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SHORT COMMUNICATION

Improving diagnostic accuracy in clinically ambiguous paediatric appendicitis: a retrospective review of ultrasound and pathology findings with focus on the non-visualised appendix

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Objective: To compare pre-operative ultrasound to histopathological results and retrospectively assess the diagnostic accuracy of ultrasound in paediatric appendicitis.

Methods: 5 year review of all appendectomies performed in patients <16 years old in a tertiary referral university hospital. 983 patients had an appendectomy over the time period while 189 patients had a preoperative ultrasound. We retrospectively reviewed all of the preoperative imaging in conjunction with the reports for the 189 patients; our aim was to determine the sensitivity of preoperative ultrasound for the diagnosis of acute appendicitis.

Results: Of the 189 patients who had an ultrasound, 102 had histology positive for appendicitis and 87 had normal histology. Sensitivity overall was 72.55% [95% confidence interval (CI) 62.82 to 80.92] and specificity was 77.01% (95% CI 66.75 to 85.36). A suggested ultrasound diagnosis of appendicitis made positive pathology three times more likely and a normal ultrasound made positive

pathology three times less likely [positive-predictive value 3.16 (95% CI 2.11 to 4.72) negative predictive value 0.36 (95% CI 0.25 to 0.50)]. 77% (67/87) of the patients whose pathology was ultimately normal had an ultrasound which was either normal or suggested an alternative diagnosis. However, in the 33 (17%) of patients with a non-visualised appendix, no secondary signs of inflammation or alternative diagnosis 16 (48%) had pathologically confirmed appendicitis.

Conclusion: Ultrasound has the potential to improve diagnostic accuracy in clinically ambiguous appendicitis.

Advances in knowledge: This paper furthers the evidence on the efficacy of ultrasound as a diagnostic tool in acute appendicitis in children, especially when the diagnosis is clinically equivocal. It also sheds further light on the "non-visualized appendix" with almost half of these patients having pathologically confirmed appendicitis; meaning advanced imaging with CT or MR may be indicated in this cohort.

INTRODUCTION

Appendicitis is the most common surgical presentation requiring admission in children.¹ At Galway university hospital, patients whose history, examination and laboratory findings are suggestive of appendicitis are treated directly with surgery. Those with equivocal findings proceed to imaging. Hence, our cohort of patients is the one which presented clinicians with a diagnostic dilemma. Despite investigation, the diagnosis is often uncertain² which can lead to delayed or suboptimal management.

While a stepwise progression from ultrasound to MRI has recently been touted as having "put the issue to bed"^{2,3} in healthcare systems with limited access to MRI the diagnosis of paediatric appendicitis still poses a significant clinical challenge.

There remains continued debate in the literature about which is the optimal diagnostic pathway in children with suspected appendicitis.^{4,5} Ultrasound offers many advantages being highly sensitive and specific, relatively cheap and available and having no associated radiation burden.⁶

Furthermore, it is rarely necessary to use sedation to complete an ultrasound examination.⁶

The diagnostic accuracy of ultrasound was prospectively assessed by Carpenter *et al* in their 2017 paper.⁷ Their study of 577 patients showed how ultrasound is highly specific but non-sensitive for differentiating perforated paediatric appendicitis. While high levels of diagnostic accuracy have been widely reported elsewhere in the literature,⁸ there is some debate as to the “real life” usefulness of the modality, outside of arranged clinical trials,⁹ and what to do in the cases where the appendix is not visualised.¹⁰ In this paper, we outline how even in cases providing a degree of diagnostic uncertainty, ultrasound of the paediatric appendix has the potential to improve diagnostic accuracy. Thus potentially avoiding unnecessary surgery as well as facilitating timely intervention in those with appendicitis.

The aim of this study was to retrospectively assess the utilisation of ultrasound in children who proceed to appendectomy and to identify the diagnostic accuracy of ultrasonography compared to the gold standard of histopathological results.

