Point-of-Care Ultrasound Predictors for the Diagnosis of Tuberculosis in HIV-Positive Patients Presenting to an Emergency Center

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Background: The performance of point-of-care ultrasound (PoCUS) to diagnose HIV-associated tuberculosis has not been evaluated in large prospective studies. We determined the diagnostic accuracy of individual PoCUS features, performed an external validation of the focused assessment with sonography for HIV/TB (FASH) protocol, and determined independent PoCUS predictors of HIV-associated tuberculosis appropriate for use by emergency center practitioners.

Setting: A cross-sectional diagnostic study was performed at the emergency center of Khayelitsha Hospital (Cape Town, South Africa).

Received for publication July 16, 2019; accepted December 9, 2019.

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G. Meintjes was supported by the Wellcome Trust (098316 and 203135/Z/16/Z), the South African Medical Research Council through its TB and HIV Research Unit, South African Research Chairs Initiative of the Department of Science and Technology and National Research Foundation (NRF) of South Africa (Grant No 64787), NRF incentive funding (UID: 85858) and the South African Research Chairs Initiative of the Department of Science and Technology and National Research Foundation (NRF) of South Africa (Grant No 64787), NRF incentive funding (UID: 85858) and the South African Medical Research Council through its TB and HIV Collaborating Centres Programme with funds received from the National Department of Health (RF/A# SAMRC-RFA-CC: TB/HIV/AIDS-01-2014). G. Maartens was supported by NRF incentive funding (UID: 85810). D.J.v.H. received a Mindray ultrasound machine from the RCA division of Ascendis Medical to use in a part of the study. The remaining authors, none were declared.

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Methods: HIV-positive adults with the suspicion of having tuberculosis were prospectively enrolled. PoCUS was performed according to a standardized protocol. Reference standard was the detection of Mycobacterium tuberculosis using Xpert MTB/RIF culture.

Results: We enrolled 414 participants: 243 female, median age 36 years, median CD4 cell count 86/mm3, and 172 (42%) had tuberculosis. Sensitivity and specificity were ≥ 1 individual PoCUS feature [73% (95% CI: 65 to 79), 54% (95% CI: 47 to 60)], FASH protocol [71% (95% CI: 64 to 78), 57% (95% CI: 50 to 63)]. Independent PoCUS predictors identified were intra-abdominal lymphadenopathy of any size (aDOR 3.7 (95% CI: 2.0 to 6.7)), ascites [aDOR 3.0 (95% CI: 1.5 to 5.7)], and pericardial effusion of any size [aDOR 1.9 (95% CI: 1.2 to 3.0)]. The c-statistic for the derivation model was 0.680 (95% CI: 0.631 to 0.729), compared with 0.630 (95% CI: 0.576 to 0.684) of the FASH protocol. Two or more independent PoCUS predictors had 91% (95% CI: 86 to 94) specificity.

Conclusion: The presence of 2 or more independent PoCUS predictors (intra-abdominal lymphadenopathy, ascites, and pericardial effusion) had moderate discrimination for HIV-associated tuberculosis in patients presenting to the emergency center.

Key Words: HIV, tuberculosis, diagnosis, prediction, ultrasound, emergency center

(J Acquir Immune Defic Syndr 2020;83:415–423)

INTRODUCTION

Tuberculosis is the leading cause of death in adults infected with the HIV globally.1 Some of these deaths could be prevented with early diagnosis and treatment. Diagnosing tuberculosis in HIV-positive patients is challenging because they have atypical clinical presentations, higher rates of smear-negative pulmonary and extrapulmonary tuberculosis, and often cannot produce sputum.2–5

Ultrasound can identify features associated with extrapulmonary tuberculosis in HIV-positive patients6 and has been included in the WHO diagnostic algorithm for seriously ill HIV-positive patients with a positive tuberculosis symptom screen.7 Point-of-care ultrasound (PoCUS) has been used to improve the diagnoses of pericardial, pleural, and abdominal...
tuberculosis in HIV-positive patients. The focused abdominal sonography for HIV/TB (FASH) protocols are easily learned and quick to perform. The FASH basic evaluates 3 easily recognized variables: pericardial effusion, pleural effusion, and ascites. The 3 additional FASH plus features are more difficult to identify upper abdominal lymph nodes (>15 mm in diameter), focal hypoechoic splenic, and focal hypoechoic liver lesions. The FASH combined (or just FASH protocol) evaluates all 6 of the features of the FASH basic and FASH plus.

