorption of intestinal fluids, the mechanism of hyperamylasemia in appendicitis is unknown and the cause remains conjectural. However, we did not find hyperamylasemia in our patients and the serum amylase values were comparable in the two groups at admission. Inflammation of a limited area of the gastrointestinal tract in a patient with AA may be the reason for not seeing a significant rise in serum amylase levels. The only study in English literature that reported a statistically significant increase in serum amylase level in the perforated group (69.2 ± 28.9 mg/dL vs. 29.9 ± 11 mg/dL; P < 0.001) was a cross-sectional study done by Amanollahi et al.[32] on 61 children from two institutions who underwent appendectomy.

The average hospital stay in our study (5.25 ± 3.88 days) was significantly higher in children with C-AA (7.39 ± 4.92 days) than those with UC-AA (3.93 ± 2.12 days). This can be attributed to the fact that these patients are at a greater risk of developing postoperative complications such as surgical site infection, pelvic abscess, and postoperative ileus owing to the presence of pus in the peritoneal cavity. Louini et al.,[33] and Fujii et al.[13,33] have also reported a longer hospitalization period in C-AA.

On logistic regression analysis, we found that the biochemical factors were more sensitive (89% vs. 71%) and specific (55% vs. 50%) compared to clinical findings in the diagnosis of C-AA. The addition of sonological parameters to the biochemical findings in differentiating C-AA from UC-AA increased the specificity to 61%. This is similar to the observations made by Miyauchi et al.[10] The addition of clinical criteria to the above did not improve the sensitivity or specificity. This showed that, though clinical parameters play an important role in the diagnosis of AA, these may not be helpful in predicting C-AA preoperatively.

Due to the limited study, the sample size of our study is considerably small. Recruitment of more subjects would have helped us perform a more comprehensive analysis.
and improve the generalization and the accuracy of the findings. Due to study design and the natural history of the disease, we could not define the transition of un C-AA to a complicated one.

In summary, our data suggested that longer duration of symptoms (> 2 days), higher WBC count (> 11000/mm³), higher CRP (> 35 mg/dL), and PCT (> 0.6 ng/mL) levels, and characteristic USG findings (nonvisualization of appendix, free fluid/loculated collection in RIF, bowel wall thickening, or dilated bowel) are independent and objective factors predicting perforated appendicitis at admission in children. Among the biochemical parameters, a PCT level > 0.6 ng/mL was the most predictive of C-AA (OR 4.02; 95% CI 1.12–14.46) whereas nonvisualization of the appendix was the most important sonological criterion in favor of C-AA (OR 8.33; 95% CI 1.84-37.82).

**Conclusion**

Combining laboratory data with sonological findings significantly improves the predictive value for differentiating C-AA from UC-AA preoperatively which could assist further surgical planning, even in resource-limited settings. These may potentially help physicians determine the severity of appendicitis, prognosticate patients, and also decide operative approach.

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**Conflicts of interest**

There are no conflicts of interest.

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