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Biochemical diagnosis of acute appendicitis

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Abstract
Acute appendicitis is the most common surgical diagnosis of abdominal pain. Perforated appendicitis can result in increased morbidity and mortality. Identifying a perforation early can reduce the impact on the patient. Bilirubin, C-reactive protein (CRP) and white cell count (WCC) have been shown to indicate perforation in appendicitis. This study aimed to identify whether these biochemical markers can be used to identify if patients are suitable for either a conservative or surgical approach. The diagnosis of appendicitis is difficult and resource consuming. New inflammatory markers have been proposed for the diagnosis of appendicitis, but their utility in combination with traditional diagnostic variables has not been tested. Our objective is to explore the potential of new inflammatory markers for improving the diagnosis of appendicitis.

Keywords: appendicitis, bilirubin, CRP, White cell count, inflammatory markers, white cell count

Introduction
Acute appendicitis is the most common suspected diagnosis of abdominal pain in the emergency department [1]. And the single most common illness requiring emergency surgery [2]. Initial work-up of a patient with an acute abdomen includes a full clinical history and examination, followed by blood tests. In addition, ultrasonography may also be useful in suspected appendicitis [3]. However, the ability of a doctor to undertake a thorough history and clinical examination are as useful at diagnosing acute appendicitis as any laboratory tests [4]. The majority of appendicitis cases are uncomplicated. Between 18.3 and 34.0% of appendicitis cases are complicated by perforation and post-operative complication rates are significantly increased with perforation [5, 6]. Identifying perforated clinical appendicitis depends on clinical examination supported by raised inflammatory and biochemical markers. An early diagnosis of perforation improves outcomes, allowing the surgeon to prepare for a relatively difficult procedure [7]. There has been much research into hyperbilirubinemia in cases of perforated appendicitis [8-10]. But these studies do not extend to also include CRP levels, which is interesting considering that it remains a part of many work-up investigations. An investigation by Kaser *et al*. looking at the usefulness of CRP and bilirubin in predicting a perforated appendix revealed that both CRP and bilirubin are raised significantly in perforations, but that CRP was more useful in predicting perforations [11]. While this research highlighted the usefulness (or lack thereof) of measuring the white cell count, it did not investigate the individual differentiated white cell counts and their ability to predict appendicitis. At the time of the publication by Kaser *et al*., our results were completed and were found to be both supportive and conflicting with different aspects of the results from this study [14]. This primary aim of this study was to establish whether there is a correlation between plasma levels of both CRP and bilirubin on initial presentation and the presence of a perforated appendix. Also, this study aimed to establish the potential clinical use for this information in identifying those unsuitable for conservative management. Additionally, this study investigated the role of leukocytes in predicting an appendix perforation and whether the combination of results can yield more accurate results.

Material & Methods
A total of 122 patients were operated under suspicion of appendicitis. From these, 23 patients had a pathologically verified inflamed appendix and 30 had a perforated appendix. Patients with acute appendicitis had significantly higher blood levels of white blood cell, bilirubin, C-reactive protein, and alanine transaminase than patients without appendicitis. Patients with perforated appendicitis had significantly higher levels of white blood cell, bilirubin, and C-reactive protein than patients with non-perforated appendicitis. The highest positive predictive value to discriminate between acute appendicitis and non-appendicitis was of a linear regression model combining white blood cell count, bilirubin, and alanine transaminase. C-reactive protein levels and a linear regression model, including white blood cell count, bilirubin, and C-reactive protein levels as variables, had the highest negative predictive values when discriminating between perforated and non-perforated appendicitis Fig-

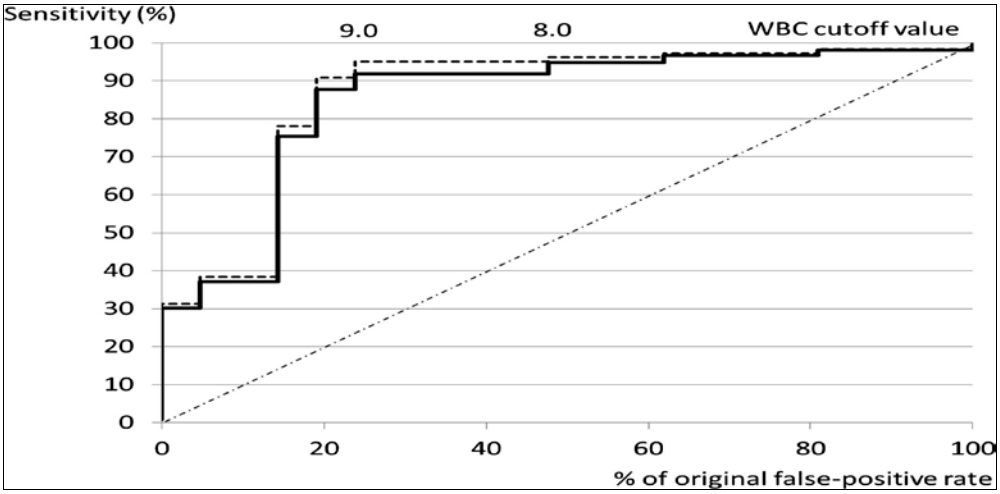

Fig 1

Table 1: Sensitivity, specificity, positive and negative predictive value of different parameters, AUC-area under curve