Most studies evaluating the diagnostic performance of abdominal ultrasound are retrospective,14,15 have a small sample size (≤100 participants),8,16–18 used a case–control design,19–21 or used reference standards that were not robust.10,18,22,23 Several studies were also limited by incorporation bias (index test incorporated in composite reference standard).8,14,15,17 which overestimates the diagnostic accuracy of the test.24 A systematic review evaluating abdominal ultrasound in bacteriologically confirmed HIV-associated tuberculosis reported pooled sensitivity of 63% and pooled specificity of 68%, and reported very low-quality evidence—only one study evaluating PoCUS met the inclusion criteria for the review.25 There are no large prospective studies evaluating the diagnostic accuracy of PoCUS to diagnose tuberculosis in HIV-positive adults using a robust reference standard. We conducted a prospective cross-sectional study to determine the diagnostic accuracy of PoCUS for HIV-associated tuberculosis using a microbiological reference standard that included systematic tuberculosis testing of multiple clinical samples. Our first objective was to determine the diagnostic accuracy of individual PoCUS features. Our second objective was to perform an external validation of the FASH protocols using FASH-specific thresholds. Our third objective was to determine independent PoCUS predictors of HIV-associated tuberculosis appropriate for use by practitioners in emergency centers.

METHODS

Study Participants

We conducted a cross-sectional diagnostic accuracy study with prospective data collection in the emergency center of Khayelitsha Hospital, which is a public sector district hospital in a densely populated partially informal settlement in Cape Town, South Africa. Khayelitsha has a HIV prevalence of 27% and an annual tuberculosis notification rate of 917 per 100,000 persons. The emergency center manages ±30,000 patients per annum with an admission rate around 30%. The HIV prevalence of patients managed in the resuscitation unit is 23%.28

Consecutive patients presenting to the emergency center were screened on Monday to Thursday from June 2016 through October 2017. HIV-positive adults (≥18 years) presenting with any one of the WHO tuberculosis symptoms (cough of any duration, fever, drenching night sweats, or weight loss) were deemed suspicious of having tuberculosis and were eligible for inclusion. HIV status was determined through clinical records or by laboratory confirmation using a rapid test algorithm. Exclusion criteria were antituberculosis treatment within the previous 3 months, pregnancy, presented to the emergency center >24 hours before being screened, a main clinical presentation of meningitis syndrome or new focal neurology, or patients presenting with primarily trauma, gynecological, or psychiatric conditions. Data from this cohort on urine lipoarabinomannan diagnostic performance were previously published.30

Written informed consent was obtained from all participants using a two-phase consent process. Severely ill participants were provided with a short one-page consent form indicating what extra tests would be performed, and that these would be used to facilitate diagnosis of tuberculosis and for research purposes. Full consent was obtained once patients had recovered and agreed to participate. The study was approved by the Human Research Ethics Committee of the University of Cape Town.

Test Methods

PoCUS was performed by a single emergency physician (the first author, with adequate training and credentials)31 according to a standardized protocol. PoCUS was performed and interpreted in real time in the emergency center directly after consent was taken and before any specimens were collected. At the time of the PoCUS, the physician performing it had access to the clinical information but not to results from the reference standard. PoCUS was performed using either a Mindray M5 ultrasound system with a 3C5s (2.5–6.5 MHz) convex probe and a 7L4s (5.0–10 MHz) linear probe (Mindray DS USA, Inc, Mahwah, NJ) or a NanoMaxx ultrasound system with a L38n (10-5 MHz) linear array probe and a C60n (5-2 MHz) curved array probe (SonoSite Inc, Bothell, WA).

