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Point-of-care ultrasound for tuberculosis diagnosis in children: a Médecins Sans Frontières cross-sectional study in Guinea-Bissau

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ABSTRACT

Objective Description of tuberculosis (TB)-focused point-of-care ultrasound (POCUS) findings for children with presumptive TB.

Design Cross-sectional study (July 2019 to April 2020).

Setting Simão Mendes hospital in Bissau, a setting with high TB, HIV, and malnutrition burdens.

Participants Patients aged between 6 months and 15 years with presumptive TB.

Interventions Participants underwent clinical, laboratory and unblinded clinician-performed POCUS assessments, to assess subpleural nodules (SUNs), lung consolidation, pleural and pericardial effusion, abdominal lymphadenopathy, focal splenic and hepatic lesions and ascites. Presence of any sign prompted a POCUS positive result. Ultrasound images and clips were evaluated by expert reviewers and, in case of discordance, by a second reviewer. Children were categorised as confirmed TB (microbiological diagnosis), unconfirmed TB (clinical diagnosis) or unlikely TB. Ultrasound findings were analysed per TB category and risk factor: HIV co-infection, malnutrition and age.

Results A total of 139 children were enrolled, with 62 (45%) women and 55 (40%) aged <5 years; 83 (60%) and 59 (42%) were severely malnourished (SAM) and HIV-infected, respectively. TB confirmation occurred in 27 (19%); 62 (45%) had unconfirmed TB and 50 (36%) had unlikely TB. Children with TB were more likely to have POCUS-positive results (93%) compared with children with unlikely TB (34%). Common POCUS signs in patients with TB were: lung consolidation (57%), SUNs (55%) and pleural effusion (30%), and focal splenic lesions (28%). In children with confirmed TB, POCUS sensitivity was 85% (95% CI) (67.5% to 94.1%). In those with unlikely TB, specificity was 66% (95% CI 52.2% to 77.6%). Unlike HIV infection and age, SAM was associated with a higher POCUS-positivity. Cohen's kappa coefficient for concordance between field and expert reviewers ranged from 0.6 to 0.9.

Conclusions We found a high prevalence of POCUS signs in children with TB compared with children with unlikely TB. POCUS-positivity was dependent on nutritional status but not on HIV status or age. TB-focused POCUS could potentially play a supportive role in the diagnosis of TB in children.

Trial registration number NCT05364593.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study was conducted under field conditions and is the first study to report on tuberculosis (TB)-focused point-of-care ultrasound (POCUS) in children performed by POCUS-naïve local health staff.
⇒ This is the first study which combined TB-focused POCUS for signs of PTB and EPTB.
⇒ This is the first study to evaluate TB-focused POCUS in malnourished children.
⇒ The main limitation of this study is that POCUS performing clinicians were also deciding on TB diagnosis and treatment.
⇒ A further limitation of the study is the lack of children's final TB outcome data.

INTRODUCTION

Despite increased access to diagnostic tests and curative and preventive therapies, tuberculosis (TB) remains an important cause of morbidity and mortality, particularly in children, for whom the diagnostic gap can be as high as 80%.[1 2] The risk of TB disease and unfavourable outcomes increases in children that are co-infected with HIV or are malnourished.[3 4] Xpert MTB/RIF or Ultra has been recommended as the first-line diagnostic test for TB since the gold standard, TB culture, is widely unavailable.[5] However, microbiological confirmation remains low in children (<30% of patients).[1 6–13] Thus, in many settings, TB diagnosis is regularly based on clinical criteria and chest radiograph (CXR) when available.[12]

In Guinea-Bissau, TB remains a major public health concern, with high incidence (374/100 000 population per year) and low treatment coverage (32%); 15% of all cases occurred in children <15 years of age.[14] HIV prevalence in the country is 3%, while the prevalence reported in those under 15 is <1%, with a paediatric antiretroviral (ARV) coverage of 25%.[15] In terms of malnutrition, national data reported that 28.5% of children <5 years old presented with stunting while 5.1% had severe acute malnutrition.[16 17] Médecins Sans Frontières (MSF) supported paediatric emergency and intensive care at the Simão Mendes hospital in Bissau from 2017 to 2020.

