ORIGINAL RESEARCH

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The diagnostic performance of Xpert MTB/RIF Ultra on Pericardial, Pleural and Ascitic cohort study fluids for diagnosis of extra-pulmonary Tuberculosis at a referral hospital in Malawi

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Abstract

Background
Extra-pulmonary tuberculosis (EPTB) accounts for 15% of the 1.4 million patients with TB notified in 2019. EPTB carries a high risk of mortality and so early diagnosis and treatment are important to reduce this risk. Diagnosis of EPTB in low- and middle-income countries is challenging. This study investigated the diagnostic performance of Xpert MTB Ultra for the diagnosis of EPTB (pericardial, pleural, and ascitic fluid) in adults at a referral hospital in Malawi.

Methods
Adults with suspected extra-pulmonary TB were screened for evidence of extra-pulmonary fluid and tested for TB using Xpert MTB Ultra, mycobacterial culture, and a Focused Abdominal Sonography in HIV-associated TB (FASH scan). The diagnostic performance of the Xpert MTB Ultra was compared to mycobacterial culture and a composite reference standard defined as a positive FASH scan or a positive mycobacterial culture or a clinical TB diagnosis (constitutional symptoms not otherwise explained with response to empirical TB treatment).

Results
There were 174 patients recruited: 99/174 (57%) pleural, 70/174 (40%) ascitic and 5/174 (3%) pericardial. Overall, 10/174 (6%) had bacteriologically confirmed TB and 30/174 (17%) were started on TB treatment based on a positive FASH scan or a clinical TB diagnosis. The sensitivity and specificity of Xpert ultra compared to culture was 83% (95%CI:36%-100%) and 98% (95%CI:94%-99%), respectively. Compared to the composite reference standard, the sensitivity of Xpert Ultra was 17% (95%CI:7%-34%) and specificity was 98% (95%CI:94%-100%).

Conclusion
Xpert MTB Ultra provides good diagnostic performance on pleural, pericardial and ascitic fluid with reference to mycobacterial culture. Improved EPTB diagnostic tests are required to improve patient outcomes. We recommend larger multi-centre studies to corroborate our findings.

Key words: Extra-pulmonary tuberculosis, Diagnostics, Xpert MTB/RIF Ultra

Introduction

There were approximately 10 million people who suffered from tuberculosis (TB) disease worldwide in 2019, out of whom 1.2 million died of the disease[1]. Clinical presentations of TB are classified as being either pulmonary (when lungs are involved) or extra-pulmonary (when organs other than the lungs are involved)[2]. Approximately 15% of all patients with TB have extra-pulmonary TB but the proportion can be as high as 50% in people living with HIV(PLWH)[3].

Making a correct diagnosis of extra-pulmonary TB is challenging. Obtaining samples from a patient suspected to have extra-pulmonary TB requires invasive procedures. In addition, extra-pulmonary TB samples tend to be generally paucibacillary[2]. Mycobacterial culture is the reference standard test for TB diagnosis but the diagnostic yield of mycobacterial culture on extra-pulmonary fluid samples is low, for example, it ranges from around 60% to 78% for pleural fluid[4]. Mycobacterial culture is only available for

reference laboratories and time to detection is long (2 to 8 weeks)[5]. The advantage of TB culture, however, is that it can be used for species identification, drug susceptibility testing (DST), and genotyping.

Xpert Ultra is a next generation nucleic amplification test endorsed by the World Health Organisation (WHO) in 2017[6]. Xpert MTB Ultra has a sensitivity of around 88% and specificity of around 99% on sputum samples[7]. Xpert MTB Ultra is shown to have a high sensitivity in extra-pulmonary samples[4]. For example, in TB meningitis, Xpert MTB Ultra was found to have a sensitivity of 95% compared to first generation Xpert MTB/RIF's sensitivity of 45% on cerebrospinal samples[4]. Xpert MTB Ultra's increased sensitivity on low bacillary samples has the potential to increase TB detection in HIV-positive subjects and on extra-pulmonary samples that are typically paucibacillary[7]. However, Xpert MTB Ultra's increased sensitivity goes along with some loss of specificity.