The PoCUS examination assessed for pericardial and pleural effusions, focal splenic and hepatic lesions, ascites, and intra-abdominal lymph nodes. Focal splenic and hepatic lesions were deemed positive if hypoechoic or hyperechoic lesions of any size or number were present.32 The maximum diameter was noted. The presence of intra-abdominal lymph nodes were assessed in the periportal, para-aortic, splenic (hilir), and mesenteric areas. The maximum diameter was documented (irrespective of axis). Two thresholds for pericardial effusion (any size and ≥5 mm) were used to determine whether minimal sized effusions, with <5 mm corresponding to <100 mL of fluid,33 should be used as the cutoff value for positivity. Different thresholds for intra-abdominal lymph nodes (any size, ≥5, ≥10, ≥15 mm) were considered because the literature differs regarding the optimal threshold to be used.10,13,34,35

FASH-specific thresholds were used to determine diagnostic accuracy of the FASH protocols.13 FASH basic was deemed positive if any of pericardial effusion, ascites, or pleural effusion were present.13 FASH plus was positive if upper abdominal lymph nodes (≥15 mm in diameter), focal hypochoic splenic lesions, or focal hypochoic liver lesions were present.13 FASH combined (or just FASH protocol) was positive if any feature of the FASH basic or the FASH plus was present.

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The reference standard was the detection of *Mycobacterium tuberculosis* from Xpert MTB/RIF or culture. Sterile single-use disposable containers were used for urine collection; participants were catheterized if needed. Test results were made available to managing clinicians as soon as they became available. Any result from other specimens from any anatomical site obtained as part of the routine standard of care by hospital or clinic clinicians (nonstudy) were included if they were taken during admission or within 6 weeks after hospital discharge.

The National Health Laboratory Service performed all the tests. The Xpert MTB/RIF assay (GX4) (Cepheid Inc, Sunnyvale, CA) was used to test sputum specimens and concentrated urine samples. Sputum specimens were cultured in mycobacterial growth indicator tubes (MGIT; Becton Dickson, Sparks, MD). BACTEC MYCO/F Lytic blood culture bottles (Becton Dickson) were filled with at least 5 mL of blood and incubated for up to 6 weeks. The MTBDRplus assay (Hain Lifescience, Nehren, Germany) was used to identify culture isolates as *M. tuberculosis* complex. CD4 cell counts were performed on admission unless performed within 3 months before enrolment. Laboratory personnel were blinded to PoCUS results.

**Statistical Analysis**

The sample size was determined with the aim of including more than the recommended 10 candidate predictors (including interaction terms) from multivariable logistic regression analyses. The tuberculosis prevalence in HIV-positive patients in the emergency center is around 25%, and a sample size of 400 HIV-positive participants was deemed adequate to include 100 tuberculosis cases.

Summary statistics were used to describe the variables. Normal distribution of quantitative variables was assessed visually (using histograms and Q-Q plots) and for statistical significance (Shapiro–Wilk test). Homogeneity of variance was determined with the Levene test. Comparisons were performed using the *t* test or Mann–Whitney *U* test when comparing means or medians, respectively. The Pearson χ²-test or Fisher exact test were used for comparing proportions. Suboptimal PoCUS views, where the presence or absence of specific PoCUS features could not be determined, were included as feature not present. Analyses for the diagnostic performance of individual PoCUS features and to externally validate the FASH protocols were performed using MedCalc for Windows, version 18.5 (MedCalc Software, Ostend, Belgium; https://www.medcalc.org; 2018) and SPSS Statistics for Windows, Version 25.0 (IBM Corp. Released 2017, Armonk, NY: IBM Corp), R statistical software version 3.4.3 (November 30, 2017) [The R Foundation for Statistical Computing Platform], and SAS software (Copyright 2018 SAS Institute Inc SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc, Cary, NC).

**RESULTS**

**Participant Characteristics**

We screened 556 patients, 414 (74.5%) of whom were included in the final data set. Reasons for exclusion are shown in Figure 1. We obtained 1390 samples [median of 3 samples per participant (25–75 percentile 2–4 samples)] for detection of *M. tuberculosis* during admission, of which 1005 (72.3%) were obtained within 24 hours (see Table, Supplemental Digital Content, http://links.lww.com/QAI/B419, which describes the clinical samples sent for mycobacterial testing). At least 2 samples from at least 2 different anatomical sites were obtained in 350 (84.5%) participants. Forty-five participants not diagnosed with tuberculosis during admission were investigated for tuberculosis within 3 months of hospital discharge; only one participant had a positive test (culture) on a sputum sample. Tuberculosis was microbiologically confirmed in 172 participants (41.5%) (only Xpert MTB/RIF positive n = 32, 18.6%; only culture positive n = 47, 27.3%; both Xpert MTB/RIF and culture positive n = 93, 54.1%). Baseline demographic and clinical characteristics of participants with and without confirmed tuberculosis are presented in Table 1. Respiratory system related diagnoses were the most frequent alternative diagnoses in those without confirmed tuberculosis (see Table, Supplemental Digital Content, http://links.lww.com/QAI/B419 for alternative diagnoses in participants without microbiologically confirmed tuberculosis); 63 participants without microbiologically confirmed tuberculosis were empirically started on antituberculosis therapy (see Table, Supplemental Digital Content, http://links.lww.com/QAI/B419, which present reasons for clinical
diagnosis of tuberculosis without microbiological confirmation). The all cause in-hospital mortality was 7.2% (n = 30), with no statistical difference between those with or without confirmed tuberculosis (15/172 versus 15/242; P = 0.33).

