THE UTILITY OF ABDOMINAL ULTRASOUND IN THE DIAGNOSIS OF PAEDIATRIC ABDOMINAL TUBERCULOSIS:

A SINGLE CENTRE REVIEW

by

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1. Declaration Page

I, Dr. Vishesh Sood hereby declare that the work on which this dissertation is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree at this or any other university.

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I. Literature Review

1. Introduction

Childhood tuberculosis is a common disease worldwide, with an increased prevalence and propensity for severe, disseminated disease in areas with a high burden of concomitant HIV infection. [1] The estimated TB burden in South Africa remains one of the highest in the world, with a reported incidence of 520 per 100 000 population in 2018, and 15 960 incident cases in children below 15 years of age in the same year. [2] Disease burden varies significantly by province, with a reported incidence in the Western Cape on 681 per 100 000 in 2015. [3] According to the World Health Organisation (WHO), at least 1 million children fall ill with TB each year, and 17% of TB deaths occur in children living with HIV. [4] Although pulmonary disease is the leading form, up to 15% of incident cases reported in 2018 involved extra-pulmonary infection, contributing to a significant increase in overall morbidity and mortality. [2]

Common forms of extra-pulmonary disease include involvement of the pleura, lymph nodes, abdomen (including peritoneum, gastrointestinal and genitourinary tracts, lymph nodes and solid organs), central nervous and musculoskeletal systems. [5] Abdominal TB, specifically, is thought to result from a range of potential mechanisms including: i) haematogenous seeding from primary pulmonary infection, ii) lymphatic spread via involved lymph nodes and iii) direct ingestion of bacilli as a result of swallowed secretions. [6] Patterns of involvement within the abdomen are thus varied, contributing to the heterogeneity in clinical presentation and subsequent challenge in timeously establishing the diagnosis. [6] A recent study reported the commonest presentation of paediatric abdominal TB within their cohort as a triad of abdominal pain, fever and loss of weight, occurring in over 50% of cases, and with median time from presentation to diagnosis of 4 months. [7]

2. Imaging in paediatric thoracic TB

Owing to the paucibacillary nature of paediatric TB, confirming the diagnosis when clinical suspicion arises presents a considerable challenge. According to consensus case definitions, children are classified as having microbiologically confirmed disease if *Mycobacterium tuberculosis* is confirmed on TB culture and/or Xpert MTB/RIF assay. [8] As children do not readily expectorate sputum, obtaining samples for the aforementioned assays is often difficult. Thus alternative methods are employed to obtain representative respiratory specimens for microbiology such as gastric lavage and sputum induction. [9] As such, a large proportion of paediatric pulmonary TB diagnoses are made without microbiological confirmation, on the basis of strong clinical suspicion, exclusion of alternative diagnoses and with supportive evidence obtained on imaging, tuberculin skin test response, and response to TB treatment.[8]

The role of chest radiography in the diagnosis of paediatric pulmonary tuberculosis has been extensively studied. [10–12] The hallmark chest radiographic feature of primary tuberculosis is hilar lymphadenopathy, however additional findings including airway attenuation, airspace opacities and pleural effusions are well described. [10] The reported sensitivity and specificity of these findings in diagnosing TB both vary, with low overall inter-rater agreement amongst individuals reviewing these studies (k=0.26, 95% CI = 0.18-0.36) [10] According to a recent study, ultrasound was found to be more effective in the diagnosis of consolidation, mediastinal lymphadenopathy and pleural effusion as compared with chest radiography, with higher levels of inter-observer agreement (consolidation k=0.67 vs 0.47, pleural effusion k=0.86 vs 0.56 and enlarged lymph nodes k=0.56 vs 0.27). [11] The sensitivity of ultrasound imaging is however, limited by operator experience, patient co-operability and available sonographic windows, the latter precluding comprehensive assessment of the lungs and mediastinum.

3. Imaging in paediatric abdominal TB

Owing to the aforementioned heterogeneity in clinical presentation amongst children with abdominal TB, several techniques have been utilised to confirm the presence of abdominal disease, including a variety of imaging techniques (abdominal ultrasound, computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography/computed tomography (PET CT)) and more invasive procedures for obtaining representative specimens for microbiology studies such as ascitic fluid tap and diagnostic laparoscopy for tissue sampling. [13–15] Imaging techniques are however, more frequently employed because they are non-invasive.

I.3.1 Computed tomography

The utility of CT has been demonstrated in several studies, with distinct advantages over alternative imaging modalities. [14,16] With the advent of multidetector CT, rapid acquisition over a large volume of tissue ensures high spatial resolution despite breathing-related motion, whilst contrast enhanced imaging facilitates characterisation of enhancement patterns which may allude to disease in the absence of discrete morphologic abnormalities.

Although non-specific, the detection of abnormal lymphadenopathy may contribute to the diagnosis of paediatric TB in the appropriate clinical setting. Visceral/ solid-organ TB most commonly manifests with multiple hypoattenuating lesions scattered throughout the affected organ, whilst mesenteric/ omental thickening and ascites are seen in the context of peritoneal involvement. [14] Further utility is demonstrated with involvement of the gastro-intestinal tract (most commonly the terminal ileum) where the commonest manifestation is mural thickening in the affected segment. [14] Disadvantages of CT include the radiation dose penalty incurred to the developing abdomen, which increases the risk of future stochastic effects (e.g. carcinogenesis), and the need for iodinated contrast media. [14] As such, CT is often reserved for cases of particular complexity or diagnostic challenge. [14]

I.3.2 Magnetic resonance imaging

Magnetic resonance imaging offers many of the same advantages as CT, with the distinct advantage that it lacks ionizing radiation and offers superior contrast resolution in the depiction of tissue inflammation. [14] In addition, dynamic MR imaging techniques provide insight into bowel wall motion/ peristalsis, thus acquiring both anatomic and functional information.[14] Lastly, in patients with deranged renal function, non-contrast MRI offers more information than an equivalent non-contrast abdominal CT scan. [14]

Disadvantages when compared to CT include availability, cost and inferior spatial resolution. MR imaging is also time consuming, requiring sedation or general anaesthesia in the majority of children under 6 years of age to ensure that images are of diagnostic quality. [14]

I.3.3 Positron emission tomography/computed tomography

Fluorine-18 fluorodeoxyglucose (FDG) PET-CT is a non-specific imaging technique with utility in infectious, inflammatory and neoplastic conditions. [16] As such, findings in abdominal TB are largely non-specific with areas of increased uptake noted in involved organ systems. [16] In areas where TB is endemic, infection with *Mycobacterium tuberculosis* is a common cause of false-positive results in patients undergoing PET-CT imaging for cancer workup. [17] Particular utility has been demonstrated in the detection of TB related disease activity in unusual sites such as the common bile duct, jejunum and adrenal gland, and in monitoring response to therapy.[16] The cost and radiation penalty are however, prohibitive, precluding its use in routine clinical practice.

