Derivation and validation of a novel clinical decision aid to distinguish between uncomplicated and complicated appendicitis in children.

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Abstract

Aim of Study:

Non-operative treatment of acute uncomplicated appendicitis (UA) in children might be equally effective to surgery but requires accurate discrimination from those with complicated appendicitis (CA) to ensure safety and maximise efficacy. We aimed to identify specific clinical and laboratory parameters that would aid distinction between UA and CA in children.

Methods:

Retrospective review of consecutive children with a clinical +/- radiological diagnosis of acute appendicitis that underwent appendicectomy in three specialist paediatric surgical centres between March 2017 and February 2018. Demographic, clinical and laboratory data were retrieved and analysed in relation to intra-operative and histopathological findings. CA was defined as gangrene and/or perforation seen intra-operatively and/or in histopathological analysis. Multiple logistic regression analysis was used to derive a novel prediction model that could accurately distinguish UA and CA. *A priori* we set analytical parameters so as to ensure the score had a positive predictive value (PPV) for UA of >95%. The resulting scoring system was validated in an independent cohort of children.

Main Results:

The prediction model was derived from 130 children (UA: 71; CA: 59) with median age (range) 10 (2-15) years. Initial univariate analysis identified six factors significantly associated ($p<0.01$) with CA (duration of abdominal pain, presence of rebound tenderness, temperature, , white cell count, , neutrophil count and C-reactive protein [CRP]). These variables were entered in the regression model, and points awarded based on the adjusted odds ratios. Receiver operating characteristic analysis demonstrated a threshold of ≥4 points for prediction of CA. The scoring system was validated in an independent cohort of 112 children (UA: 51; CA: 61); it was found to have a sensitivity of 98% and specificity 78%. A score of <4 points had a PPV for UA of 98%.

Conclusions:

Our novel scoring system can discriminate between UA and CA in children with high accuracy. Children with a score <4 could be eligible for non-operative treatment.

Background

Non-operative management (with antibiotics alone) of children with uncomplicated acute appendicitis is emerging as a viable alternative to appendicectomy [1–4]. Indeed the current literature supports the efficacy and safety of non-operative treatment and a number of groups worldwide are evaluating the comparative efficacy of this treatment modality compared to the traditional surgical approach [5–7]. Central to the likely success rate of non-operative treatment is the accurate identification of children who

have uncomplicated acute appendicitis as opposed to more advanced disease [8]; non-operative treatment is likely most effective in cases of uncomplicated appendicitis and the inclusion of children with complicated appendicitis may lead to reduced overall efficacy. This is supported by the current literature [1, 9, 10]. In this context it becomes critical to be able to accurately identify cases of uncomplicated appendicitis.

In healthcare settings where diagnostic imaging is routinely used for the assessment of children with abdominal or right iliac fossa pain then ultrasound may provide a means of accurately providing this distinction. However ultrasound is not routinely used in all healthcare settings and in the United Kingdom it is only used in approximately one third of cases prior to appendicectomy [11, 12] Therefore diagnostic imaging is not a universally applicable tool for the routine identification of cases that may be suitable for non-operative treatment. Whilst there are a number of clinical decision aids that may assist in the identification of children with or without appendicitis [12–14], we are aware of just one that is designed to support the distinction we are seeking to make but this relies heavily on imaging findings [8]. Therefore we sought to develop an evidence based clinical decision tool to aid distinction between uncomplicated and complicated appendicitis in children in whom a diagnosis of appendicitis has been made. We determined *a priori* that this would *not* include diagnostic imaging.

Methods

Patients

Data were collected from three specialist children's hospitals in the United Kingdom for consecutive children with a clinical and/or radiological diagnosis of acute appendicitis between March 2017 and February 2018. Some of these children were participants in a feasibility randomised controlled trial comparing non-operative management with appendicectomy for uncomplicated acute appendicitis and data from these cases were collected prospectively. Data from all other cases were collected retrospectively. A range of clinical, physiological and laboratory parameters were collected on each case (guided by parameters included in clinical decision aids for the diagnosis of appendicitis) along with a final diagnosis classified as either no appendicitis (i.e. negative appendicectomy) uncomplicated acute appendicitis or complicated appendicitis. Uncomplicated appendicitis was defined as either surgeon finding of acute inflammation without macroscopic evidence of gangrene or perforation and no evidence of perforation on histological analysis. Complicated appendicitis was therefore defined as appendicitis with any features consistent with more advanced disease including gangrene, perforation, abscess and appendix mass. As a result, these outcomes of uncomplicated and complicated appendicitis were mutually exclusive. Formal ethical approval was not required for this study in accordance with guidance from the United Kingdom Health Research Authority. The study was registered as a service evaluation in each participating centre and was completed according to a predefined protocol.