Point-of-care ultrasound (POCUS) is an attractive bedside imaging tool for children that is non-invasive, easily repeatable, inexpensive[18] and can be performed by non-specialised healthcare providers in low-income and middle-income countries (LMIC).[19] Focused Assessment with Sonography for HIV-associated Tuberculosis (FASH) is the most widely studied application of POCUS for infectious disease diagnosis in LMIC to date[20–23] and is becoming increasingly implemented in adult care.[24 25]

TB-focused POCUS detects the frequent features of extra pulmonary TB (EPTB): pleural effusion,[26] pericardial effusion,[27 28] abdominal lymphadenopathy and splenic microabscesses.[28] Lung ultrasound has repeatedly demonstrated a high diagnostic performance for pneumonia in children,[29 30] and lung POCUS for TB could be a valuable imaging tool in the absence of CXR.[31–33] Studies have pointed out the utility of FASH methodology for clinical decision-making in paediatric TB cases as well as for monitoring treatment response in low-resource settings.[34–38] However, evidence on the use of TB-focused sonography is limited for those with limited access to CXR.[38]

This study describes the primary sonographic signs seen in a group of children <15 years of age with presumptive TB in a tertiary care hospital in Guinea-Bissau, as well as the main signs in patients with TB stratified by age, HIV and nutritional status.

METHODS

Study design

This observational, cross-sectional study was carried out at Simão Mendes National Hospital (in Bissau, Guinea-Bissau) between July 2019 and April 2020. Children with presumptive TB underwent clinical and laboratory evaluation and a clinician-performed POCUS prior to having a final diagnosis established. TB treatment outcomes were not available for this study.

Study population, clinical and laboratory procedures

Inclusion criteria: children between 6 months and 15 years of age were considered to have presumptive TB if they presented with any of the following signs or symptoms: (1) persistent cough for more than 2 weeks, (2) unexplained fever for more than 1 week, (3) extra pulmonary signs of TB (ie, angular deformation of the spine (gibbous), lymphadenopathy, subacute meningitis, abdomen distended with ascites, >2 weeks of diarrhoea, painless enlarged joints or pleural effusion. They were also considered to be presumptive TB cases if they had one or more of the following symptoms after 1 week of inpatient admission: (1) low weight gain despite nutritional treatment, (2) persistent pneumonia or cough after adequate and well-followed antibiotic therapy, (3) persistent fever (>38°C) for more than 1 week after classical causes such as malaria or pneumonia were excluded, (4) persistence or aggravation of fatigue and (5) chest radiograph imaging suggestive of TB (if available).

Screening for TB consisted of taking a patient's medical history and evaluating their clinical presentation, TB contacts and past TB treatment as well as conducting a physical examination including anthropometrics (mid upper-arm circumference (MUAC), weight and height, body mass index (BMI)); HIV testing, and GeneXpert Ultra testing of at least one pulmonary or extrapulmonary sample. After diagnostic evaluation, patients were categorised as *Confirmed TB* (patients who were GeneXpert Ultra positive in at least one sample); *Unconfirmed TB* (no microbiological confirmation but clinical diagnosis of TB and initiation of TB treatment, according to a clinical-decision based algorithm which can be found as online supplemental file 1); *Unlikely TB* (no TB treatment initiation and good response to other treatments during admission or ambulatory follow-up, noting a resolution (ie, fever, cough) or significant clinical improvement (ie, weight gain) of the clinical presentation). The categorisation was done for patients' diagnosis and analysis purposes. Hypoxaemia was defined as oxygen saturation ≤92%. Clinicians performing ultrasound were those in charge of clinical evaluation and final diagnosis. All results were communicated to the National TB Programme (NTP) focal point who decided on patient's treatment initiation and carried out the clinical follow-up.

Ultrasound methodology

TB-focused sonography was performed by two clinicians who underwent a total of 128 hours of full POCUS methodology training in two separate month-long sessions over a 7-month period. The training included two 8-hour sessions for FASH and chest, as well as hands-on ultrasound practice and completion of 25 full exams reviewed by the trainer. Due to human resource constraints, study logistics did not allow to blind clinicians to clinician-performed TB-focused sonography. Ultrasound was performed with a Sonosite M-Turbo machine using a combination of convex, cardiac and linear probes. In addition to the standard supine position, a sitting position or lateral decubitus position were used for pulmonary views. All children enrolled in the study were sonographically examined for eight signs: lung consolidation and subpleural nodules (SUNs), pleural effusion, pericardial effusion, hepatic focal lesions, splenic focal lesions, ascites and abdominal lymphadenopathy. The study's POCUS protocol is provided as online supplemental file 2.

Representative sonographic stills or clips with predefined landmarks of the following positions were saved electronically: lung, spleen, liver, right upper quadrant (RUQ), left upper quadrant (LUQ), suprapubic view and heart, epigastric view. POCUS findings were documented and interpreted by the examiner. Saved POCUS stills/clips were reviewed and interpreted separately for all patients by an expert reviewer blinded to the examiner's interpretation and clinical data. In case of discordance with the field POCUS interpretation, stills/clips were reviewed by a second expert blinded to the TB diagnosis. Expert reviewer's read was used to determine concordance, while field interpretations were considered as the final reads.