Table 1. Demographic and clinical characteristics of study participants

Characteristic	Treated for TB n(%)	Not treated for TB n(%)	Total n(%)	p-value
Total	40	134	174	
Sex				0.580
Male	27 (68)	84 (60)	111 (64)	
Female	13 (33)	50 (40)	63 (36)	
Age, Mean (SD)	38(13)	46 (18)	44 (17)	0.02
HIV status				<0.001
Positive	27 (68)	46 (34)	73 (42)	
Negative	13 (33)	88 (66)	101(50)	
ART coverage (if HIV positive) %	24/27(89)	43/46(94)	92 67/73(92)	<0.001
ART duration (months), median (IQR)	8 (1-54)	36 (5-72)	24 (3-60)	0.11
Symptom Duration (weeks), Median (IQR)	1 (1-2)	1 (1-2)	1 (1-2)	0.09
Type of specimen				0.02
Pleural	27 (68)	72 (54)	99 (57)	
Ascitic	10 (25)	60 (45)	70 (40)	
Pericardial	3(7)	2 (1)	5 (3)	

Table 2. Diagnostic performance of Xpert MTB Ultra

		Xpert MTB/RIF Ultra				
Reference test	n/N	Sensitivity	n/N	Specificity	PPV [b]	NPV [c]
		% (95% CI) [a]		% (95% CI)	% (95% CI)	% (95% CI)
Mycobacterial culture	5/6	83% (36% - 100%)	164/168	98% (94% - 99.3%)	56% (21% - 86%)	99% (97% - 100%)
Compositive reference standard	6/35	17% (7% - 34%)	134/139	98% (94% - 100%)	67% (34.5% - 88%)	82% (80% - 84)

[a] CI: confidence interval

[b] PPV: positive predictive value

[c] NPV: negative predictive value

Table 3: Xpert MTB Ultra in comparison to mycobacterial culture by type of effusion (microbiological diagnosis)

|		Xpert MTB Ultra with reference to mycobacterial culture				
Fluid type		Sensitivity		Specificity	PPV[b]	NPV[c]
	n/N	% (95% CI)[a]	n/N	% (95% CI)	% (95% CI)	% (95% CI)
Pleural fluid	4/4	75% (66% - 83%	93/95	98% (93% - 99%)	60% (94 - 100%)	99% (94% - 100%)
Ascitic fluid	2/2	100% (95 - 100%)	66/68	97% (90% - 99%)	50% (39% - 61%)	100% (95% - 100%
Pericardial fluid	0/0	N/A[d]	0/5	N/A	N/A	N/A
[a]CI: confidence interval; [b]NPV: Negative predictive value; [c]NPV: Positive predictive value; [d]N/A: Not applicable						
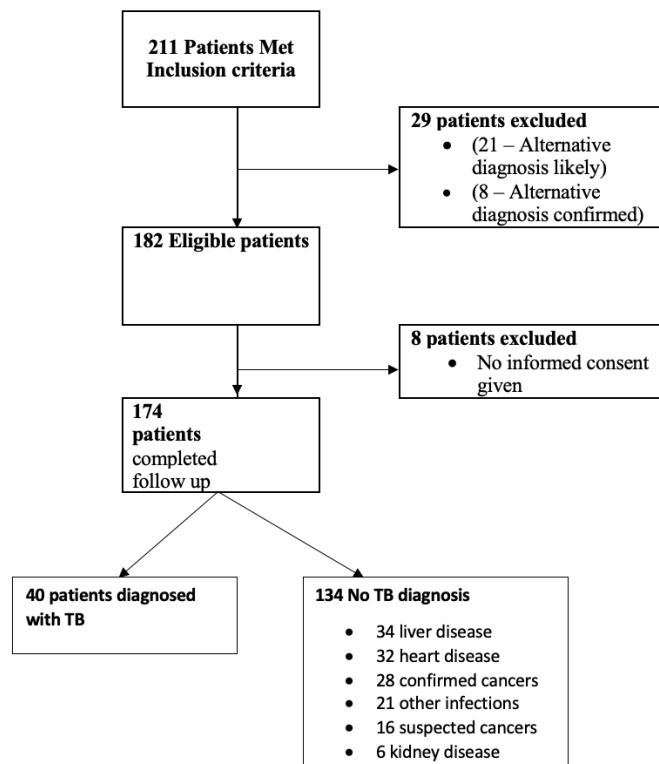
Figure 1: Study profile (flow of participants during the study)
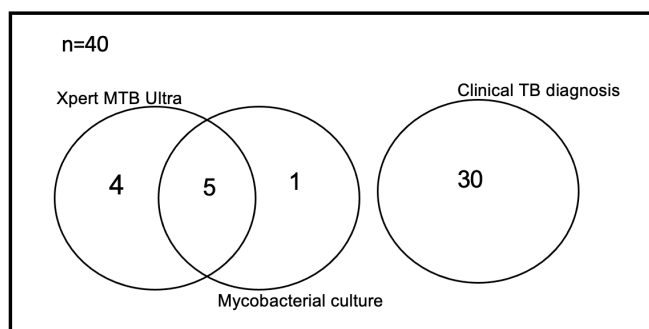