Analysis

For the purposes of analysis the cohort was divided in two groups of approximately equal number of cases to allow for score derivation and external validation. The derivation cohort comprised all cases treated in two of the three centres and the validation cohort comprised all cases treated in the third centre. To derive the prediction model initially univariate analysis was performed to identify factors that were significantly associated with complicated appendicitis in the derivation cohort. Fishers exact test was used for categorical data and Mann Whitney U test for continuous data. Based on the magnitude of the difference in factors that were significantly associated with complicated appendicitis (defined by $p<0.01$), variables were entered into a multivariate logistic regression model to determine the strength of their adjusted association with complicated appendicitis. Each of these variables was subsequently assigned a score based on the adjusted odds ratio within this multivariate model. Receiver operating characteristic (ROC) analysis was then used to identify an optimum threshold for each component of the score for the prediction of complicated appendicitis.

From the outset we determined that the clinical decision aid would need to provide a highly accurate prediction of cases of uncomplicated appendicitis since we wished to be as certain as possible that all cases being selected for non-operative treatment would truly have uncomplicated appendicitis. We therefore sought a score with a positive predictive value of ≥95%, that is if the score suggested that the child had uncomplicated rather than complicated appendicitis then the clinician could be 95% certain that the child did indeed have uncomplicated appendicitis. We recognised from the outset that this may result in a lower sensitivity and specificity of the decision aid overall but were willing to accept this for this specific clinical situation. To achieve this we validated the score internally within the derivation cohort and subsequently identified revised thresholds for each of the included clinical variables that would allow for a scoring system with the diagnostic accuracy that we sought.

Having successfully derived a scoring system in the derivation cohort we validated it externally in the independent validation cohort.

Results

Between March 2017 and February 2019, a total of 269 consecutive children were treated for suspected acute appendicitis in the 3 specialist paediatric surgery centres included in our study (Centre A: 79; centre B: 64; centre C: 122). Most patients (253; 94%) underwent appendicectomy, and only 16 patients (6%) were treated non-operatively (antibiotics with/without drainage) due to the formation of a well-defined appendix mass/abscess. In 8 children (3% of operated), the appendix was found to be normal in histopathological analysis, and an additional 3 (1% of operated) were excluded due to incomplete data collection. The remaining 242 patients had a median (range) age of 10 (2–16) years and weight 34 (13–112) kg. One hundred and forty-eight (61%) were male, 195 (81%) underwent laparoscopic appendectomy (7% of these converted to open), and 120 (49%) met the criteria for complicated appendicitis based on either surgeon assessment and/or histological analysis.

Score Derivation

The score derivation cohort (treated at centres A and B) included a total of 130 patients with a median age of 9 (2–15) years and weight 32 (13–105) kg; 77 (59%) were male and 59 (45%) had complicated appendicitis. The clinical and laboratory findings in children with uncomplicated and complicated appendicitis are summarised in Tables 1 and 2.

Children with complicated appendicitis were more likely to be male, were significantly younger, and had longer duration of abdominal pain than their peers with uncomplicated appendicitis. Moreover, more patients with complicated appendicitis had rebound/percussion/hopping tenderness and significantly higher body temperature when admitted to the hospital. Laboratory analysis demonstrated significantly higher white cell count, neutrophil count, and CRP in the complicated compared to the uncomplicated appendicitis group. Based on the magnitude of the inter-group difference in univariate analysis, 3 clinical parameters (right iliac fossa rebound/percussion/hopping tenderness, duration of pain, and temperature) and 3 laboratory parameters (white cell count, neutrophil count, CRP) were included in the multivariate logistic regression analysis model.

ROC analysis was used to determine cut-off values for the 5 continuous variables for inclusion in our prediction model (Figure 1). The most appropriate cut-off value for each variable was identified based on the optimum combination of sensitivity and specificity to achieve maximal area under the curve (AUC). This analysis led to the following cut-off values: duration of pain ≥ 2 days, temperature ≥ 37.3°C, white cell count ≥ $17x10^9$/L, neutrophil count ≥ $13x10^9$/L, CRP ≥ 50g/L.

Dichotomised values (i.e. above or below cut-off value) for each of these variables were entered into a multivariate logistic regression model (Table 3) that accounted for 71% of the variance. Each of the score parameters was awarded 1 or 2 points based on the adjusted odds ratio in this model. As a result, the maximum possible value is 9 points. ROC analysis identified a threshold of < 4 points for the score to predict uncomplicated appendicitis (AUC 0.92 (95%CI 0.88–0.96; Figure 2).