Our hypothesis was that ultrasonography would improve diagnostic accuracy by reducing the number of false-positive (FP) diagnoses of appendicitis.

As a study of diagnostic accuracy this manuscript was prepared in accordance with the STRAD checklist.¹¹

METHODS AND MATERIALS

Study design

This retrospective cohort study was approved by our institutional review board. Our institution is a university affiliated tertiary urban referral centre servicing a population of approximately 750,000 people.

Eligibility criteria were all those patients aged 16 years or younger at the time of presentation who had a preoperative ultrasound and proceeded to appendectomy.

We retrospectively examined pathology records for all appendectomies carried out on patients <16 years of age over a 5-year period from July 2011 to July 2016 (*i.e.* a consecutive series). In all, 983 appendectomies were carried out of which 189 had a pre-operative ultrasound. The reference standard for diagnosis of appendicitis was histopathological results and ultrasonography was the index test.

Test methods

Our local Radiologic Information and Picture Archive and Communication systems were searched for all those patients identified from the pathological database. If the patient had a pre-operative ultrasound they were included for analysis.

Included patients underwent graded compression ultrasound using 5–12 MHz linear transducer. Sonography was in all cases carried out by paediatric specialist sonographers or attending radiologists. Where the appendix was not visualised,

transabdominal pelvic examination as carried out patients to look for secondary signs of inflammation or alternative diagnoses such as gynaecological pathology in females.

Both images and radiologic reports were reviewed by two authors (one from the department of surgery and one from the department of radiology) and were given an Appy Score.¹² Results were then divided into “positive” or “negative” for appendicitis according to the same methods described by Trout *et al* (Strategy 1).⁹ Cases where the appendix was not visualised were classified as “negative” for purposes of analysis. Both authors were blinded to the pathology results when reviewing the radiologic reports and images. Any disagreements were resolved by consensus.

Pathologic reports were reviewed for the presence or absence of appendicitis. No alternative diagnoses (*e.g.* neoplasm) were found within our sample.

Results were then cross tabulated with a “positive” ultrasound leading to a positive pathologic diagnosis being deemed a “true-positive” and so on. Sensitivity and specificity were then calculated with 95% confidence intervals (CIs). Subgroup analysis was also carried out comparing radiologist and sonographer operators. A *p*-value of 0.05 was deemed to represent significance. All data were analysed using SPSS 24 for Mac (IBM Corporation New York 2016).

RESULTS

In total, there were 983 appendectomies performed on patients aged <16 in the period reviewed, of who 189 had pre-operative ultrasound. [Figure 1](#) outlines the flow of patients in our sample. An outline of basic patient demographics is available in [Table 1](#). The average age was 11 (range 2–16 standard deviation 3) 69% were female. Only 54% (103) of patients who had an appendectomy had pathologically confirmed appendicitis. Overall, the sensitivity of ultrasound for acute appendicitis was 72.55% (95% CI 62.82 to 80.92) and specificity was 77.01% (95% CI 66.75 to 85.36). A suggested diagnosis of appendicitis yielded a positive likelihood ratio of 3.16 and a negative report a negative likelihood ratio of 0.36. [Table 2](#) outlines the results of the tests of diagnostic accuracy of ultrasound. The appendix was not visualised in 33 (17%) cases of which 16 (48%) had pathologically confirmed appendicitis. 46 (24%) cases were scanned by an attending radiologist and the remaining 143 (76%) by paediatric specialist sonographers. There was no statistically significant difference between either sensitivity 75.86 and 71.23% (95% CI 56.46 to 89.70% and 59.45 to 81.23%) or specificity 88.24 and 71.23% (95% CI 63.56 to 98.54% and 62.44 to 83.99%) (*p* > 0.1) respectively. In the 33 (17%) of patients with a non-visualised appendix, no secondary signs of inflammation or alternative diagnosis 16 (48%) had pathologically confirmed appendicitis. [Figure 2](#) outlines the increasing trend toward utilisation of ultrasound over the 5 years of the study (2011 and 2016 contain only 6 months of data each).