Operational POCUS aspects were recorded, including the duration of the examination in minutes, time point after enrolment and interpretation of POCUS (positive if one or more signs present, negative if no signs detected) and compliance with the procedure of the examination which was labelled as high (patient cooperative and calm), moderate (patient was crying but remained calm) or low (patient was crying and moving during the exam). The examiner also documented the clinical appraisal for clinical suspicion of TB prior to and after POCUS.

Data collection and analysis

All data were collected in structured, paper-based forms, anonymised and double entered and managed using REDCap (Research Electronic Data Capture)[39 40] software. Data were analysed using SPSS V.21 (IBM, Armonk, New York, USA).

Continuous variables were summarised using means and SD or medians and IQRs as appropriate and expressed as ordinal categories with frequencies. Frequencies were reported with corresponding 95% CIs. Anthropometric indicators for patient age were calculated using the WHO Multicentre Growth Reference.[41] Severe acute malnutrition (SAM) and moderate acute malnutrition (MAM) were defined based on WHO criteria (SAM: weight-for-height Z-score <−3 SD or MUAC <11.5 cm for children <5 years or oedema and BMI-for-age Z-score <−3 SD for those 5–15 years. MAM: weight-for-height Z-score between ≥−3 and <−2 SD or MUAC between 11.5 and 12.4 cm for children <5 years and BMI-for-age Z-score between ≥−3 and <−2 SD for those with age 5–15 years).

Statistical differences were tested in univariable analyses using χ^2, Fisher's exact test, Wilcoxon rank-sum or Kruskal-Wallis tests, as appropriate. A multivariable logistic regression model was constructed to determine clinical and demographic factors associated with TB diagnosis (TB vs unlikely-TB). Risk factors with p<0.1 on the bivariable analysis were included in the model. Bivariable analysis was carried out for TB versus unlikely TB, HIV positive versus HIV negative (HIV+/HIV−), and for SAM versus not SAM (SAM+/SAM−). A prespecified stratified analysis was carried out to determine the association of POCUS results with TB diagnosis in children with HIV, SAM and age <5 years. All estimates are presented with respective 95% CI. P values below the <0.05 cut off were considered statistically significant. Cohen's kappa coefficient was used to determine the agreement of TB-focused POCUS classification by the operator, second reader and third reader.

Patient and public involvement

Patients were not involved in the protocol's development.

Written informed consent was obtained from a parent or legal guardian and additional verbal assent was obtained from children >10 years old.

RESULTS

Demographics and clinical presentation

A total of 140 patients were enrolled between July 2019 and April 2020. All eligible patients were consecutively included in the study. Written consent by caregivers was obtained for all but one eligible patient, who was excluded from the study. Of 139 patients with presumptive TB, 27 (19%) had confirmed TB; 62 (45%) had unconfirmed TB; 50 (36%) patients had unlikely TB. All but nine patients with a diagnosis of confirmed or unconfirmed TB were started on TB treatment; three of nine patients with 'Unconfirmed TB' died prior to TB treatment initiation and in six patients the NTP focal point did not support start of TB treatment. No patient with 'Unlikely TB' was initiated on TB treatment. Fifty-nine (42%) patients had HIV infection and 83 (60%) presented with SAM.

The median (IQR) age was 7 years old (2–12) and 55 (40%) were under 5 years old. Demographic information and clinical presentation are shown in table 1. Demographic characteristics (including age, gender and history of contact with patients with TB) were similar in the TB categories. In terms of clinical presentation, hypoxaemia (40 (45%) vs 9 (18%), p<0.05) and pleural effusion (27 (30.3%) vs 0 (0%), p<0.001) were significantly higher in patients with TB.

HIV status was similar in both TB and unlikely TB groups (40 (45%) vs 19 (38%)), as well as the CD4 count mean (IQR) and the proportion of patients with low CD4 (<200), though patients with unconfirmed TB presented with non-significant higher rates of HIV and lower CD4. Most patients with HIV with unlikely TB were antiretroviral therapy (ART) experienced compared with patients with HIV with TB co-infection (18 (95%) versus 28 (70%), p<0.05). While not statistically significant at p<0.05 level, multivariable logistic regression showed important trends for increased odds of TB diagnosis for: children with SAM (adjusted OR (aOR)=2.1, 95% CI 0.9 to 4.6, p=0.07); children with MAM (aOR 1.6, 95% CI 0.3 to 7.7, p=0.55); children who were ART naïve (aOR 5.0, 95% CI 0.6 to 43.5, p=0.15); and for the children who had contact with a person with TB (aOR 1.5, 95% CI 0.7 to 3.2, p=0.29).