I.3.4 Abdominal ultrasound imaging

Abdominal ultrasound is the generally considered the imaging modality of choice when evaluating children with abdominal symptoms that may be attributed to TB or for screening for possible abdominal TB. [18] Its relative ease of availability, low cost, high temporal and spatial resolution and the ability to perform repeated examinations without any related risks or complications make it highly suitable for use in the workup of these patients. [19] Imaging features reported to correlate with the presence of abdominal TB include [15]:

i. Hepatomegaly +/- hepatic granulomas/ microabscesses
ii. Splenomegaly +/- splenic microabscesses
iii. Lymphadenopathy (considered abnormal based on a short axis diameter of greater than/ equal to 10 mm as measured in the axial plane, and an abnormal morphology characterised by loss of the normal fatty centre and a rounded configuration) [20,21]
iv. Ascites (free or multiloculated fluid collections, the latter often containing multiple fibrin strands)
v. Bowel wall thickening, most often seen in the ileo-caecal region and thought to be related to the regional abundance of lymphoid tissue

4. Challenges in diagnosis

The aforementioned sonographic findings are not considered pathognomonic but rather suggestive of abdominal tuberculosis since they may result from a wide spectrum of other underlying causative pathologies. Despite the wide range of reported abnormalities in patients with abdominal TB, the sensitivity and specificity of these features, considered alone or in combination, have not been determined.

In the setting of a high concomitant HIV burden, and its known association with asymptomatic lymph node enlargement, the specificity of abdominal lymphadenopathy may be reduced. The cut-off of 10 mm for lymphadenopathy is also contentious, as the size limit for abdominal normal lymph nodes undoubtedly changes with increasing age. This feature is supported by the literature in which various publications suggest upper limits of normal for abdominal lymph nodes in children ranging from 4 – 10 mm. [21–24]

The finding of splenic microabscesses is non-specific, with a wide range of potential aetiologies including, but not limited to, abdominal TB. [25] There is limited literature on tissue biopsy, post-mortem histology and microbiological studies to confirm intra- abdominal infection caused by *Mycobacterium tuberculosis* in the paediatric population. Although splenic parenchyma in adults has typically been described as acoustically homogenous, significant variability occurs in echo patterns amongst children as the lymphoid system matures with age, due to changing splenic white-pulp to red-pulp ratio. [26,27] One study reported that the frequency and intensity of a reticulonodular splenic echo pattern (defined as an echogenic background containing multiple hypoecohic nodules immersed within it) increases with patient age (up to 5 years), and occurs most frequently amongst patients in the age group >1 to ≤ 5 years. [27]

Additional confounders include patient related factors affecting visibility of the intra-abdominal contents, patient co-operation, operator technique and experience level. Lastly, the provision of specific clinical information at the time of requesting an imaging study (e.g. a positive tuberculin skin test for TB, chest radiographic features of TB or the presence of HIV infection) may influence the way borderline imaging features are interpreted and reported.

With specific regard to lymph node characterisation in abdominal TB, CT and MRI offer potential advantages over ultrasound. On CT, the most commonly described finding is peripheral rim-enhancement with central low-density, corresponding to histological features of central caseation and surrounding reactive inflammation. [28] Additional findings of multi-loculation, diffuse hypo-enhancement and calcification have also been reported. [28] Signal intensity of involved lymph nodes on MRI has been shown to differ with the stage of evolution, with hypointensity on T2-weighted imaging corresponding to liquefactive necrosis and varied patterns of post-contrast enhancement as noted on CT. [14] Despite these advantages, the utilisation of these imaging modalities in routine clinical practice is limited as previously discussed.

5. Active versus inactive disease

Determination of tuberculous disease activity remains challenging. Pulmonary disease activity on chest radiograph has generally been characterized by new airspace opacification/ consolidation, thick-walled cavities, miliary nodules and pleural effusions, however these findings must also be considered in the context of clinical presentation and, if possible, with comparison to previous imaging. [16] The expected evolution of sonographic findings pertaining to a diagnosis of abdominal TB in children are not reported in the published literature.

6. Implications for patient management

Delayed initiation of appropriate therapy may result in higher rates of morbidity and mortality associated with disease, whilst the administration of TB treatment is itself associated with a risk of severe adverse events including hepatitis, gastro-intestinal disturbances and central nervous system dysfunction. [29]

Although abdominal ultrasound serves as an easily accessible way to screen the abdomen for pathology, a burden of poorly defined imaging requests within a resource constrained environment has significant downstream effects including delayed access to imaging services for the remaining patient population. The characterisation of extent of disease in a patient, although potentially useful from a clinical perspective, only affects the treatment of a subset of patients, as stipulated by the current South African treatment guidelines for childhood TB which state that: [29]

i. Children with disseminated TB involving 1 or more extra-pulmonary site(s) but excluding CNS TB and miliary TB are treated with a 4-drug intensive phase for 2 months followed by a 2-drug continuation phase for 4 months compared to most children with pulmonary TB who are treated with a 3-drug intensive phase of 2 months followed by a 2-drug continuation phase for 4 months

ii. All children with co-existing HIV infection are automatically regarded as having complicated TB and treated with a 4-drug intensive phase for 2 months followed by a 2-drug continuation phase for 4 months Thus, the presence or absence of abdominal tuberculosis may not influence the TB treatment in HIV-infected children.

7. Conclusion

In clinical practice, abdominal ultrasound is utilized for diagnosis in patients with symptoms of abdominal TB and as screening in patients with suspected TB. Findings on abdominal ultrasound are however non-specific and the variability in reporting practices amongst individuals performing this study are not well documented in the literature.