Score Optimisation

Prior to validating the score in the independent validation cohort, we first validated it internally in the derivation cohort in order to optimise its performance. Based on a threshold of ≥4 for the identification of complicated appendicitis, the non-optimised score had a sensitivity of 54/59 92%, specificity of 62/71 87%, negative predictive value of 62/67 93% and positive predictive value of 54/63 86% (Table 5). Although the score was based on the best-fitting prediction model, it resulted in a false negative rate of 7.5% (5/67) that was considered to be unacceptably high for its intended purpose. For this reason, we undertook an optimisation process aiming to maximise the number of cases of uncomplicated appendicitis correctly identified by the score and therefore minimise the number of patients with complicated appendicitis falsely assigned to the uncomplicated appendicitis group. The optimisation process resulted in an updated version of the score, which is summarised in Table 6 (note that the white

cell value cut-off was adjusted to ≥ 15x109/L), and ROC curve analysis re-confirmed the threshold of < 4 points for the prediction of uncomplicated appendicitis (Figure 2). The revised score resulted in a significant reduction in the false negative rate; only 1 of 60 patients (1.5%) with a score <4 was found to have complicated appendicitis (Table 7). The sensitivity was 98%, specificity 83% and the positive and negative predictive values were 82% and 98% respectively.

External validation

The score validation cohort (centre C) comprised a total of 112 patients, 71 (63%) of which were male and 61 (54%) had a final diagnosis of complicated appendicitis. Their demographic and clinical features were similar to those in the derivation cohort. (Supplementary tables S1 and S2).

The results of the independent validation process in the validation cohort are summarised in Table 8. The scoring system was shown to be highly sensitive for the detection of cases of complicated appendicitis (sensitivity 98%), but only moderately specific (specificity 78%). However, a score of <4 achieved a high diagnostic accuracy (negative predictive value) for uncomplicated appendicitis of 98%.

Discussion

In this study we aimed specifically to create a clinical decision aid based on clinical and laboratory parameters that would aid clinicians in their distinction between cases of uncomplicated and complicated appendicitis in children. Our primary aim was to facilitate the identification of cases of uncomplicated appendicitis that may be candidates for non-operative treatment either in routine clinical practice or in ongoing research. Specifically, we did not include any diagnostic imaging modality in our scoring system because in our current clinical setting diagnostic imaging is not routinely used and it is therefore impractical to propose it at present.

Of interest, the distinction between uncomplicated and complicated appendicitis is not one that surgeons are routinely required to make unless they are considering a treatment modality other than appendicectomy. The majority of children suspected to have appendicitis are simply treated with appendicectomy [11] and the findings at surgery typically guide subsequent postoperative management. It is only within the context of considering treatment of cases for non-operative treatment that such a distinction becomes important. In a recent feasibility trial of non-operative treatment compared to appendicectomy surgeons were less accurate at identifying cases of uncomplicated appendicitis that had been anticipated. When surgeons were simply given guidance to use their clinical judgement to identify cases of uncomplicated appendicitis the accuracy of their prediction was just 78% [15]. We anticipate therefore that this evidence-based scoring system will be useful in clinical practice and ongoing research.

From the outset we wished to provide a scoring system that had very high (95%) positive predicted value for identification of cases of uncomplicated appendicitis. Whilst we have achieved this, we note that

approximately 15% of cases in both derivation and validation cohorts who had a score of 4 or more actually had uncomplicated appendicitis. These cases would be considered ineligible for non-operative treatment were such a scoring system to be used in the future. Whilst this is a potential limitation of the use of this scoring system it is important to acknowledge that firstly no scoring system is perfect and secondly that the aim was to be able to select cases with an extremely high likelihood of having uncomplicated appendicitis in an effort to reassure surgeons considering non-operative treatment that they were selecting appropriate cases. The trade off in being able to confidently predict the presence of uncomplicated appendicitis is the lower specificity of the scoring system overall; some cases of uncomplicated appendicitis may be overlooked as candidates for non-operative treatment as a result.

It is of interest but perhaps not surprising that the clinical and laboratory variables we have that are included in this scoring system are similar to those present in many of the scoring systems designed for the diagnosis of appendicitis such as the Alvarado score [13], Paediatric Appendicitis Score [14] and Shera score [16]. We emphasise that this present scoring system should not be used for the diagnosis of appendicitis but moreover may be applied only once a diagnosis of appendicitis has been determined by the clinical team who then wish to distinguish between uncomplicated and complicated disease. Thus the pre-test population for our scoring system and those aimed at aiding a diagnosis of appendicitis are notably and importantly different.