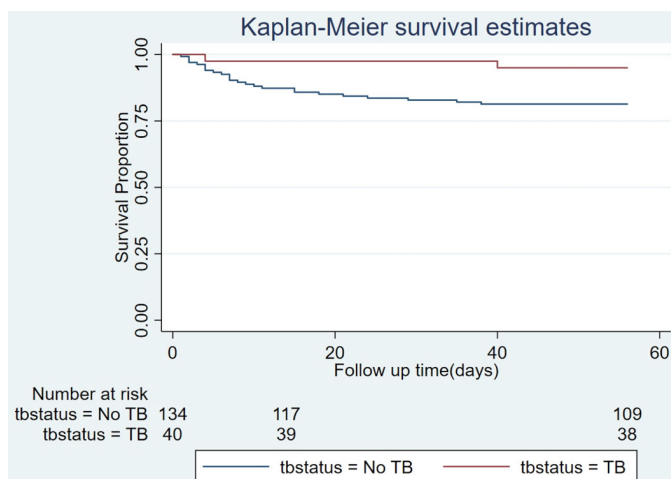**Figure 2: TB diagnostic modalities**

Figure 3: Survival estimate by TB status

The aim of this study was to investigate the diagnostic accuracy of Xpert MTB Ultra on pleural, ascitic and pericardial fluid for diagnosis of TB against culture and a composite reference standard. We also investigated clinical outcomes of patients with suspected extra-pulmonary TB at 8 weeks.

Methods

Study design and setting

This was a prospective cohort study conducted at Queen Elizabeth Central Hospital (QECH) in Blantyre, Malawi. QECH is the main referral hospital in the Southern Region of Malawi with a bed capacity of 1,200. Each year, about 240 patients are treated with extra-pulmonary TB at the hospital.

Study participants

All adult (≥18 years old) male and female patients admitted to the adult medical wards or presenting to the adult accidents and emergency department and medical outpatient clinics suspected of extra-pulmonary TB between September 2019 to February 2020 were eligible to be enrolled in the study. Adult medical wards were screened for newly admitted patients with suspected EPTB every weekday morning for the entire study duration. All eligible patients were invited to participate in the study. We excluded patients with confirmed alternative diagnoses for pleural effusion, pericardial effusion, and ascites (e.g., congestive heart failure, kidney disease, lung malignancies and/or liver disease).

Sample size

Sample size was calculated using Buderer's formula of sensitivity and specificity of diagnostic health studies (8). Validated Buderer sample size calculators can be accessed online (9). The primary outcome was the sensitivity and specificity of Xpert Ultra compared to culture. We calculated that 173 samples were required assuming a prevalence of culture confirmed tuberculosis of 25% (10) and a sensitivity of Xpert on culture positive specimens of 88% (7) accepting a 95% confidence interval (CI) of ±5% width.

Data collection

A structured questionnaire in paper form was completed at enrolment capturing patient sociodemographic characteristics (including age, sex, and residential area), and clinical information (including HIV status, presenting symptoms, diagnosis, samples collected, investigations done and available results). The questionnaire was also administered at 2 and 8 weeks to capture follow up data which included vital status, final diagnosis on discharge (if admitted), type of treatment at the time of follow-up and subjective response to TB treatment if started on empirical TB treatment.