8. Aims and objectives

Our study aims to explore the utility of abdominal ultrasound in the diagnosis abdominal TB at Red Cross War Memorial Children's Hospital by examining the prevalence of disease and the range of abnormalities on ultrasound that are used when suggesting the diagnosis. Furthermore, we aim to explore the variability in interpretation of these studies amongst radiologists. The findings of this study may assist in refining the indications for performing abdominal ultrasound and standardizing reporting practices in the context of suspected abdominal TB.

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II. Full Text Journal Article For Submission

1. Title page

The utility of abdominal ultrasound in the diagnosis of paediatric abdominal tuberculosis: a single centre review

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All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Vishesh Sood, Tracy Kilborn and Brian Eley. The first draft of the manuscript was written by Vishesh Sood and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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1. **Funding:** None
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3. **Ethics approval:** This research study was approved by the University of Cape Town, Faculty of Health Sciences Human Resources and Ethics committee (Ethics approval number 290/2019).

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2. Abstract

Background:

Childhood tuberculosis (TB) is a common disease worldwide, with an increased propensity for severe, disseminated disease in settings with a high burden of concomitant HIV infection. Ultrasound is commonly used in diagnosing abdominal TB, however the indications for its use are unclear and often vary amongst clinicians.

Objective:

In this study, we describe the findings of ultrasound examinations performed for suspected abdominal TB at a tertiary children's hospital and examine the variability in reporting patterns amongst radiologists performing these imaging investigations.

Materials and methods:

Ultrasound studies performed for "suspected abdominal TB" between 01 January 2013 – 31 December 2018 were reviewed. In studies reported as suggestive of abdominal TB, evidence of microbiologically confirmed disease was sought. Subsequently, a selection of images from these studies were independently reviewed by three paediatric radiologists to determine their level of agreement when interpreting imaging findings.

Results:

During the study period 1093 studies were performed for suspected abdominal TB, of which 166 (15%) had abnormal features suggestive of TB. Forty-seven percent of these patients (78/166) had microbiologically confirmed disease. The commonest reported features were lymphadenopathy, 77% (128/166) and splenic microabscesses, 55% (92/166) for which substantial inter-reader agreement was documented, Fleiss' kappa = 0.64 and 0.66

respectively. There was moderate inter-reader agreement in the diagnosis of abdominal TB among radiologists (Fleiss' kappa=0.47).

Conclusion:

Caution is advised when basing clinical decisions on ultrasound studies performed for suspected abdominal TB, as imaging features are non-specific and there is considerable variability in interpretation of studies among reporting radiologists.

3. Introduction

Childhood tuberculosis (TB) is a common disease worldwide, with an increased prevalence and propensity for severe, disseminated disease in areas with a high burden of concomitant HIV infection. [1] The estimated TB burden in South Africa remains one of the highest in the world, with a reported incidence of 520 per 100 000 population in 2018, and 15 960 incident cases in children below 15 years of age in the same year. [2] According to the World Health Organisation (WHO), at least 1 million children develop TB each year, and 17% of TB deaths occur in children living with HIV. [4] Although pulmonary disease is the leading form, up to 15% of incident cases reported in 2018 involved extra-pulmonary infection, contributing to a significant increase in overall morbidity and mortality. [2]

Common forms of extra-pulmonary disease include involvement of the pleura, lymph nodes, abdomen (including peritoneum, gastrointestinal and genitourinary tracts, lymph nodes and solid organs), central nervous and musculoskeletal systems. [5] Abdominal ultrasound is the imaging modality of choice when evaluating children with abdominal symptoms that may be attributed to TB or when screening for possible TB. [18] Its relative ease of availability, low cost, high temporal and spatial resolution and the ability to perform repeated examinations without any related risks or complications make it highly suitable for use in the workup of these patients. [19] Although more advanced imaging techniques offer significant value, they may be more suited to complex cases as CT incurs a radiation dose penalty whilst MRI is technically more challenging to perform and has comparatively lower spatial resolution.[14]

The range of findings commonly reported on ultrasound in abdominal TB are however, non-specific and may result from a wide variety of underlying aetiologies. In the setting of a high concomitant HIV burden and its known association with asymptomatic lymph node enlargement, the specificity of this finding may be further reduced. In addition, lack of certain age-specific normal reference ranges (e.g. for abdominal lymph node size) results in heterogeneity amongst reporting sonographers/ radiologists when considering whether findings are representative of underlying disease or within normal limits. Furthermore, although splenic parenchyma in adults has typically been described as acoustically homogenous, significant variability occurs in echo patterns amongst children as the lymphoid system matures with age. [26,27] Lastly, the provision of specific clinical information at the time of requesting an imaging study (e.g. a positive tuberculin skin test for TB, chest radiographic features of TB or the presence of HIV infection) may influence the way borderline imaging features are interpreted and reported. Although intuitively familiar amongst individuals performing these imaging studies, these limitations may be less well known to treating physicians who would initiate/ alter TB treatment based on the result of these examinations.

In this study, we describe the findings of ultrasound examinations performed for suspected abdominal TB at a tertiary children's hospital and examine the variability in reporting patterns amongst radiologists performing these imaging investigations.

4. Research Methods and Study Design

II.4.1 Study design and setting

This retrospective study was conducted at Red Cross War Memorial Children's Hospital, Cape Town, South Africa, in children who had abdominal ultrasound for suspected abdominal tuberculosis between 1 January 2013 and 31 December 2018. Two ultrasound machines were utilised over the course of the study period: i) Philips iU22 xMATRIX (Philips Medical Systems, Netherlands) and ii) Toshiba Aplio 400 (Toshiba Medical Systems 2010-2014). The study was conducted in two phases. The first phase involved a review of abdominal ultrasound imaging reports for patients with suspected abdominal TB. For patients whose ultrasound studies were reported as positive for abdominal TB, Xpert MTB/RIF (Cepheid, Sunnyvale, CA, USA) and TB culture results were extracted from the National Health Laboratory Service (NHLS) information system. These patients were classified as having microbiologically confirmed TB if *Mycobacterium tuberculosis* was confirmed on TB culture and/or Xpert MTB/RIF assay. [8]