Appraisal pre-POCUS and post-POCUS

All patients received a pre-POCUS appraisal by the clinician, with 15 (11%) and 124 (89%) classified as high and low risk of TB, respectively. At post-POCUS appraisal, the same clinician classified 69 (50%), 24 (17%) and 45

Table 1 Baseline demographic and clinical of children with presumptive TB at Simão Mendes hospital in Guinea-Bissau (July 2019 to April 2020)

	Confirmed TB (n=27)	Unconfirmed TB (n=62)	TB total (n=89)	Unlikely TB (n=50)	Total	*OR (95% CI)	P value
Age group (years), n (%)							
<1	0 (0)	11 (17.7)	11 (12.4)	5 (10)	16 (11.5)	1.2 (0.4 to 3.7)	0.80
1-<5	6 (22.2)	17 (27.4)	23 (25.8)	16 (32)	39 (28.1)	0.8 (0.4 to 1.7)	0.49
5–15	21 (77.8)	34 (54.8)	55 (61.8)	29 (58)	84 (60.4)	Ref	
Median (IQR) age	8 (5–12)	6 (1–11)	8 (2–12)	6.5 (1–11)	7 (1–11)		
Gender, n (%)							
Male	9 (33.3)	38 (61.3)	47 (52.8)	28 (56)	75 (54)	0.9 (0.5 to 1.9)	0.82
Female	18 (66.7)	22 (35.5)	40 (44.9)	22 (44)	62 (44.6)	Ref	
Missing	0 (0)	2 (3.2)	2 (2.2)	0 (0)	2 (1.4)	(0.1 to –1)	0.54
Nutrition status, n (%)							
SAM	16 (59.3)	42 (67.7)	58 (65.2)	25 (50)	83 (59.7)	2.2 (1 to 4.7)	**0.039**
MAM	3 (11.1)	3 (4.8)	6 (6.7)	3 (6)	9 (6.5)	1.9 (0.4 to 13.2)	0.48
No malnourished	8 (29.6)	14 (22.6)	22 (24.7)	21 (42)	43 (30.9)	Ref	
Missing	0 (0)	3 (4.8)	3 (3.4)	1 (2)	4 (2.9)	2.9 (0.2 to 157.4)	0.61
HIV status, n (%)							
Positive	9 (33.3)	31 (50)	40 (44.9)	19 (38)	59 (42.4)	1.3 (0.7 to 2.7)	0.43
Negative	18 (66.7)	31 (50)	49 (55.1)	31 (62)	80 (57.6)	Ref	
CD4 count, n (%)							
<200	4 (14.8)	13 (21.0)	17 (19.1)	7 (14)	24 (17.3)	1.2 (0.4 to 4.0)	0.75
>200	5 (18.5)	17 (27.4)	22 (24.7)	11 (22)	33 (23.7)	Ref	
HIV negative	18 (66.7)	32 (51.6)	50 (56.2)	32 (64)	82 (59)	0.8 (0.3 to 1.8)	0.57
Median (IQR) CD4 count	232 (54–473)	342 (68–619)	291 (68–572)	328 (99–954)	306 (71–647)		
ART status, n (%)							
ART naïve	1 (3.7)	8 (12.9)	9 (10.1)	1 (2)	10 (7.2)	5.8 (0.7 to 267.4)	0.14
ART experienced	7 (25.9)	21 (33.9)	28 (31.5)	18 (36)	46 (33.1)	Ref	
Missing data	1 (3.7)	2 (3.2)	3 (3.4)	0	3 (2.2)		
TB contact, n (%)							
Yes	14 (51.9)	31 (50)	45 (50.6)	18 (36)	63 (45.3)	1.8 (0.9 to 3.7)	0.098
No	13 (48.1)	31 (50)	44 (49.4)	32 (64)	76 (54.7)	Ref	
Past TB treatment, n (%)							
Yes	1 (3.7)	6 (9.7)	7 (7.9)	3 (6)	10 (7.2)	1.3 (0.3 to 8.3)	1.00
No	26 (96.3)	55 (88.7)	81 (91)	46 (92)	127 (91.4)	Ref	