At enrolment, a bedside Focused Abdominal Sonography of Tuberculosis in HIV (FASH scan) was done in both HIV positive and HIV-negative participants to look for features of extra-pulmonary TB. The FASH scan sought the following features: enlarged para-aortic lymph nodes, splenic hypoechoic lesions (micro-abscesses), and pericardial/ pleural/ascitic effusions with or without strands. The FASH scan was done on a Mindray DP-30 (Version 3.0, 2018 Model, Shanghai International Holding Corp. GmbH-Europe) Ultrasound machine using 3.5 MHZ and 5 MHZ probes and the findings were documented on the patient's questionnaire. An ultrasound-guided ascitic, pleural or pericardial tap was performed in patients if effusions were detected. In patients with multiple effusions, a pericardial sample was preferably collected over ascitic and pleural fluid. All data collection, ultrasound scans and ultrasound-guided taps ware done by a trained Internal Medicine Registrar.

Laboratory procedures

On average, 10 millilitres of sample fluid were collected into a sterile bottle. The bottle with the sample was put in a cooler

box with icepacks and taken to the TB laboratory at the University of Malawi, College of Medicine, within two hours of sample collection. Sample collection took place from 8:00 AM to 3:00 PM from Monday to Friday to ensure that samples were processed upon arrival in the TB laboratory.

The 10 millilitres of specimen were centrifuged at 1200xg for 10 minutes then 5 millilitres of the supernatant were decanted to make a 5-millilitre pellet. Out of the 5 millilitres of the pellet, 2 millilitres were used for Xpert MTB Ultra (one part sample and two parts reagent) and incubated for 15 minutes. The 2 millilitres of the sample and reagent mixture was used to run Xpert MTB Ultra and automated results were available after an hour and 25 minutes.

For the MTB culture, the remaining 3 millilitres of the pellet was mixed with 3 millilitres of 3% N-acetyl-L-cysteine-sodium hydroxide (NALC-NaOH) and a timer was set for 15 minutes (culture decontamination procedure). Vortexing was done at 5-minute intervals. The action of NaOH was neutralized by adding sterile phosphate buffer (PH at 6.8) to fill a 50 ml mark of the centrifuge tube. The content was mixed by several inversions and centrifuged at 3000xg for 20 minutes. The supernatant fluid was poured off, then 0.5 millilitres of the pellet was inoculated for liquid culture media (MGIT=Mycobacteria Growth Indicator Tube) and 0.2 millilitres inoculated for solid culture media (Lowenstein Jensen). BACTEC MGIT 960 machine was used. Interpretation was based on the confirmatory results. Ziehl-Neelsen (ZN) confirmation was done on all MGIT culture positives, and an antigen test done on all ZN positive specimens.

Participants living with HIV with a CD4 count less than 200 cells/microliter had urinary lipoarabinomannan (Urine LAM) testing performed as per standard of care and chest x-rays were done as indicated. Urine LAM test was not routinely done in the study period because of the erratic supply of test strips and CD4 reagents (stock outs) but, where available, contributed to making the clinical diagnosis of TB.

Results were made available to clinicians looking after the patients who decided whether to start TB treatment or not.

Definitions

Generally, extra-pulmonary TB includes pericardial, pleural, abdominal, spinal, TB meningitis and lymph node TB. But in this study, this was limited to serosal fluid (pericardial, pleural and ascitic fluid only). A patient with bacteriologically confirmed TB was defined as being a participant with a positive result by Xpert MTB/RIF or mycobacterial culture. Participants started on tuberculosis treatment without bacteriological confirmation were classified as having 'clinical TB diagnosis'. In this study, a composite reference standard was defined as a positive FASH scan or a positive mycobacterial culture or a clinical TB diagnosis (constitutional symptoms not otherwise explained with response to empirical TB treatment).

Ethics Approval

The study was approved by the College of Medicine Research and Ethics Committee (ethics approval number P.07/19/2719). Participants gave written informed consent.

Data Management and Analysis

Collected data was anonymized prior to entry and analysis. The data was captured using a structured questionnaire which was then transcribed onto a Microsoft Excel spreadsheet and analyzed using STATA 15.1 ® (StataCorp, Texas, USA).

Categorical data was summarized as counts and proportions (%) while continuous data was summarized as means with standard deviations (SD). For descriptive data, means, ranges and confidence intervals were reported. Chi square and fisher exact tests were used for comparing proportions and a probability value (p-value) of <0.05 was considered statistically significant.

The diagnostic performance of Xpert MTB Ultra was separately compared to either TB culture alone or composite reference standard. For either comparison, we calculated the sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV).