The second phase involved the selection of representative images from the cohort to form a data set containing 284 studies (140 studies considered positive for abdominal TB, of which 65 had microbiologically confirmed disease, and 144 normal controls). This data set was reviewed independently by three radiologists, with a combined experience of 36 years in paediatric imaging in a TB endemic area, using a tick-sheet (see Appendix I) to determine the extent of agreement in reporting individual findings and their overall assessments. Reviewers were blinded to all clinical information (besides patient age), and specifically to the indication for the investigation (i.e. screening vs diagnostic study). In order to facilitate analysis and provide direction for meaningful clinical action, a subjective classification with four options were provided for the reviewer's overall assessment of the studies as follows:

I. **highly likely to be in keeping with abdominal TB**
   - findings would be sufficient, in the appropriate clinical context, to support initiation of TB treatment

   OR

   - to support adjusting the TB treatment regimen as needed, in a patient with confirmed pulmonary TB

II. **possibly in keeping with abdominal TB**
   - abdominal TB may be considered in the differential diagnosis for these findings, and additional supportive evidence for TB should be sought

III. **unlikely to be in keeping with abdominal TB**
   - an alternative diagnosis is considered more likely

IV. **normal**

Lastly, reviewers were then asked whether they would alter their initial assessment based on the presence of additional information, limited to changing an overall assessment from **"III to II", "II to I"** or **staying the same**. This additional information included: i) the presence of a TB contact, ii) presence of failure to thrive, iii) a positive tuberculin skin test result, iv) the presence of HIV infection and v) a recent chest radiograph suggestive of pulmonary tuberculosis

II.4.2 Data collection

Patients were identified by searching for specific phrases in ultrasound radiology reports on the Red Cross War Memorial Children's Hospital Philips Picture Archiving and Communicating System (PACS), which included: "Abdominal TB"; "Tuberculosis"; "TB"; "TBM"; "TB meningitis" and "Disseminated TB". Data was recorded in Microsoft Excel where a number cypher was used to protect patient confidentiality. Data from the second phase of the study was recorded on individual tick-sheets and subsequently entered into the aforementioned Excel database.

II.4.3 Data analysis

Results from the retrospective review were summarised using descriptive statistics, including frequency distributions and percentages. Associations between sonographic findings, final reviewer assessment and microbiological assays were analysed using a chi-squared test. A two-tailed p-value of <0.05 was regarded as statistically significant. Inter-reader agreement amongst the three reviewers was described using Fleiss' kappa statistic and 95% confidence intervals, with strength of agreement described according to categories stipulated by Landis and Koch. [30] Statistical analyses were performed using IBM SPSS Statistics Version 25 software (Armonk, New York, USA).

II.4.4 Ethical considerations

Ethical approval was granted by the Human Research Ethics Committee of the University of Cape Town (HREC Ref 290/2019) and permission to conduct the study was obtained from the Research Committee, Red Cross War Memorial Children's Hospital.

5. Results

During the 6-year study period, a total of 1093 abdominal ultrasound studies, in 1042 children, were performed for suspected abdominal TB. (Figure 1) The mean number of studies performed per year was 182 (range 174 – 206). One hundred and sixty-six studies (15%) were reported as having imaging features supporting a diagnosis of abdominal TB, and microbiological confirmation of TB was present in 78 of these studies (47%: 78/166). Demographic data for the 166 studies reported as positive for abdominal TB are summarized in Table 1, with the largest proportion noted in the age group 1 – 5 years (55%, n = 92).

Nine individual findings pertaining to a diagnosis of TB were noted amongst studies reported positive for abdominal TB, summarized in Table 2. The commonest findings were lymphadenopathy (n=128) and splenic microabscesses (n=92). With the exception of lymphadenopathy (p=0.03) and ascites (p=0.05), individual imaging features were not significantly more likely to occur in children with microbiologically confirmed TB, refer table 2. Multiple ultrasound findings were frequently reported together, with the largest proportion of studies reported as positive for abdominal TB having 2 findings pertaining to a TB diagnosis (n=59), Table 3. In the studies where only 1 finding was present (n=51), the most frequently documented feature was lymphadenopathy (62.7%, n=32), followed by splenic microabscesses (27.5%, n=14), and microbiological confirmation was present in 39.2% of studies (n=20). When 1-2 imaging features were present, 41.8% of studies (n=46/110) had microbiologically confirmed TB, whilst a higher percentage with 3 or more findings had microbiologically confirmed TB, 57.1% of studies (n=32/56), p = 0.06.

Of the total number of studies which were reported negative for abdominal TB (n=927), 540 (58%) had at least one finding considered to be of possible clinical relevance, summarised by frequency of occurrence in Table 4, and 387 (35%) were normal.

Review of a subset of ultrasound studies (140 originally considered positive for TB and 144 normal controls) by three independent reviewers showed varying degrees of agreement in identifying individual findings, as summarised in Table 5. Perfect or substantial agreement was noted for the presence of psoas abscess, pericardial effusion, ascites, hepatic granulomas, splenic microabscesses and lymphadenopathy, moderate or fair agreement for pleural effusion and bowel wall thickening, and poor agreement for hepatomegaly and splenomegaly.

Examples from studies in which reviewers demonstrated discrepancy when reporting lymphadenopathy and splenic microabscesses, the two commonest TB-related findings noted in the retrospective review, are shown in Figures 3 and 4 respectively.

The initial overall assessments of the 3 reviewers, and their revised overall assessments when provided with additional clinical or chest radiograph information are summarised in Figure 2. All 3 reviewers were more likely to make an assessment of *"highly likely in keeping with TB"* when informed that the tuberculin skin test was positive or the chest radiograph suggestive of TB, though the effect was substantially larger amongst reviewers 1 and 2. Reviewers 1 and 2 were more likely to change their assessments based on knowledge of HIV infection, whilst this did not influence the revised overall assessments of reviewer 3. Reviewer 2 made substantial changes based on a history of failure to thrive, whilst all three reviewers made little to no change based on the history of a confirmed TB contact.

In the studies reported as suggestive of abdominal TB (combination of studies reported as "possibly in keeping with TB" and "highly likely in keeping with TB"), microbiologically confirmed disease was present in 51 % (Reviewer 1), 48% (Reviewer 2) and 58% (Reviewer 3) of studies respectively. When reviewers were allowed to revise their initial overall assessments in response to additional clinical or chest radiograph information, no single factor resulted in a simultaneous increase in percentage of microbiologically confirmed studies suggestive of abdominal TB among all 3 reviewers. Interestingly, when informed that the children had chest radiograph features suggestive of TB, the proportion of studies reported as "highly likely in keeping with abdominal TB" and with microbiologically confirmed disease *decreased* amongst all 3 reviewers, although none of these decreases were statistically significant (Reviewer 1: 61% to 51%, p=0.3, Reviewer 2: 57% to 50%, p=0.4, Reviewer 3: 63% to 60%, p=0.8).