Continued

Table 1 Continued

	Confirmed TB (n=27)	Unconfirmed TB (n=62)	TB total (n=89)	Unlikely TB (n=50)	Total	*OR (95% CI)	P value
Unknown	0 (0)	1 (1.6)	1 (1.1)	1 (2)	2 (1.4)	0.6 (0.01 to 45.5)	1.00
Clinical characteristics						**RR (95% CI)**	**P value**
TB Type, n (%)							
PTB	11 (40.7)	44 (71)	55 (61.8)	0 (0)	55 (39.6)		
EPTB	8 (29.6)	2 (3.2)	10 (11.2)	0 (0)	10 (7.2)		
PTB and EPTB	8 (29.6)	16 (25.8)	24 (27)	0 (0)	24 (17.3)		
Unlikely TB	0 (0)	0 (0)	0 (0)	50 (100)	50 (36)		
Signs and symptoms, n (%)							
Cough	18 (66.7)	55 (88.7)	73 (82)	41 (82)	114 (82)	1 (0.7 to 1.4)	0.584
Tachypnoea	5 (18.5)	5 (8.1)	10 (11.2)	2 (4)	12 (8.6)	1.3 (1 to 1.8)	0.124
Hypoxaemia	6 (22.2)	34 (54.8)	40 (44.9)	9 (18)	49 (35.3)	1.5 (1.2 to 1.9)	**0.001**
Fever	18 (66.7)	45 (72.6)	63 (70.8)	33 (66)	96 (69.1)	1.1 (0.8 to 1.4)	0.345
Gibbous	8 (29.6)	5 (8.1)	13 (14.6)	4 (8)	17 (12.2)	1.2 (0.9 to 1.7)	0.194
Lymph nodes	7 (25.9)	0 (0)	7 (7.9)	5 (10)	12 (8.6)	0.9 (0.6 to 1.5)	0.444
Subacute meningitis	0 (0)	0 (0)	0 (0)	1 (2)	1 (0.7)		0.360
Distended abdomen	1 (3.7)	4 (6.5)	5 (5.6)	1 (2)	6 (4.3)	1.3 (0.9 to 1.9)	0.296
Osteoarticular	1 (3.7)	4 (6.5)	5 (5.6)	0 (0)	5 (3.6)	1.6 (1.4 to 1.8)	0.207
Pleural effusion	7 (25.9)	20 (32.3)	27 (30.3)	0 (0)	27 (19.4)	1.8 (1.5 to 2.1)	**<0.001**

P-values shown in bold highlight statistical significance at p<0.05 level of significance.
*OR from bivariate analysis.
ART, antiretroviral therapy; EPTB, extra pulmonary TB; MAM, moderate acute malnutrition; PTB, pulmonary TB; SAM, severe acute malnutrition; TB, tuberculosis.

Table 2 Field POCUS* versus expert POCUS† signs stratified by type of TB diagnosis and concordance with expert reviewer

		TB total (n=89), n (%)		Unlikely TB (n=50), n (%)		Total (n=139), n (%)		Concordance - kappa cohen (95% CI)
		Field	Expert reviewer	Field	Expert reviewer	Field	Expert reviewer	
SUN		49 (55.1)	42 (47.2)	2 (4)	7 (14)	51 (36.7)	49 (35.3)	0.69 (0.56 to 0.82)
SUN specification	>5 SUNs	11 (12.4)	9 (10.1)	0 (0)	0 (0)	11 (7.9)	9 (6.5)	–
	1–5 SUNs	34 (38.2)	21 (23.6)	2 (4)	7 (14)	36 (25.9)	28 (20.1)	–
SUNs side	Bilateral	23 (25.8)	19 (21.3)	2 (4)	3 (6)	25 (18)	22 (15.8)	–
	Unilateral	26 (29.2)	15 (16.9)	0 (0)	4 (8)	26 (18.7)	19 (13.7)	–
Consolidation		51 (57.3)	59 (66.3)	13 (26)	16 (32)	64 (46)	75 (54)	0.84 (0.75 to 0.93)
Pleural effusion		27 (30.3)	30 (33.7)	0 (0)	3 (6)	27 (19.4)	33 (23.7)	0.72 (0.58 to 0.86)
Pericardial effusion		13 (14.6)	12 (13.5)	0 (0)	1 (2)	13 (9.4)	13 (9.4)	0.91 (0.78 to 1)
Ascites		15 (16.9)	11 (12.4)	2 (4)	3 (6)	17 (12.2)	14 (10.1)	0.68 (0.47 to 0.89)
Ascites RUQ		6 (6.7)	2 (2.2)	2 (4)	2 (4)	8 (5.8)	4 (2.9)	–
Ascites LUQ		6 (6.7)	4 (4.5)	0 (0)	0 (0)	6 (4.3)	4 (2.9)	–
Ascites suprapubic		13 (14.6)	9 (10.1)	1 (2)	3 (6)	14 (10.1)	12 (8.6)	–
Focal liver lesions		3 (3.4)	2 (2.2)	0 (0)	0 (0)	3 (2.2)	2 (1.4)	0.8 (0.41 to 1.2)
Focal splenic lesions		25 (28.1)	24 (27)	2 (4)	5 (10)	27 (19.4)	29 (20.9)	0.72 (0.57 to 0.87)
Abdominal LN		15 (16.9)	6 (6.7)	0 (0)	4 (8)	15 (10.8)	10 (7.2)	0.59 (0.29 to 0.89)
POCUS interpretation	Positive	83 (93.3)	80 (89.9)	17 (34)	25 (50)	100 (71.9)	105 (75.5)	0.8 (0.67 to 0.91)
	Negative	5 (5.6)	5 (5.6)	33 (66)	22 (44)	38 (27.3)	27 (19.4)	–
	Indeterminate	1 (1.1)	4 (4.5)	0 (0)	3 (6)	1 (0.7)	7 (5)	–