For the secondary outcome of survival at 8 weeks, we expressed cumulative risk as a proportion and used Kaplan Meir survival plots to report participant survival during the follow-up period. We also assessed for risk factors for death, reporting risk ratios and 95% confidence intervals.

Results

We approached 211 patients who presented during the study period with either pleural effusion, pericardial effusion, or ascites (Figure 1). We excluded 29 participants on account of a confirmed alternative diagnosis. Eight potential participants refused to provide consent for the study. In the end, we recruited 174 participants, meeting our target sample size, and followed them up for 8 weeks (Figure 1). There were 40/174 (23%) participants that had been initiated on TB treatment and the remaining 134/174 (77%) participants had other diagnoses.

Patient characteristics

Table 1 shows the characteristics of the participants with comparisons between those that were started on TB treatment and those that had other diagnoses. Overall, the majority of the participants were male 111/174 (64%) and the mean age was 43.8 years (SD: 16.9). There were 73/174 (42%) participants who were HIV-positive with 67/73 (92%) of these being on ART for a median duration of 24 months (IQR: 3 to 60 months).

Only one sample type was taken from each participant so a total of 174 samples were analysed. The sample types analysed were as follows: 99/174 (57%) pleural, 70/174 (40%) ascitic and 5/174 (3%) pericardial fluid

Diagnostic performance of Xpert MTB Ultra

Overall, 10/174 (6%) of the sample fluids had bacteriologically confirmed TB, and 30/174 (17%) were started on TB treatment based on a positive FASH scan or a clinical TB diagnosis and 134/174 (77%) had other diagnoses. The diagnosis category of the patients by Xpert MTB Ultra, mycobacterial culture and clinical TB diagnosis are shown in Figure 2.

Compared to mycobacterial culture, the sensitivity and specificity of Xpert MTB ultra was thus 83% (95% CI: 36 to 100% and 98% (95% CI: 94% to 99%), respectively (Table 2). Xpert Ultra had a PPV of 56% (95% CI: 21 to 86%) and a NPV of 99% (95% CI: 97 to 100%) (Table 2).

Compared to the composite diagnosis, the sensitivity of Xpert MTB Ultra was 17% (95% CI: 7% - 33%) and specificity was 98% (95% CI: 94% - 100%) -Table 2.

Table 3: Xpert MTB Ultra in comparison to mycobacterial culture by type of effusion (microbiological diagnosis)

Bacteriologically confirmed TB results of pleural, ascitic and pericardial fluids were assessed to examine Xpert MTB Ultra's diagnostic performance by type of effusion with mycobacterial culture as the reference test.

In pleural fluid samples, the sensitivity and specificity of Xpert MTB Ultra compared to mycobacterial culture were 75% (95% CI: 66% - 83%) and 98% (95% CI: 93 – 99%), respectively, with a PPV of 60% (95% CI: 94 – 100%) and an NPV of 99% (95% CI: 94 – 100%). The sensitivity and specificity of Xpert MTB Ultra compared to mycobacterial culture in ascitic fluid samples were 100% (95% CI: 95% - 100%) and 97% (95% CI: 90 – 99%), respectively, with a PPV of 50% (95% CI: 39 – 61%) and an NPV of 100% (95% CI: 95 – 100%). Only 5 patients with pericardial effusion were recruited in this study and all of them had a negative result on both Xpert MTB Ultra and mycobacterial culture so we could not calculate sensitivity and specificity.

Survival by TB status

Overall, there were 47/174 (27%) participants who had died at 8 weeks follow-up which represents 10% (4/40) of those treated for EPTB and 32% (43/134) in those with no EPTB. The four EPTB deaths were in PLWH. Three of these participants had severe immunosuppression and/ or probable immune reconstitution syndrome (antiretroviral therapy ≤4 months) and one was due to suspected ART failure patient after being on ART for 12 years.

Figure 3 graphically shows the time to death for the two groups. The adjusted risk ratio of death in non-TB patients compared to TB patients was 3.02 (95% CI: 1 to 8).