Diagnostic Accuracy of Individual PoCUS Features

The sensitivity and specificity of ≥1 individual PoCUS feature was 73% (95% CI: 65% to 79%) and 54% (95% CI: 47% to 60%) (Table 2) (see Table, Supplemental Digital Content, http://links.lww.com/QAI/B419, which lists the number of true positives, false positives, true negatives, and false negatives for each individual PoCUS feature). In participants with a CD4 cell count ≤100/mm³, the sensitivity increased to 82% (95% CI: 74% to 89%) and the specificity to 55% (95% CI: 46% to 65%) (see Table, Supplemental Digital Content, http://links.lww.com/QAI/B419, which describes the diagnostic accuracy of PoCUS in participants with CD4 cell count ≤100/mm³).

External Validation of FASH-Protocols

The FASH-combined protocol (any abnormal FASH-specific feature) had a sensitivity of 71% (95% CI: 64% to 78%) and specificity of 57% (95% CI: 50% to 63%) (Table 3). Sensitivity increased to 80% (95% CI: 71% to 87%) and specificity was 56% (95% CI: 47% to 66%) in participants with CD4 cell counts ≤100/mm³ (Table 3). The c-statistic for the FASH-basic was 0.609 (95% CI: 0.554 to 0.664), for the FASH-plus 0.598 (95% CI: 0.542 to 0.654) and for the FASH-combined 0.630 (95% CI: 0.576 to 0.684).
Independent PoCUS Predictors

The most significant independent predictors of tuberculosis were any intra-abdominal lymph node [adjusted diagnostic odds ratio (aDOR) 3.7 (95% CI: 2.0 to 6.7)], ascites [aDOR 3.0 (95% CI: 1.5 to 5.7)], and any pericardial effusion [aDOR 1.9 (95% CI: 1.2 to 3.0)] (Table 4). The presence of any 2 independent PoCUS predictors had 91% (95% CI: 86% to 94%) specificity and a positive likelihood ratio of 3.7 (95% CI: 2.4 to 5.8) (see Table, Supplemental Digital Content, http://links.lww.com/QAI/B419, which describes the diagnostic accuracy of independent PoCUS predictors for the diagnosis of HIV-associated tuberculosis). Good agreement between the occurrence of tuberculosis estimated by the derived model and the frequency of tuberculosis observed in the study population was indicated in the calibration curve and by the Hosmer–Lemeshow test ($\chi^2 = 0.210; P = 0.90$). The c-statistic of the model was 0.680 (95% CI: 0.631 to 0.729). Good stability of the model was indicated with bootstrap internal validation (c-statistic 0.679, 95% CI: 0.668 to 0.680), with an optimism estimate of 0.003 (95% CI −0.052 to 0.059) (see Figure, Supplemental Digital Content, http://links.lww.com/QAI/B419, which presents validation plots for the assessment of variables included in the multivariable logistic regression model aimed for the diagnosis of HIV-associated tuberculosis).