DISCUSSION

While appendicitis is the most common surgical emergency in children,¹ the best method for diagnosis is still a matter for

Figure 1. The flowchart of patients included in our study. Flowchart of patients in our sample. FN, false negative; FP, false positive; TN, true negative; TP, true positive.

debate.¹³ In this study, we have shown how ultrasound in clinically equivocal cases has the potential to reduce the FP rate. There is a push in some healthcare systems toward increasing use of imaging for cases of suspected appendicitis¹⁴ with the majority of patients undergoing CT in some institutions.¹⁵ While in the UK, Ireland and Australasia only the minority of patients receive imaging and ultrasound is the front-line test¹⁶; CT is used sparingly.

At our institution, paediatric patients with suspected appendicitis are treated directly with surgery without imaging if there is a sufficiently high clinical suspicion. Ultrasound is the first-line

imaging investigation, used in 19% of cases while CT was only used in 3 (0.3%) of almost 1000 cases. Within usual hours (8 am to 6 pm Monday to Friday), patients who require ultrasound are imaged by paediatric specialist sonographers and outside these hours by radiology attendings. Our sample is representative of real-life practise in Ireland (and the UK and Australasia) but may not reflect the population as a whole. This is because only patients who provide a diagnostic dilemma proceed to ultrasound at our institution and most obvious cases bypass imaging altogether.

Table 1. Demographics and pathology results

Total	189
Male:female	59:130 (31%:69%)
Mean age, years [Range]	11 SD 3 [2–16]
Appendicitis, n (%)	103 (54%)
Normal appendix, n (%)	86 (46%)

Table 2. Summary of results

Statistic	Value	95% CI
Sensitivity	72.55%	62.82 to 80.92%
Specificity	77.01%	66.75 to 85.36%
Positive likelihood ratio	3.16	2.11 to 4.72
Negative likelihood ratio	0.36	0.25 to 0.50
Positive predictive value	78.72%	71.21 to 84.70%
Negative predictive value	70.53%	63.11 to 77.00%

CI, confidence interval.

Figure 2. Annual relative increase in the use of preoperative ultrasound expressed as a percentage.

Figure 3. Clockwise from top left: Two ultrasound images showing a normal appendix as a blind ended tubular structure in the RIF measuring less than 6 mm in diameter. A gross histology specimen. Normal vermiform appendix and mesoappendix. There is some congestion of the serosal capillaries which is procedural (clamp mark evident on the right). Two histopathological specimens with Hand E staining showing normal appendix with no evidence of suppurative inflammation. The dense lymphoid tissue in the submucosa is a normal feature. Vegetable matter is present in the appendiceal lumen. RIF, right iliac fossa.

Figure 4. Clockwise from top left: two ultrasound images transverse and longitudinal showing an inflamed appendix as a blind ended tubular structure in the RIF measuring >6 mm in diameter. A gross histology specimen showing a markedly inflamed appendix with dense cream exudates extending from tip to base. The appendiceal tip appears dilated. Two histopathological specimens with Hand E staining Transmural inflammation with serositis, extending out to the mesoappendix. in the appendiceal lumen. RIF, right iliac fossa.

This potentially could impact the perceived diagnostic accuracy of ultrasound. Even allowing for this, our sensitivity and specificity compares favourably with the literature,⁸ especially in comparable “real-life” studies.⁹

The appendix was not visualised, with absence of secondary signs of inflammation and no alternative diagnosis was given, in 33 (17.5%) of patients of whom 16 (48%) had pathologically

confirmed appendicitis. This is interesting as it runs contrary to recently published literature, with a similar sample size and non-visualised rate, which suggested a likelihood of <2%.⁹ This clinical importance of the “non-visualised” appendix is a noteworthy findings for centres that does not routinely use CT in paediatrics.