	AUC	Cut off	Sensitivity	Specificity	PPV	NPV	P value
Serum bilirubin	0.997 (0.0-1.00)	2.1	100%	92.9%	72.7%	100%	<0.001
TLC	0.525 (0.307-0.704)	13500	37.5%	78.6%	25%	86.8%	0.379
CRP	0.973 (0.0-1.000)	149	100%	95.2%	80%	100%	<0.001
AST	0.567 (0.336-0.798)	28	50%	69%	23.5%	87.9%	0.419
ALT	0.723 (0.556-0.890)	35	75%	64.3%	28.6%	93.1%	0.056
ALP	0.507 (0.297-0.718)	172.5	87.5%	40.5%	21.9%	94.4%	0.231
Alvardo score	0.781 (0.556-1.000)	9.0	62.5%	95.2%	71.4%	93%	<0.001

AUC, area under the curve; PPV, positive predictive value; NPV, negative predictive value; TLC, total leukocyte count; CRP, C-reactive protein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase

Diagnostic Properties of the six most promising out of 21 new inflammatory markers (interleukin [IL]-6, chemokine ligand [CXCL]-8, chemokine C–C motif ligand [CCL]-2, serum amyloid A [SAA], matrix metalloproteinase [MMP]-9, and myeloperoxidase [MPO]) were compared with traditional diagnostic variables included in the Appendicitis Inflammatory Response (AIR) score (right iliac fossa pain, vomiting, rebound tenderness, guarding, white blood cell [WBC] count, proportion neutrophils, C-reactive protein and body temperature) in 432 patients with suspected appendicitis by uni- and multivariable regression models. Of the new inflammatory variables, SAA, MPO, and MMP9 were the strongest discriminators for all appendicitis (receiver operating characteristics [ROC] 0.71) and SAA was the strongest discriminator for advanced appendicitis (ROC 0.80) compared with defense or rebound tenderness, which were the strongest traditional discriminators for all appendicitis (ROC 0.84) and the WBC count for advanced appendicitis (ROC 0.89). CCL2 was the strongest independent discriminator beside the AIR score variables in a multivariable model [11]. The AIR score had an ROC area of 0.91 and could correctly classify 58.3 % of the patients, with an accuracy of 92.9 %. This was not improved by inclusion of the new inflammatory markers [12].

Table 2

Laboratory finding	Noncomplicated appendicitis	Complicated appendicitis	P-value
WBC (1,000/μL)	12.57 ± 4.1	13.38 ± 4.4	0.124
Neutrophil proportion (%)	76.33 ± 12.4	80.55 ± 8.9	0.004
CRP (mg/dL)	2.05 ± 2.8	11.47 ± 8.4	<0.001
AST (IU/L)	24.74 ± 16.5	29.06 ± 20.2	0.049
ALT (IU/L)	21.27 ± 18.7	23.68 ± 19.4	0.308
Total bilirubin (mg/dL)	0.95± 0.4	1.24 ± 0.7	<0.001

Table 3

Status of appendix	Bilirubin positive (>1.5 mg/dl)	Bilirubin negative (<1.5 mg/dl)	Total	Positive rate %
Perforated	33	9	42	78.57
Nonperforated	6	52	58	10.34
Total	39	61	100	

χ^2=47.66; df=1; P<0.0001

Discussion

The results of this study mirror previous studies in that they reveal that CRP, bilirubin, white cell count and differentiated