Reviewers showed only moderate agreement in their initial overall assessments (Fleiss' kappa 0,47), with minimal change after revising these assessments in response to additional clinical or chest radiograph information (Table 6). When all 3 reviewers reported studies as suggestive of abdominal TB and microbiological confirmation of TB was obtained, they were significantly more likely to report the presence of lymphadenopathy (all p-values < 0.001). Similarly, reviewers 1 and 3 were also significantly more likely to report splenic microabscesses in ultrasound studies where microbiological confirmation of TB was obtained. (Reviewer 1: 63.4% vs 8.3%, p < 0.001 and Reviewer 3: 53.1% vs 12.5%, p = 0.004).

6. Discussion

Paediatric TB is a diagnostic challenge owing to its paucibacillary nature and as such, multiple investigations are often necessary to confirm the diagnosis when clinical suspicion of TB arises. Disseminated disease is common in the presence of co-existent HIV infection. Abdominal TB results from several possible mechanisms including: i) haematogenous seeding from primary pulmonary infection, ii) lymphatic spread via involved lymph nodes and iii) direct ingestion of bacilli as a result of swallowed secretions. [6] As a result, patterns of intra-abdominal involvement vary, contributing to the heterogeneity in clinical presentation and subsequent challenge in timeously establishing the diagnosis. [6,7] Early, accurate diagnosis is preferable as delayed initiation of appropriate therapy may result in higher rates of morbidity and mortality, whilst TB treatment itself may cause adverse events including hepatitis, gastro-intestinal disturbances and central nervous system dysfunction. [29]

The paucibacillary nature of paediatric TB often necessitates the initiation of therapy without microbiological confirmation, but rather based on clinical suspicion and the results of investigations such as tuberculin skin testing, chest radiography and abdominal ultrasonography. The limitations of chest radiography in the diagnosis of paediatric pulmonary TB are well documented, with studies demonstrating poor to fair inter-observer agreement in reporting individual findings such as hilar lymphadenopathy and in the overall assessment of chest radiographic findings. [10,11] According to a recent study, ultrasound was found to be more effective in the diagnosis of mediastinal lymphadenopathy and pleural effusion as compared with chest radiography, with higher levels of inter-observer agreement. [11]

The variability in interpretation of findings on abdominal ultrasound examinations is however, less well documented in the literature. The role of point-of-care ultrasound examination for detecting pericardial effusion, pleural effusion, ascites, abdominal lymphadenopathy and splenic and hepatic microabscesses in children with pulmonary tuberculosis was evaluated in a recent study. High inter-observer agreement ($k = 0.8$) for these extra-pulmonary findings was documented. [19] In our study, the 3 reviewers were asked to identify the spectrum of abnormal abdominal ultrasound findings and determine whether or not the findings were consistent with abdominal TB. In contrast to the study of Bélard et al. (2018), in which children were included based on clinical features of TB, our reviewers were blinded to the indication for ultrasound investigation (i.e. as a diagnostic vs purely screening investigation) and the inter-observer agreement for interpretation of findings was moderate (k = 0.47), highlighting the variability in interpretation of ultrasound findings when making a diagnosis of abdominal TB. Furthermore, as shown in Figure 2, reviewer assessments may be influenced by clinical or chest radiographic information.

The most frequently reported ultrasound findings in our study were lymphadenopathy and splenic microabscesses, and the inter-observer agreement for these findings were 0.64 and 0.66 respectively. These are important considerations when noting that 31% (n = 51/166) of abdominal TB diagnoses identified in this study were based on only one sonographic finding. This degree of variability in interpretation is understandable as size-based criteria for abnormal lymph nodes in children are more contentious, with some published sources using cut-offs ranging from 4-10 mm, in addition to morphologic abnormalities relating to shape and echogenicity (Figure 3). [21–24]

Additional confounders unique to the paediatric population, such as the occurrence of mesenteric adenitis and the variability in splenic echo pattern due to changing splenic white-pulp to red-pulp ratio during maturation of the lymphoid system, further reduce the specificity of these sonographic findings. [25,27] Doria et al. reported that the frequency and intensity of a reticulonodular splenic echo pattern (defined as an echogenic background containing multiple hypoecohic nodules immersed within it) increases with patient age (up to 5 years), and occurs most frequently amongst patients in the age group >1 to ≤ 5 years. Interestingly, 55% of the 166 sonographic diagnoses of abdominal TB in our study occurred in the age group 1 – 5 years raising suspicion that the finding of splenic microabscesses in some of these ultrasound studies may have represented mischaracterization of normal paediatric splenic echo patterns (Figure 4).

Although absence of microbiological confirmation does not exclude disease, our data suggests that in ultrasound studies with a greater number of TB related findings, a higher proportion had microbiological evidence of disease, although the sample size of ultrasound studies with more than 4 findings was small. This observation requires validation in larger research studies.

The ultrasound studies of more than 50% of patients with suspected abdominal TB during the study period were considered negative for abdominal TB despite having at least one abnormal sonographic finding (58%, n = 540). Several of these abnormal findings, occurring either alone or in combination may pertain to abdominal TB, particularly lymphadenopathy (n=29), hepatomegaly (n=259), splenomegaly (n=51), non-TB related splenic microabscesses (n=12) and ascites (n=80). The reason abdominal TB was not considered likely in some of these instances is unclear but is likely related to subjective interpretation at the time of reporting. As variability in reviewers' interpretation of findings was demonstrated in our study, it may be reasonable to speculate that a certain number of these ultrasound studies would have been reported as consistent with abdominal TB by a different radiologist. It is imperative that an ultrasound for suspected abdominal TB is performed in patients with clinical features suggestive of the disease, as incidental/ unrelated findings could be misinterpreted as features of abdominal TB in children without features suggestive of TB.