**DISCUSSION**

This is the first large prospective study to assess the diagnostic accuracy of PoCUS for diagnosing HIV-associated tuberculosis using a robust microbiologic reference standard. A

| TABLE 1. Baseline Demographics and Clinical Characteristics of Study Population |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
| Characteristics at Enrolment    | All (N = 414)   | M. tuberculosis Confirmed (N = 172) | M. tuberculosis Not Confirmed (N = 242) | P               |
| Demographics                    | N               | n (%) Unless Otherwise Specified | n (%) Unless Otherwise Specified | n (%) Unless Otherwise Specified |                |
| Age (yrs) [median (Q1–Q3)]     | 414             | 36 (30–43)       | 35 (30–42)       | 36 (31–44)       | 0.12           |
| Gender: male                    | 414             | 171 (41.3)        | 71 (41.3)        | 100 (41.3)       | 0.99           |
| Clinical history                |                 |                  |                  |                  |                |
| Current cough of any duration   | 414             | 352 (85.0)        | 148 (86.0)       | 204 (84.3)       | 0.62           |
| Weight loss within last month   | 414             | 355 (85.7)        | 156 (90.7)       | 199 (82.2)       | 0.02           |
| Night sweats within last month  | 414             | 218 (52.7)        | 102 (59.3)       | 116 (47.9)       | 0.02           |
| Fever within last month         | 414             | 200 (48.3)        | 75 (43.6)        | 125 (51.7)       | 0.11           |
| Previous tuberculosis (any time)| 413             | 218 (52.8)        | 73 (42.4)        | 145 (60.2)       | <0.01          |
| Previous tuberculosis ≤ 2 yrs   | 218             | 76 (34.9)         | 29 (39.7)        | 47 (32.4)        | 0.29           |
| Antiretroviral therapy naïve    | 414             | 125 (30.2)        | 64 (37.2)        | 61 (25.2)        | 0.13           |
| Currently on antiretroviral therapy | 414      | 195 (47.1)        | 62 (36.0)        | 133 (55.0)       | 0.07           |
| Defaulted antiretroviral therapy | 414          | 87 (21.0)         | 44 (25.6)        | 43 (17.8)        | 0.28           |
| Unknown if on antiretroviral therapy | 414    | 7 (1.7)           | 2 (1.2)          | 5 (2.1)          | 0.44           |
| First-line antiretroviral regimen | 195          | 120 (61.5)        | 40 (64.5)        | 80 (60.2)        | 0.04           |
| Second-line antiretroviral regimen | 195             | 42 (21.5)         | 11 (17.7)        | 31 (23.3)        | 0.46           |
| Unknown antiretroviral regimen  | 195             | 33 (16.9)         | 11 (17.7)        | 22 (16.5)        | 0.84           |
| Clinical findings               |                 |                  |                  |                  |                |
| Weight (kilogram) [median (Q1–Q3)] | 383      | 54 (46–65)        | 53 (46–61)       | 55 (47–67)       | 0.15           |
| Body mass index (kg/m²) [median (Q1–Q3)] | 382 | 20 (17–24)       | 20 (17–24)       | 20 (18–25)       | 0.41           |
| Underweight (body mass index < 18.5 kg/m²) | 382 | 138 (33.3)      | 61 (35.5)        | 77 (31.8)        | 0.54           |
| Temperature (centigrade) (mean ± SD) | 411     | 36.8 (36.1–37.8) | 36.8 (36.1–38)   | 36.8 (36.2–37.8) | 0.68           |
| Systolic blood pressure (mm Hg) [median (Q1–Q3)] | 414 | 111 (98–125)    | 112 (99–124)     | 110 (97–127)     | 0.94           |
| Diastolic blood pressure (mm Hg) [median (Q1–Q3)] | 414 | 71 (61–81)      | 72 (60–80)       | 71 (61–82)       | 0.91           |
| Heart rate (beats per minute) (mean ± SD) | 414          | 122 ± 22         | 127 ± 23         | 119 ± 21         | <0.01          |
| Respiratory rate (breaths per minute) [median (Q1–Q3)] | 411 | 24 (19–30)      | 24 (18–30)       | 24 (20–32)       | 0.15           |
| Oxygen saturation level [median (Q1–Q3)] | 406 | 97 (94–99)     | 97 (95–99)       | 96 (93–99)       | 0.11           |
| Hemoglobin (g/dL) (mean ± SD)    | 410             | 9.7 (± 2.7)       | 9.0 (± 2.4)       | 10.2 (± 2.7)     | <0.01          |
| Mean corpuscular volume (fL) (mean ± SD) | 407 | 86.6 ± 8.9      | 84.8 ± 8.1       | 87.9 ± 9.3       | <0.01          |
| White blood cell count (×10³/L) [median (Q1–Q3)] | 412 | 8.3 (5.8–13.6)  | 7.4 (5.4–12.6)   | 9.1 (6.2–14.7)   | <0.01          |
| Platelet count [median (Q1–Q3)]  | 410             | 284 (195–390)     | 272 (199–383)    | 288 (187–400)    | 0.46           |
| CD4 cell count (×10³/mm³) [median (Q1–Q3)] | 408 | 86 (30–218)    | 65 (23–155)      | 121 (37–266)     | <0.01          |