The strengths of our study are that we have developed a novel scoring system and used separate derivation and validation cohorts. The scoring system performed extremely well in accurate case identification in the independent validation cohort. Although both cohorts comprised over 100 children, this sample size remains relatively small when considering the overall population of children who develop appendicitis annually. We now therefore recommend further prospective validation of the scoring system in larger external cohorts to ensure that it is generalisable. To our knowledge this is the first scoring system to be developed specifically to aid distinction between cases of uncomplicated and complicated appendicitis. Previous clinical trials of non-operative treatment have selected cases of uncomplicated appendicitis based on a variety of methods including clinician assessment, radiology and apparently arbitrary cut-offs in clinical and laboratory parameters which as far as we are aware are not evidence based [7, 17]. We hope that this evidence-based approach will facilitate more accurate identification of cases of uncomplicated appendicitis in the future.

Declarations

Acknowledgements

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Tables

Due to technical limitations, Tables 1-6 are provided in the Supplementary Files section. Table 4 was not provided with this version.

Figures

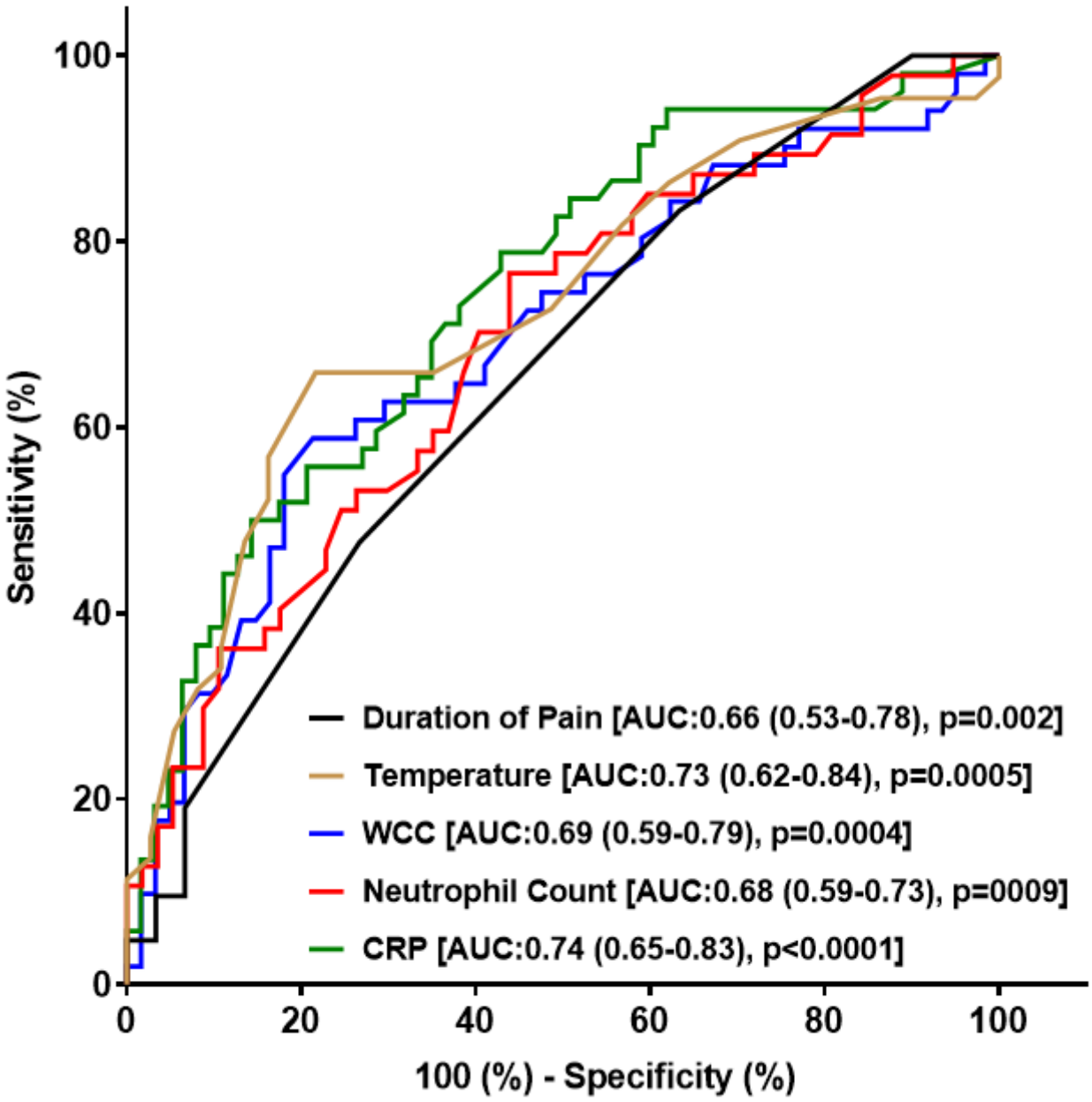

Figure 1

Area under curve analysis for each component of the score

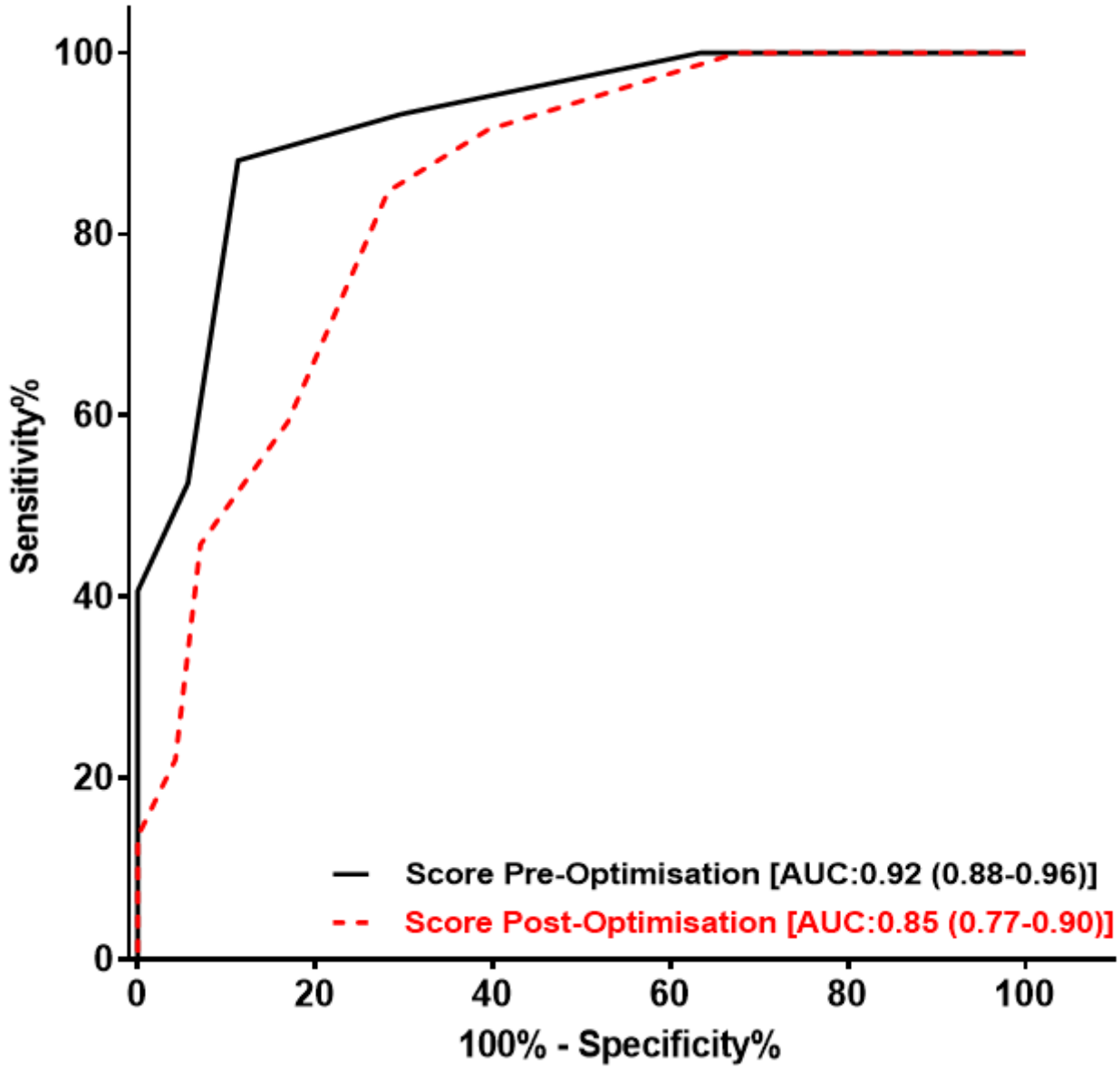

Figure 2

Area under curve analysis for performance of the score overall

Supplementary Files

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- Supplementarytables.docx
- Tables.docx