*For field POCUS, 1.4% POCUS views were documented as non-evaluable.
†At expert evaluation, a total of 7% of the signs were rated as not evaluable, excluding images lost for two patients.
LN, lymph node; LUQ, left upper quadrant; POCUS, point-of-care ultrasound; RUQ, right upper quadrant; SUN, subpleural nodule; TB, tuberculosis.

(32%) children with high, low and no suspicion of TB, respectively (data for one post-POCUS appraisal missing). Thus, subsequent to POCUS, 58 (42%) patients switched from low to high, 3 (2%) from high to low, 44 (32%) from low to no TB suspicion and 1 (1%) from high to no suspicion of TB. After POCUS assessment, 55 (62%) of patients with TB were diagnosed with pulmonary TB (PTB), 10 (11%) of patients with EPTB and 24 (27%) with a combination of PTB and EPTB.

POCUS findings at enrolment

The POCUS findings per TB category are described in table 2. A complete table including POCUS signs in confirmed and unconfirmed TB is displayed in online supplemental file 3. According to the field interpretation, 83 (93%) patients with TB presented with a positive POCUS, while 33 (66%) of patients with unlikely TB had a negative POCUS. For patients with confirmed TB, POCUS sensitivity and specificity (95% CI) were 85% (23/27) (67.5% to 94.1%) and 66% (33/50) (52.2% to 77.6), respectively.

For patients with TB, the most frequent sonographic signs were consolidation in 51 (57%) and SUNs in 49 (55%) patients. The rest of the signs ranged between 15% and 30%, except for focal liver lesions which were only present in 3 (3%). In patients with unlikely TB, the most frequent sign was consolidation, found in 13 (26%); two patients with unlikely TB were found with focal splenic lesions by the field operator, but the expert reviewer only identified splenic lesions in one of them, who was finally diagnosed with pneumonia and presented a good clinical evolution with antibiotic treatment. Pleural and pericardial effusion, focal liver lesions and abdominal lymph nodes were not found in children with unlikely TB.

All POCUS images were evaluated by an expert reviewer except for two whose clips and images were lost. According to these expert evaluations, 80 (90%) patients with TB presented with a positive POCUS, while 25 (50%) of patients with unlikely TB had a POCUS-positive result. The POCUS findings by expert reviewer are also presented in table 2.

POCUS signs in patients with TB according to age, HIV and SAM status are presented in table 3. Unlike HIV-infection, patients with SAM had a significantly higher risk of having a POCUS positive result (p<0.05). HIV-uninfected children presented with more pleural effusion (4 (10%) versus 23 (47%), p<0.05), while children with SAM presented with significantly more SUNs (38 (62%) versus 10 (48%), p<0.05). There was no difference in POCUS signs per age, though children >5 years

Table 3 POCUS signs for patients with TB by HIV status, nutritional status and age

	HIV status, n (%)		Nutrition status, n (%)		Age group, n (%)	
	Positive | negative	P value	SAM | not SAM	P value	<5 years | ≥5 years	P value
SUNs	25 (62.5) | 24 (49)	0.2	38 (65.5) | 10 (35.7)	**0.009**	17 (50) | 32 (58.2)	0.45
Consolidation	19 (47.5) | 32 (65.3)	0.09	35 (60.3) | 14 (50)	0.36	21 (61.8) | 30 (54.5)	0.5
Pleural effusion	4 (10) | 23 (46.9)	**0.0003**	17 (29.3) | 8 (28.6)	0.94	10 (29.4) | 17 (30.9)	0.88
Pericardial effusion	6 (15) | 7 (14.3)	0.92	7 (12.1) | 5 (17.9)	0.47	2 (5.9) | 11 (20)	0.12
Ascites	7 (17.5) | 8 (16.3)	0.92	8 (13.8) | 6 (21.4)	0.22	3 (8.8) | 12 (21.8)	0.18
Focal liver lesions	1 (2.5) | 2 (4.1)	0.99	3 (5.2) | 0 (0)	0.59	1 (2.9) | 2 (3.6)	0.99
Focal splenic lesions	15 (37.5) | 10 (20.4)	0.09	20 (34.5) | 4 (14.3)	0.07	7 (20.6) | 18 (32.7)	0.11
Abdominal LN	8 (20) | 7 (14.3)	0.49	13 (22.4) | 2 (7.1)	0.12	2 (5.9) | 13 (23.6)	0.05
POCUS positive	38 (95) | 45 (91.8)	0.99	57 (98.3) | 23 (82.1)	**0.006**	32 (94.1) | 51 (92.7)	0.75