*Q1–Q3 = 25th–75th percentile.
### Table 2. Diagnostic Accuracy of Individual Point-Of-Care Ultrasound Features for Diagnosing Tuberculosis in HIV-Positive Participants

| Individual ultrasound feature | n* | DOR (95% CI) | Sensitivity (95% CI) | Specificity (95% CI) |
|-------------------------------|----|-------------|----------------------|---------------------|
| Intra-abdominal nodes (any location, any size) | 70† | 4.9 (2.8 to 8.8) | 30% (23% to 37%) | 92% (88% to 95%) |
| Intra-abdominal nodes (any location, ≥5 mm) | 69† | 4.8 (2.7 to 8.5) | 29% (22% to 36%) | 92% (88% to 95%) |
| Intra-abdominal nodes (any location, ≥10 mm) | 39† | 4.1 (2.0 to 8.5) | 16% (11% to 23%) | 95% (91% to 98%) |
| Intra-abdominal nodes (any location, ≥15 mm) | 8† | 2.4 (0.6 to 10.1) | 3% (1% to 7%) | 99% (97% to 100%) |
| Ascites | 54 | 4.0 (2.2 to 7.5) | 22% (16% to 29%) | 93% (89% to 96%) |
| Splenic lesions (hypoechoic, any size) | 94‡ | 3.9 (2.4 to 6.4) | 37% (29% to 44%) | 87% (82% to 91%) |
| Splenic lesions (any) | 104‡ | 3.0 (1.9 to 4.7) | 37% (30% to 45%) | 83% (78% to 88%) |
| Pericardial effusion (≥5 mm) | 106§ | 2.7 (1.7 to 4.2) | 37% (29% to 44%) | 82% (77% to 87%) |
| Pericardial effusion (any size) | 141§ | 2.6 (1.7 to 3.9) | 47% (39% to 54%) | 75% (69% to 80%) |
| Pleural effusion (any) | 72 | 1.5 (0.9 to 2.5) | 21% (15% to 28%) | 85% (80% to 89%) |
| Hepatic lesions | 1 | 0.5 (0.0 to 11.5) | 0% (0% to 2%) | 100% (98% to 100%) |

**Combination of individual ultrasound features**

| ≥ 1 positive feature | 237 | 3.1 (2.0 to 4.7) | 73% (65% to 79%) | 54% (47% to 60%) |
| ≥ 2 positive features | 123 | 4.2 (2.7 to 6.6) | 47% (39% to 55%) | 83% (77% to 87%) |
| ≥ 3 positive features | 58 | 4.6 (2.5 to 8.4) | 24% (18% to 32%) | 93% (89% to 96%) |
| ≥ 4 positive features | 19 | 8.2 (2.3 to 28.3) | 9% (5% to 15%) | 99% (96% to 100%) |