Overall, our FP rate of 23% when the appendix was visualised, is higher than much of the reported literature (but in keeping

Figure 5. Left to right a transverse ultrasound image of a perforated appendix with a fluid filled defect in the posterior part of the appendix. (arrow). A gross pathology specimen of a perforated appendix and a histopathology specimen showing ulceration of the luminal surface. RIF, right iliac fossa,

with real-life studies). Negative appendicectomies are becoming perceived as increasingly unacceptable. Indeed, there is a >10% complication rate reported in the recent literature.¹ However, the overall FP appendicectomy rate was 32% ($n = 983$) and within the clinically equivocal group that underwent ultrasound that rose to 46% showing the potential for ultrasound to reduce the rate of negative appendicectomies. Our institution's overall negative appendicectomy rate of 32% (29% removing the equivocal cases) which is higher than other comparable institutions.¹

Our false negative (FN) rate was 27.5% which again is higher overall than reported in the literature. While there are obvious negative outcomes associated with delayed diagnosis of appendicitis, the option remains in these equivocal cases to repeat ultrasound if the patient deteriorates or to proceed to CT.

The rate of use of ultrasound steadily increased over the years included in keeping with international trends. It also shows that while FP and FN rates are an issue, referring clinicians are increasingly aware and accepting of the important role of ultrasound in the diagnosis of acute appendicitis in children.

It is interesting that in our study there were no differences in diagnostic accuracy when the examination was carried out by a sonographer or radiologist. Ultrasound is well established as a user-dependent modality, however all of our operators were paediatric trained. This might explain our finding of equivalent compared to other studies where a user-dependent variability in diagnosis was seen.⁹

Our institution's 0.03% CT rate is in stark contrast to some American institutions,^{14,15} but exactly in line with a large study in Singapore¹⁰ and overall rates in the UK and New Zealand.¹⁶ CT, however bears a significant radiation burden with each abdominal CT estimated to increase the lifetime risk of cancer related death by 0.18% in children. Our institution, like others, strives to keep all radiation use, especially in children, as low as reasonably achievable. We believe that in general ultrasound has the potential to reduce FP diagnoses of appendicitis to an acceptable level thus reducing reliance on CT. Indeed, we strive to minimise the use of CT in children overall. There is, however, clearly potential to improve the 48% negative appendicectomy rate in the 33 appendix-not-visualised cases and CT may well have been under utilised in this cohort.

Point Of Care Ultrasound (POCUS) has gained traction recently especially in the emergency literature. Ultrasound is well-established as a user dependent modality, and this is especially true in paediatrics. Recent studies have shown some potential for POCUS in reducing the need for CT in suspected paediatric appendicitis.¹⁷ This small study also however demonstrated the how imaging performed in the radiology department was more specific and more consistent. The authors tend to agree with a recent meta-analysis of the relevant data, that while

"In the hands of an experienced operator, POCUS is an appropriate initial imaging modality for diagnosing appendicitis ... it is premature to utilize POCUS as a stand-alone test or to rule out appendicitis".¹⁸

Our study had several limitations, the first being its retrospective design. Using pathology records as our starting point means that we did not examine every paediatric abdominal ultrasound undertaken within the study period, this does however provide a definitive "truth" as all patients have a confirmed diagnosis. Our sample consists of the subset of patients who had ultrasound. These patients posed clinicians a diagnostic dilemma and sensitivity and specificity may have been impacted up to because of this. Furthermore, unfortunately we have no information regarding the body mass index or centile weight of the patients included.

We have again confirmed the usefulness of ultrasound in the management of suspected paediatric appendicitis in children in a real-world clinical setting. This is necessary due to the controversy about the best imaging modality, the increasing use of CT, and the debate around the significance of the non-visualised appendix. In a healthcare system where only the minority of patients undergo imaging, we have shown the potential for ultrasound to identify those patients suitable for appendicectomy and expedite treatment when needed. As a cost-effective resource without an associated radiation burden, the authors advocate for a low threshold for the use of sonography and for the reservation of CT for only the most challenging of cases.

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