neutrophil count are not reliable enough to be used alone in predicting a perforation in patients presenting with clinical acute appendicitis [13]. Despite the limitations of the results individually, combining the results can improve the sensitivity of the tests, but adding all tests together, while impacting positively on the specificity, reduces the sensitivity too much. Despite this research base, the definitive diagnosis of perforated appendicitis still requires an operative and histological diagnosis. The perforation rate in the setting of acute appendicitis was 12.12%, which is similar to other studies published in Western Europe [12]. The main difference in demographics was the increased rate of perforation in men (14.64%) compared with females (9.52%). The ratio of acute appendicitis patients between genders was approximately 1:1.CRP has a higher sensitivity than other blood test results, mainly because of the relatively low normal value cut-off. Bilirubin outperforms any of the other biochemical markers investigated in terms of specificity [14]. Combining the results of CRP and bilirubin improves the specificity without significantly reducing the sensitivity of the tests. The white cell count and neutrophil count can be useful in predicting a perforated appendix if they are both raised, but the low sensitivity means that if they are normal, it cannot be assumed that the appendix is not perforated. Although the results do not confidently show the blood tests to be diagnostic tools, they can be useful in prioritizing patients and, if considered together with the clinical picture, whether a patient is suitable for conservative management, such as 'watch-and-wait'. This study found that the WBC count, levels of bilirubin, CRP, and ALAT levels were all significantly increased in patients with appendicitis compared to patients without. Furthermore, it was shown that WBC count, bilirubin levels, and CRP levels were significantly increased in patients with perforated appendicitis compared to patients suffering from non-perforated appendicitis [15]. The level of CRP was not significantly increased among patients suffering from acute appendicitis compared to patients suffering a differential diagnosis. An explanation could be that CRP reacts slower compared to, for example, WBC [1, 5]. Thus, in the patient with appendicitis, who normally has a short and acute symptomatic history, the CRP may not react until later. In contrast, the patients with perforated appendicitis may have a more severe disease and a longer duration of inflammation. This may result in the significant elevation of CRP levels for perforated disease. Acute appendicitis causes an inflammatory response. Literature has shown that WBC count was significantly increased during an inflammatory response, which was caused by a bacterial infection in the appendix [5]. Other studies have shown that levels of bilirubin and CRP were significantly increased in the early diagnosis of acute appendicitis. The mechanisms behind this sepsis-related hyperbilirubinemia may be explained through increased hemolysis, and a decrease in bile uptake and excretion [6]. Other studies have shown that bacterial endotoxins, including toxins produced by the bacteria *Escherichia coli*, decreased the hepatic bile secretion contributing to intrahepatic cholestasis [9] and sinusoidal damage [9]. In rodent models, endotoxins reduced bile-salt uptake in hepatocytes [12]. Our study showed that levels of ALAT were significantly increased, especially among patients suffering from appendicitis. This could be a result of an inflammatory reaction in the hepatocytes or sinusoidal damage. Being retrospective, this study has inherent limitations. Nonetheless, since the parameters recorded in this study were collected prospectively, information bias may be limited. Numerous studies have been conducted to identify factors or biomarkers, which can be used diagnostically to differentiate between patients suffering from appendicitis and differential diagnoses and thereby reduce the number of patients undergoing surgical treatment. The similar has been attempted for patients suffering from perforated and non-perforated appendicitis. As stated above, many biomarkers have indeed been identified as being related to appendicitis and appendiceal perforation, the most important and well documented being WBC, CRP, and bilirubin. These biomarkers have generally had a high specificity, but low sensitivity [2, 3]. Combining biomarkers increases the specificity without a great change in sensitivity. Therefore, relevant biomarkers, alone or in combination, cannot be used as a differential tool but rather as a supportive tool alongside the patient's clinical appearance and symptomatic history. ROC curves for bilirubin and CRP are similar, showing that these two markers are of nearly equivalent use when trying to diagnose perforated appendicitis, with bilirubin being of slightly, but not significantly, more use. This is different to other work, which has shown that CRP is better than bilirubin at predicting a perforation, especially at higher levels [11]. The mechanisms behind a raised bilirubin level are not fully understood, but are believed to be linked to the inflammatory response to bacteraemia [1, 3]. The low specificity of CRP is a result of the well-known relationship between a raised CRP level and a myriad of medical conditions, especially in sepsis [1, 4].

Summary

Our results identify all four of the blood test markers as being significantly raised in perforated appendicitis, and that combining the results of bilirubin and CRP can improve the sensitivity and specificity of the investigations. Utilizing white cell count and neutrophil count improves the specificity of the results, but reduces the sensitivity. Logistic regression analysis results identified bilirubin, CRP and WCC as significant markers of a perforated appendicitis, with CRP being found to have the highest odds ratio for an one-unit increase. The use of a definitive WCC as a sign of appendicitis is difficult, as it is well known that the WCC can be either raised or lowered in sepsis [15]. As a result of this variation in WCC in sepsis, using 'raised WCC' as a marker for appendicitis is wrong as patients with a low WCC would cancel out those with a raised WCC in our analysis. This highlights the use of scoring mechanisms for identifying pathology, for example, the Alvarado scoring for appendicitis [16]. This difficulty demonstrates the need for a clinician to utilize biochemical markers as an aide to diagnosis in appendicitis, not a definitive measure.

Conclusion

The conventional diagnostic variables for appendicitis, as combined in the AIR score, is an efficient screening instrument for classifying patients as low-, indeterminate-, or high-risk for appendicitis. The addition of the new inflammatory variables did not improve diagnostic

performance further. Combining blood markers was useful in predicting appendicitis and perforated appendicitis. In addition to C-reactive protein and white cell count, blood levels of bilirubin and alanine transaminase may be useful.

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