P-values shown in bold highlight statistical significance at p<0.05 level of significance.
LN, lymph node; POCUS, point-of-care ultrasound; SAM, severe acute malnutrition; SUN, subpleural nodule; TB, tuberculosis.

presented with more abdominal lymph nodes (13 (24%) vs 2 (6%), p<0.05).

Inter-reader concordance

Cohen's kappa coefficient[39] showed moderate-to-high agreement between clinician and expert POCUS readers. The concordance per sign is shown in table 2. Pericardial effusion (0.9) and consolidation (0.8) were more concordant while the weakest concordance was found in abdominal lymph nodes (0.6), ascites (0.7) and SUNs (0.7). The concordance of a POCUS-positive result was 0.8.

Operational aspects of POCUS

POCUS compliance was high in 37 (28%), moderate in 71 (55%) and low in 22 (17%) children, respectively (data missing for 9 (7%)). The mean (95% CI) duration of the POCUS exam was 23.5 (16 to 35) minutes. The vast majority (125 patients) underwent POCUS on the day of enrolment. The median time (IQR) to diagnosis for unlikely TB for patients with POCUS positive was 3 (2–6) days and for patients with POCUS negative was 2 (1–5) days; the median time (IQR) to treatment for patients with TB with POCUS positive was 2 (1–4) days and for POCUS negative 2 (1–6) days. The vast majority of POCUS field examinations were complete, only 1.4% POCUS views were documented as non-evaluable. At expert evaluation, a total of 7% of the signs were rated as not evaluable, excluding images lost for two patients.

DISCUSSION

To the best of our knowledge, this is the first study to investigate the utility of POCUS to diagnose both PTB and EPTB in children, the first to document TB-focused paediatric POCUS results when performed by ultrasound-naïve local operators and the first to correlate TB-focused POCUS signs with a patient's nutritional status. In resource-limited contexts where radiology is often not available, POCUS represents a bedside, non-invasive and inexpensive imaging tool for children[18] which can be easily performed by non-specialised healthcare providers.[42] The results from this study will inform POCUS operators and help refine POCUS approaches in suspects with historically difficult-to-diagnose paediatric TB.

In our sample, two-thirds of patients with presumptive TB were ultimately diagnosed with the disease (though less than one-third among them were microbiologically confirmed). The prevalence of HIV (42%) and severe malnutrition (60%) were also high, confirming that TB, HIV and SAM are highly prevalent in Guinea-Bissau.[43 44] We examined two of the three TB-focused POCUS applications that have thus far been reported for the technology: lung POCUS for signs of PTB (SUNs, consolidation) and POCUS for EPTB (FASH).[30] Mediastinal POCUS for lymph node evaluation was not part of this study as it is a more complex methodology which needs additional probing and for which low concordance between operators and reviewers has previously been reported.[32] In our study, it was not feasible to have the expert reviewer on site and performing a second hands-on evaluation. Thus, we decided to use the field operator's interpretation as the final read as we could not guarantee expert review within 48 hours and decisions were taken at field level based on their own interpretation. Additionally, expert reviewers were limited to the provided stills and clips, hence accuracy may have also been limited.

The high prevalence (51%) of SUNs in children with PTB (independent of HIV status) is the first such paediatric data to be reported on the topic, though SUNs have previously been described as highly prevalent in adults with confirmed PTB.[30 33] In patients with TB, some of our findings mirrored evidence from other countries and contexts: the most prevalent POCUS findings were pulmonary signs (consolidation and SUNs), in line with evidence from South Africa (consolidation prevalence in paediatric PTB cases);[30] splenic focal lesions were more common in children with confirmed TB compared with those who remained unconfirmed (40.7% vs 22.6%),

though this was not statistically significant and is in line with previous reports (splenic microabscesses may indicate a more advanced clinical condition and therefore be more common in patients with confirmed TB);[35] and patients with TB had more pleural effusion than patients with unlikely TB (30.3% vs 0%), as described elsewhere.[33] Yet, given the overall paucity of data (and often small cohorts) in this emerging field of POCUS use, our results add depth to these other studies and bolster their findings.