Discussion

Our primary objective in this study was to determine the performance of Xpert MTB Ultra in the diagnosis of EPTB in patients presenting with pericardial effusion or pleural effusion or ascites. The diagnosis of EPTB remains a challenge despite many technologies that have been developed in the last 20 years; more so in people living with HIV[5]. As with many other series[11,12], males in this study outnumbered women by 2:1, and the cohort had a significant proportion of PLWH (42%). Since the introduction of the ART program in Malawi in 2004, there has been a steady decline in the proportion of PLWH diagnosed with TB. Twenty years ago, almost three quarters of patients diagnosed with TB were living with HIV[13]. The impact of ART has been impressive in the reduction of both infectious comorbidities like TB and mortality related to HIV infection[14].

Sensitivity/specificity of Xpert MTB/RIF Ultra compared to MTB culture

Many of the current diagnostic tests for EPTB are either too expensive to be used on everyone who presents with EPTB or are not sensitive enough to pick up those with the disease. Hence the need for more sensitive, reasonably cheap, and practical diagnostic tests. Xpert MTB Ultra is one of the most recent tests to be deployed for diagnosis of TB including for specimen from EPTB sites. In this study, Xpert MTB Ultra's diagnostic performance was compared with MTB culture, and pooled diagnostic tests consisting of MTB culture, FASH and clinical TB diagnostic criteria. Xpert MTB Ultra's sensitivity and specificity compared to mycobacterial culture was 83% and 98%, respectively, similar to previously published data from a systematic review by Meng Zhang et al(around 88 and 96%, respectively, for sensitivity and

specificity[15]. This was a systematic review that examined studies that assessed Xpert MTB Ultra in both sputum and EPTB specimens such as pleural fluid[15].

The results in our study also correlate well with findings from a study conducted in China by Xiao et al, who included 250 HIV-negative participants and found that the sensitivity and specificity of Xpert MTB Ultra compared to mycobacterial culture in diagnosis of EPTB was around 84% and 92%, respectively[13]. The main difference between our study and the study by Xiao et al is that they excluded HIV-positive patients and they included Fine Needle Aspirations (FNA) from lymph nodes which generally have a higher TB detection rate compared to pleural fluid (FNA TB detection rate was around 79% vs 44% for pleural fluid)[13].

The performance of Xpert MTB/RIF Ultra in a resource-rich low-TB-incidence setting was assessed by Claudio Piersimoni et al in Italy (16). The study examined Xpert MTB Ultra's sensitivity in comparison to mycobacterial culture on several extra-pulmonary samples that were culture-positive. The specimens included urine, gastric aspirates, sterile body fluids (synovial, ascites and pleural), cerebrospinal fluids, fine needle aspirates, pus, and biopsies (contributed 50% of the specimens)[16]. The sensitivity and specificity of Xpert MTB Ultra was 95% and 98% respectively[16]. This is much higher than the performance demonstrated in our study and there are several possible explanations for this. Firstly, that study was done in a high-income setting with a low TB prevalence which enabled researchers do invasive procedures such as tissue biopsy in about 50% of the participants and so increase the diagnostic yield. Secondly, the participants in that study were predominantly HIV-negative as opposed to the Malawian cohort that was around 42% HIV-positive. It is known that samples from PLWH are paucibacillary[7].

Aggarwal et al. examined 74 publications in a systematic review that assessed diagnostic performance of Xpert MTB/ RIF and Xpert MTB/RIF Ultra in tuberculous effusions(17). The sensitivity and specificity of for Xpert MTB Ultra in pleural effusions with mycobacterial culture as reference were 68% (95% CI: 55 – 79%) and 97% (95% CI: 97 – 99%), respectively[17]. This is similar to findings in our study.

Sensitivity/specificity of Xpert MTB/RIF Ultra compared to composite reference standard

Compared to composite diagnosis, the sensitivity of Xpert MTB Ultra in our study was 17% (95 CI 7-34) and specificity was 98% (95 CI 94-100). Several studies compared the sensitivity and specificity of Xpert MTB Ultra to a composite reference standard in diagnosis of EPTB among adults cognizant of the fact that MTB culture also has sensitivity and specificity limitations. The main thing to note here is that various studies used different components in their definition of EPTB and so comparison of these results should be done contextually.