II.6.1 Limitations:

The strength of this study is that it reflects routine clinical and reporting practice at our institution and while the study results may not be generalizable, variability in reporting and interpreting abdominal ultrasound findings may be occurring in other hospitals located in TB high burden countries. As paediatric TB is generally paucibacillary in nature, microbiological confirmation is not always possible. Thus, negative TB culture and Xpert MTB/RIF results do not necessarily rule out TB, and imaging features of abdominal TB in children without microbiological confirmation may in fact represent true TB disease. As such, our study was not able to comment on the diagnostic usefulness of ultrasound in diagnosing abdominal TB, but rather serves to highlight the degree of variability in interpretation of imaging findings amongst reporting radiologists. The HIV status of the children in our study would have been of interest when examining the prevalence of solitary findings such as abdominal lymphadenopathy and its association with microbiological evidence of TB, but unfortunately this data was not available at the time of our analysis. Follow-up imaging was not routinely performed to assess response to TB treatment or evolution of the initial intra-abdominal findings. Furthermore, invasive procedures such as tissue biopsy for histology and microbiological studies to confirm intra-abdominal infection caused by *Mycobacterium tuberculosis* was not undertaken.

With regards to the prospective component of our study, reviewers were required to interpret findings based on a series of digital images from ultrasound studies which they had not personally performed. Abdominal ultrasound is a dynamic examination with the overall assessment based on findings at the time of scanning, and only representative images were stored for later review. For example, a solitary image of an abnormal lymph node may have been saved when in fact, multiple abnormal lymph nodes were present. Reviewers may thus have been disadvantaged by reviewing a limited series of images from prior studies. Reviewers were also not asked to elaborate on the criteria used when making an assessment of abnormal abdominal lymphadenopathy, which would have been of interest considering the variability in the published literature on normal limits for abdominal lymph nodes in children. In addition, the Fleiss' kappa may have been exaggerated by the small sample sizes of certain abdominal findings such as psoas abscess. Lastly, it is worth noting that the criteria provided to reviewers for classifying the likelihood of abdominal TB relies on subjective assessment of the imaging findings and have not been validated scientifically. Rigorously defined criteria for a diagnosing abdominal TB do not exist, and thus a certain degree of subjectivity exists when applying the qualitative criteria that were used in our study.

II.6.2 Implications and recommendations:

Given the challenges in making a diagnosis of abdominal TB, we believe that it is important to carefully select the patients in whom ultrasound studies are requested, limited to those with clinical features suggestive of abdominal disease. Institutions should standardize the way in which these studies are both performed and reported. A high-frequency linear-array transducer (10 – 13 MHz) should be used in all studies to ensure adequate characterisation of splenic parenchyma. An awareness of the variability in splenic echo patterns during early childhood is necessary to prevent misinterpretation of potentially normal sonographic findings as splenic microabscesses. Lastly, routine screening of the pleura, pericardial space and mediastinum at the time of abdominal ultrasound study may be of value in describing the extent of extra-pulmonary TB.

7. Conclusion

Diagnosis of paediatric abdominal tuberculosis remains a challenge, with no imaging technique definitively confirming presence of disease. In our study, lymphadenopathy and splenic microabscesses were the most frequent findings reported in abdominal ultrasound studies that were assessed to be consistent with the diagnosis of abdominal TB, and there was moderate inter-reader agreement with the diagnosis of abdominal TB. To improve the reporting consistency, it is important to clearly define the indications for abdominal ultrasound, standardize the ultrasound procedure and reporting methods. Treating physicians need to be aware of the inherent limitations of abdominal ultrasound in paediatric practice to ensure judicious interpretation of abdominal ultrasound results when making therapeutic decisions in everyday clinical practice. Further prospective studies using a structured reporting format and routine follow-up imaging may be of value in refining the imaging criteria used when making a diagnosis of abdominal TB.

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9. Tables

Table 1 Frequency distribution for age and sex in ultrasound studies reported positive for abdominal TB (n=166)

Sex	**N**	**%**
Males	90	54
Females	76	46
Age (in years)		
< 1	27	16.3
1 to 5	92	55.4
6 to 10	37	22.3
11 and above	10	6.0

Table 2 Distribution of imaging features in ultrasound studies reported positive for abdominal TB (n=166)

Imaging Feature	**All abdominal ultrasound studies called positive for TB N=166 n (%)**		**Microbiologically confirmed TB N=78 n (%)**		**TB not confirmed by culture / Xpert MTB/RIF N=88 n (%)**		**P value**
Psoas abscess	3	1.8	0	0.0	3	3.4	-
Bowel wall thickening	5	3.0	1	1.3	4	4.5	0.4
Pericardial effusion	9	5.4	6	7.7	3	3.4	0.4
Hepatic granulomas	12	7.0	6	7.7	6	6.8	0.8
Splenomegaly	15	9.0	10	12.8	5	5.7	0.1
Ascites	34	20.5	21	26.9	13	14.8	0.05
Hepatomegaly	58	34.9	31	39.7	27	30.7	0.2
Splenic microabscesses	92	55.4	41	52.6	51	58.0	0.2
Intra-abdominal lymphadenopathy	128	77.1	66	84.6	62	70.5	0.03

Table 3 Number of imaging features per study in ultrasound studies reported as having abdominal TB (n=166)

Number of imaging features	Number of ultrasound studies	Number of studies with microbiologically confirmed TB (n/%)	
1	51	20	*39*
2	59	26	*44*
3	40	20	*50*
4	12	9	*75*
5	3	2	*67*
6	1	1	*100*

Table 4 Range of alternative findings noted in ultrasound studies reported negative for abdominal TB

Clinically relevant findings in studies reported negative for abdominal TB (N=540)	**Number of times reported n**	**% (n/N)**
Abdominal findings		
Hepatomegaly	259	48,0
Ascites	80	14,8
Echogenic liver	70	13,0
Splenomegaly	51	9,4
Bladder debris	43	8,0
Lymphadenopathy	29	5,4
Echogenic kidneys	27	5,0
Non-TB splenic microabscesses	12	2,2
Hydatid disease	9	1,7
Abscess/ collection (various locations)	9	1,7
Gallstones	7	1,3
Bowel wall thickening	6	1,1
Appendicitis	6	1,1
Acalculous cholecystitis	5	0,9
Mass (various locations)	5	0,9
Calcified splenic granulomas	4	0,7
Ascariasis	4	0,7
Hydronephrosis	3	0,6
Pancreatitis	2	0,4
Hepatitis	2	0,4
Intussusception	2	0,4
Large splenic lesions	2	0,4
Renal mass	1	0,2