The two less specific signs were ascites and focal liver lesions, for which prevalence was also low. Considering the low prevalence of liver abscesses and that all patients with ascites presented with suprapubic ascites, a more simplified TB-focused POCUS protocol could remove the other two views for ascites (LUQ/RUQ) and the liver examination. Abdominal lymph nodes, which are often reported as difficult to view,[34] presented a low concordance with the expert reviewer, however, this sonographic sign remains specific and prevalent.

In patients with TB, POCUS positivity was independent of HIV status and age, but it was associated with nutritional status. Patients with TB and HIV had more SUNs and focal splenic lesions, as described elsewhere,[33 35 36] while individuals who are HIV-negative had more consolidation and pleural effusion. Patients with SAM also had more SUNs and focal splenic lesions more often underlining the increased risk for severe or disseminated forms of TB in SAM. We did not find differences in POCUS signs by age (<5 vs >5 year olds), though the latter had a non-statistically significant higher rate of pleural effusion, ascites and abdominal LN. Overall our data are in line with previous paediatric reports showing that POCUS can support diagnosis of TB in children regardless of HIV and age; larger studies are needed to further consolidate the utility of POCUS for childhood TB and to confirm a possible value in children with TB/SAM.

In our study we found a high prevalence of positive POCUS results among patients with TB (93%) when compared with individuals who were unlikely to have TB (34%), though this may have been influenced by the fact that the ultrasound findings were not blinded to clinicians. It is important to note that all patients in the study had an appraisal prior to receiving their POCUS that was indicative of TB. After POCUS, one-third of the patients switched from TB suspicion to no suspicion, which may indicate a 'rule out' role instead of a 'rule in' role for the technology. In addition, the high sensitivity (85%) observed in confirmed TB cases is encouraging and may indicate a supportive role for POCUS in paediatric TB diagnoses, though specificity was moderate (66%). These findings will need to be confirmed in future studies with POCUS blinded clinicians.

Having a diagnostic tool with high sensitivity and moderate specificity to support clinical suspicion may entail an overtreatment of patients. However, careful assessment of the balance between overtreating (with well tolerated TB treatments that have low side effects in children) may overcome the risk of mortality in patients with untreated TB and support the use of POCUS for diagnosis, while reinforcing that a negative POCUS should never rule out TB.

TB-focused methodology can be taught to local clinicians and implemented in LMIC contexts.[25–27] In our study, the inter-reader agreement by sign was moderate to high. The signs with lower concordance were abdominal lymph nodes and SUNs, which are highly dependent on the views collected by the field operator. Concordance was also low in ascites, possibly due to the absence of a quantity threshold, the fact that traces are easily detectable and though often physiological, may be incorrectly labelled as significative ascites. In contrast to other studies that used expert sonographers and had high concordance, this study used POCUS-naïve clinicians. Research like ours, where previously untrained local staff were the POCUS operators, was shown to be a noteworthy gap in the literature in a recent systematic review.[45]

In terms of POCUS operationalisation, our study showed a mean POCUS examination time of 23 min, which is a feasible time to be integrated into a diagnostic workflow and incomparably shorter than obtaining imaging reports after transfer of a patient to a radiology department. In addition, most of the examinations (83%) had a good-to-moderate performance, and 99% of the views were evaluable, which confirms its feasibility in field conditions. Finally, the mean time from POCUS to diagnosis was substantially shorter (3 to 4 days) when compared with estimated time to TB diagnosis in children.[1 12]

Limitations

Our study was limited by its relatively small sample size, the lack of TB follow-up available and the lack of access to TB outcome data, which could have been useful to ensure the final categorisation of patients (especially for those with unconfirmed TB and unlikely TB). Additionally, clinicians were unblinded to POCUS results and therefore a risk of misclassifying cases depending on POCUS signs is possible, which may overestimate the sensitivity and specificity. Future, larger studies should address these limitations.

Conclusions

This study was carried out during routine care provision in a resource-limited context and found POCUS to be a useful tool for identifying sonographic signs in children with TB regardless of HIV status or age. POCUS positivity was associated with nutritional status. Findings of this study may indicate that POCUS could be a supportive tool for recognising difficult-to-diagnose paediatric TB in LMIC such as Guinea-Bissau. Though further evidence on TB-focused sonography (blinding the clinician) is needed to confirm the findings of this study, POCUS may play a role in supporting clinicians to mitigate the existing paediatric TB diagnosis gap in resource-limited settings.

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