A study by Bahr et al at Mbarara Regional Referral Hospital, Uganda, used a composite reference standard in their assessment of Xpert MTB Ultra's diagnostic performance of EPTB[18]. It was conducted in patients living with HIV and it included 129 cerebrospinal fluid (CSF) samples that were collected originally for a cryptococcal meningitis study[18]. The study's composite reference standard diagnosis included MTB culture, conventional Xpert and Xpert MTB Ultra[18]. Xpert MTB Ultra had a sensitivity of 70% (95% CI: 47-87) and specificity of 93% (95% CI: 87-97) compared to the

composite reference standard[18]. The sensitivity in this study was slightly higher than ours'. However, the difference is that they analysed CSF while we analysed serosal fluid. They also recruited an HIV-positive population but HIV prevalence in our study was only 42%. In addition, they included Xpert MTB Ultra in its composite reference standard, which was not the case in our study.

Qing Sun et al compared the diagnostic performance of Xpert Ultra to a composite diagnosis comprising of clinical, laboratory (smear, Xpert MTB/RIF and MTB culture on osteoarticular pus), radiological and 6 months follow-up data in diagnosis of osteoarticular TB(19). The study was conducted between June 2017 and June 2018 at Beijing Chest Hospital in China. A total of 166 samples were used in the final analysis. The sensitivity of Xpert MTB Ultra compared to the composite reference standard was 91% (85-95) and specificity was 97% (85-100)(19). This sensitivity is significantly higher than ours but this could be explained by the fact that they used pus instead of serosal fluid and because all the patients recruited in their cohort were HIV-negative unlike our study that had an HIV prevalence of 42%.

Study mortality

There were no post-mortem examinations done on patients in this study, so the deaths discussed in the results section refer to the working diagnosis at the time of death. EPTB contributed around 9% (4/47) of all deaths in this cohort. All four EPTB deaths were among PLWH. Three out of the 4 TB deaths occurred within the first 4 days of admission. The fourth death occurred on the 40th day of follow-up.

A TB mortality study conducted in Malawi by Harries et al showed a similar pattern of TB death as that found in the current study in that the mortality was significantly high in the first 1 week to 1 month of TB treatment (20). They also showed that TB mortality was about 20% on day 7 of treatment but increased to 40% by 1 month of treatment (20). The high mortality in that study could be a result of limited access to ART by PLWH because the study was conducted prior to the expanded access to ART in Malawi.

Study strengths and limitations

Our study is the first of its kind in Malawi as it attempts to address the challenges clinicians face when diagnosing extra-pulmonary TB. It gives an insight into Xpert Ultra diagnostic performance in both PLWH and HIV-negative patients, and it uses mycobacterial culture as the reference standard which enables its results to be comparable to studies done in other parts of the world.

This study, however, had several limitations. Firstly, the study's sample size calculation was assumed, based on a study conducted on sputum samples in Malawi, that TB prevalence among medical inpatients was higher than what was found. This might have resulted in a small sample size which limits the strength of our conclusions. Secondly, the study used a small volume of specimen (an average of 10 millilitres) for all the needed laboratory work (Xpert Ultra, MGIT and LJ culture) which might explain the low TB detection rate by mycobacterial culture. A larger volume of sample may have produced a different result. Thirdly, the study included subjective clinical response to TB treatment as one of the diagnostic modalities in the composite reference standard. This makes comparison with other studies difficult. The study also included FASH which has not been validated by WHO

for EPTB diagnosis and was performed by a non-radiology-specialist as part of its composite reference standard.

Conclusion and Recommendations

Within the limitations of the present study, we conclude that Xpert MTB/RIF Ultra has a reasonably good diagnostic yield on pleural, ascitic and pericardial fluid in comparison to mycobacterial culture in both HIV-negative and PLWH. We also note that there is a high all-cause mortality at 2 weeks in patients presenting with significant ascitic, pericardial and pleural effusions. We recommend that Xpert MTB/RIF Ultra be incorporated into routine EPTB diagnostic algorithms and, where resources allow, it should replace Xpert MTB/RIF as the first-line diagnostic test in patients being investigated for disseminated TB as recommended by the WHO in 2017. Xpert MTB/RIF Ultra cartridges use the GeneXpert platform and cost the same as Xpert MTB/RIF cartridges, so the switch will not have any cost implications but will significantly improve TB diagnosis. We also recommend that more multi-centre studies with large sample sizes and using various extra-pulmonary samples be conducted to confirm our observations and that more resources should be invested in improving TB diagnosis worldwide because it has the potential to save a lot of lives.

Data Availability

All relevant data are within the manuscript.

Competing interests

None declared

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