Gallbladder polyps	1	0,2
Renal calculus	1	0,2
Renal papillary necrosis	1	0,2
Cirrhosis	1	0,2
Pyelonephritis	1	0,2
Pancreatic pseudocyst	1	0,2
Choledocal cyst	1	0,2
Medullary nephrocalcinosis	1	0,2
Inguinal hernia	1	0,2
Extra-abdominal findings		
Pleural effusion	39	7,2
Pericardial effusion	28	5,2
Pulmonary consolidation	14	2,6

Table 5 Inter-reader agreement of abdominal ultrasound findings reported by the 3 reviewers

Finding	**Fleiss' Kappa**	**95% Confidence interval**
Psoas abscess	1,0	N/A
Pericardial effusion	0,75	0,52 – 0,90
Ascites	0,73	0,63 – 0,82
Hepatic granulomas	0,70	0,46 – 0,87
Splenic microabscesses	0,66	0,55 – 0,74
Lymphadenopathy	0,64	0,56 – 0,71
Pleural effusion	0,49	0,14 – 0,72
Bowel wall thickening	0,30	0,12 – 0,43
Hepatomegaly	0,21	0,05 – 0,35
Splenomegaly	0,20	0,06 – 0,35

Table 6: Inter-reader agreement amongst all three reviewers in their initial assessments, and subsequent assessments based on the provision of additional information.

	Fleiss' kappa	**95% confidence intervals**
Initial overall assessments	0,47	0,41 – 0,52
Revised assessment based on additional information:		
Confirmed TB contact	0,45	0,40 – 0,52
Failure to thrive	0,40	0,34 – 0,45
Positive tuberculin skin test	0,48	0,42 – 0,54
HIV infection	0,39	0,33 – 0,45
Chest radiograph suggestive of TB	0,46	0,40 – 0,51

10. Figures

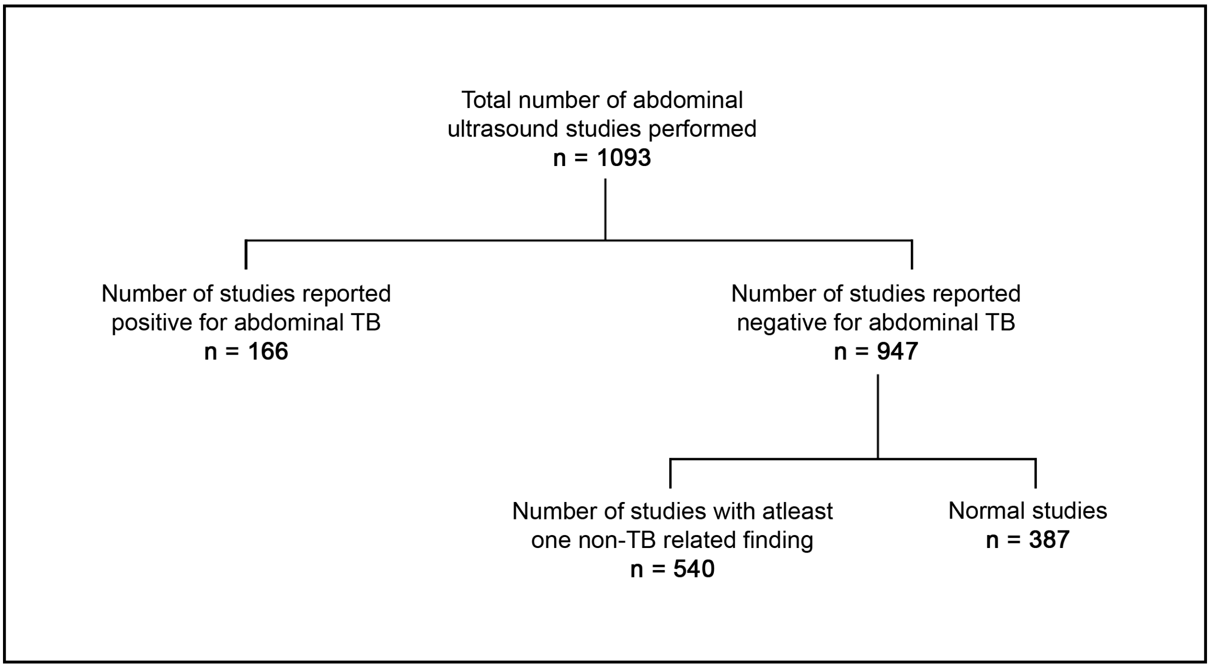

Fig. 1 Classification of abdominal ultrasound studies performed during the study period.

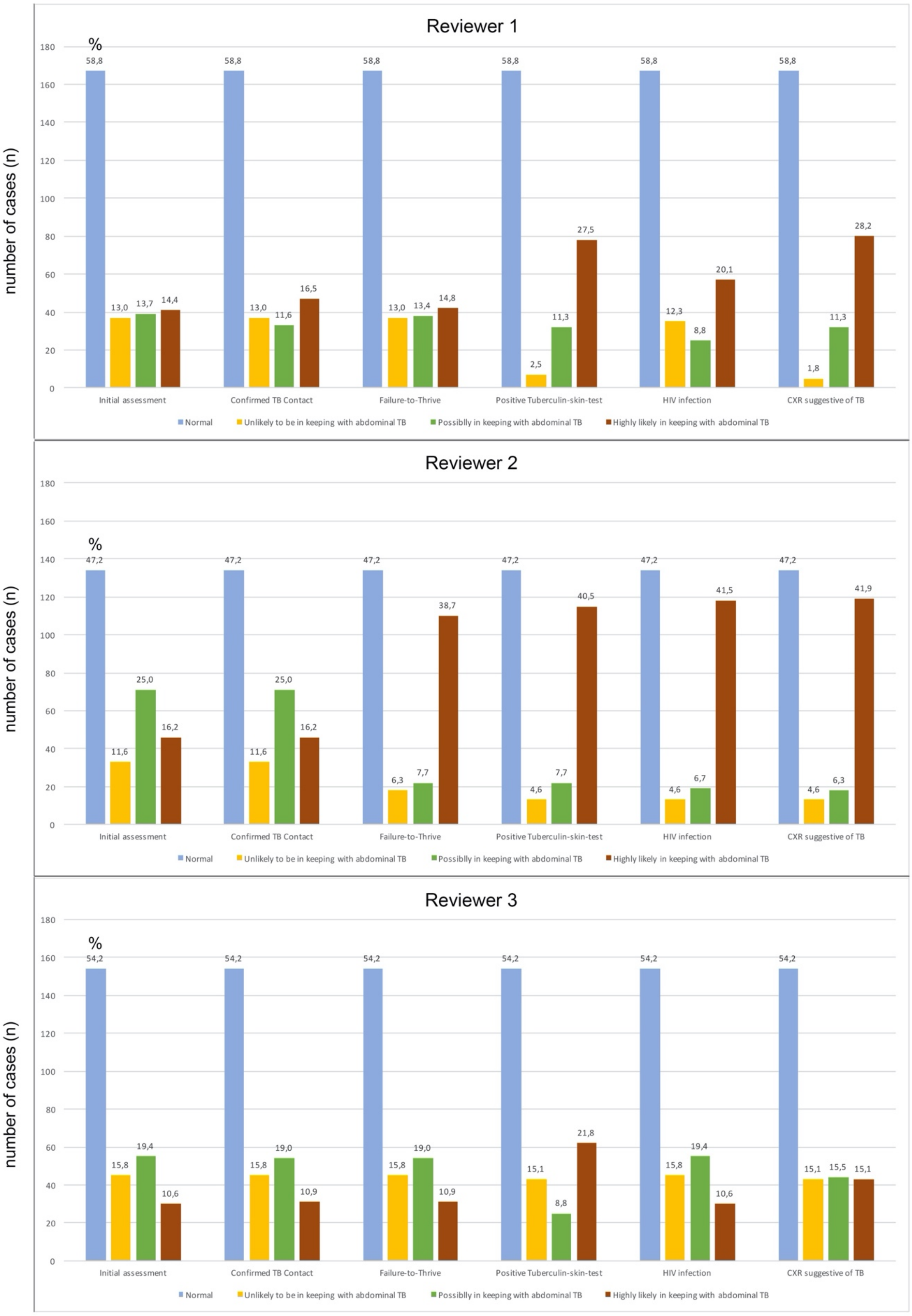

Fig. 2 Distribution of initial overall and revised assessments amongst the 3 reviewers (n=284)

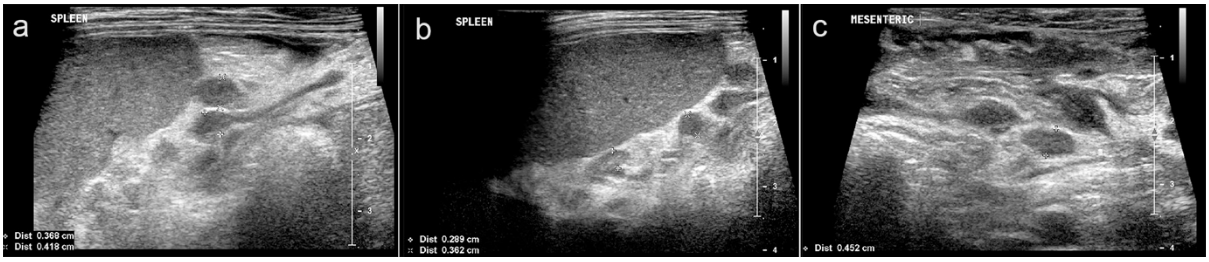

Fig. 3 Sonographic images from an 8-year-old child in whom reviewers demonstrated discrepancy when reporting lymphadenopathy. (a-b) Perisplenic subcentimetre lymph nodes, some with a rounded morphology. c) Subcentimetre mesenteric lymph nodes with preserved morphology

Fig. 4 Sonographic images from < 1-year-old (a), 3-year-old (b) and 6-year-old (c) children in whom reviewers demonstrated discrepancy when reporting splenic microabscesses

III. Addenda:

1. Addendum 1: Ethics approval letter

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E53-46 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 404 7682
Email: suraya.basterman@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

16 May 2019

HREC REF: 290/2019

A/Prof T Kilborn
Paediatric Radiology
Red Cross Children's Hospital

Dear A/Prof Kilborn

PROJECT TITLE: THE UTILITY OF ABDOMINAL ULTRASOUND IN THE DIAGNOSIS OF PAEDIATRIC TUBERCULOSIS: A SINGLE CENTRE REVIEW (MMED candidate Mr. V Sood)

Thank you for submitting your protocol application to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30 May 2020.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

Please quote the HREC REF number in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

The HREC acknowledge that Mr Vishesh Sood will be involved in this study.

Yours sincerely

Signature Removed

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

HREC 290/2019

2. Addendum 2: Reviewer's questionnaire form

CASE NUMBER: 1

IMAGING FINDINGS: (TICK ALL WHICH APPLY)

- HEPATOMEGALY ☐
- HEPATIC GRANULOMA(S) ☐
- SPLENOMEGALY ☐
- SPLENIC ABSCESS(ES) ☐
- LYMPHADENOPATHY ☐
- ASCITES ☐
- OTHER: ______________________ ☐
- OTHER: ______________________ ☐

IMAGING FINDINGS ARE: (TICK ONE)

I. HIGHLY LIKELY TO BE IN KEEPING WITH ABDOMINAL TB ☐
II. POSSIBLY IN KEEPING WITH ABDOMINAL TB ☐
III. UNLIKELY TO BE IN KEEPING WITH ABDOMINAL TB ☐
IV. NORMAL ☐

IF (II/III) ABOVE: IF THE PATIENT HAD EITHER OF THE FOLLOWING, WOULD YOUR ASSESSMENT CHANGE FROM **(III TO II, OR II TO I)**

- **A CONFIRMED 'POSITIVE' TB CONTACT**
  FROM III TO II ☐ FROM II TO I ☐ STAY THE SAME ☐
- **FAILURE TO THRIVE**
  FROM III TO II ☐ FROM II TO I ☐ STAY THE SAME ☐
- **POSITIVE TUBERCULIN SKIN TEST**
  FROM III TO II ☐ FROM II TO I ☐ STAY THE SAME ☐
- **HIV INFECTION**
  FROM III TO II ☐ FROM II TO I ☐ STAY THE SAME ☐
- **CHEST RADIOGRAPH SUGGESTIVE OF TB**
  FROM III TO II ☐ FROM II TO I ☐ STAY THE SAME ☐