| PPV (95% CI) | NPV (95% CI) | LR (+) (95% CI) | LR (−) (95% CI) |
|--------------|--------------|-----------------|-----------------|
| Intra-abdominal nodes (any location, any size) | 73% (62% to 81%) | 65% (62% to 67%) | 3.8 (2.3 to 6.2) | 0.8 (0.7 to 0.9) |
| Intra-abdominal nodes (any location, ≥5 mm) | 72% (62% to 81%) | 65% (62% to 67%) | 3.7 (2.3 to 6.1) | 0.8 (0.7 to 0.9) |
| Intra-abdominal nodes (any location, ≥10 mm) | 72% (57% to 83%) | 62% (60% to 63%) | 3.6 (1.8 to 7.0) | 0.9 (0.8 to 0.9) |
| Intra-abdominal nodes (any location, ≥15 mm) | 63% (29% to 87%) | 59% (58% to 60%) | 2.3 (0.6 to 9.7) | 1.0 (1.0 to 1.0) |
| Ascites | 70% (58% to 83%) | 63% (61% to 65%) | 3.3 (1.9 to 5.8) | 0.8 (0.8 to 0.9) |
| Splenic lesions (hypoechoic, any size) | 67% (58% to 75%) | 66% (63% to 69%) | 2.9 (2.0 to 4.2) | 0.7 (0.6 to 0.8) |
| Splenic lesions (any) | 62% (53% to 69%) | 65% (62% to 68%) | 2.2 (1.5 to 3.1) | 0.8 (0.7 to 0.9) |
| Pericardial effusion (≥5 mm) | 59% (51% to 67%) | 65% (62% to 67%) | 2.1 (1.5 to 2.9) | 0.8 (0.7 to 0.9) |
| Pericardial effusion (any size) | 57% (50% to 63%) | 66% (63% to 70%) | 1.8 (1.4 to 2.4) | 0.7 (0.6 to 0.8) |
| Pleural effusion (any) | 50% (40% to 60%) | 60% (58% to 62%) | 1.4 (0.9 to 2.1) | 0.9 (0.9 to 1.0) |
| Hepatic lesions | 0% | 58% (58% to 59%) | 0 | 1.0 (1.0 to 1.0) |

**Combination of individual ultrasound features**

| ≥ 1 positive feature | 53% (49% to 57%) | 73% (68% to 78%) | 1.6 (1.3 to 1.9) | 0.5 (0.4 to 0.7) |
| ≥ 2 positive features | 66% (58% to 73%) | 69% (65% to 72%) | 2.7 (2.0 to 3.6) | 0.6 (0.6 to 0.8) |
| ≥ 3 positive features | 72% (60% to 82%) | 63% (61% to 66%) | 3.7 (2.1 to 6.3) | 0.8 (0.7 to 0.9) |
| ≥ 4 positive features | 84% (61% to 95%) | 61% (59% to 62%) | 7.5 (2.2 to 25.4) | 0.9 (0.9 to 1.0) |

*Suboptimal views included as negative feature (see Table, Supplemental Digital Content, http://links.lww.com/QAI/B419, where suboptimal views were excluded).
†Number of suboptimal views included as negative feature = 46.
‡Number of suboptimal views included as negative feature = 8.
§Number of suboptimal views included as negative feature = 46.

Further strength of our study was that tuberculosis testing for defining the reference standard was performed on multiple samples. Individual PoCUS features had poor sensitivity but moderate specificity, in keeping with published literature. FASH protocols performed similarly to the individual PoCUS features, with improved sensitivity in participants with CD4 cell counts ≥100/mm³. Independent PoCUS predictors of tuberculosis were ascites, any intra-abdominal lymph node(s), and any pericardial effusion. The derived model had moderate discrimination and good calibration. We suggest that the presence of 2 or more of the independent PoCUS features (specificity 91%, positive likelihood ratio 3.7) would be appropriate to initiate treatment for tuberculosis in high-burden settings while awaiting results of microbiological tests.

The sensitivity of at least one individual positive feature on PoCUS for HIV-associated tuberculosis was 73%, whereas the specificity of at least 2 abnormalities present was 83% (Table 2). These findings are comparable with other studies assessing formal ultrasound and not PoCUS.23,35

The FASH protocols were developed based on clinical intuition, and their diagnostic accuracy was not reported.12,13 A spatial external validation (same investigators, different cities) in keeping with published literature. FASH findings are comparable with other studies.

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setting) was performed in India of 81 HIV-positive participants, and the reference standard included both confirmed and possible tuberculosis. The FASH protocol tested differed from the original, with any versus multiple focal splenic and liver lesions, and ascites was excluded. The 60% sensitivity and 78% specificity (calculated from presented data) is different from our findings (sensitivity 71%, specificity 57%). A full external validation (different investigators, different settings) was performed in Tanzania but included HIV-negative participants, their reference standard included a probable tuberculosis group without microbiological confirmation, and they included an additional ultrasound variable (ileum wall thickening >4 mm or destroyed architecture); they reported sensitivity and specificity of 56% and 61%, respectively.

The sensitivity of individual PoCUS features and the FASH-protocols improved in participants with CD4 cell count ≤100/mm³, whereas specificity was similar. These findings are similar to other studies where low CD4 cell counts were associated with extrapulmonary tuberculosis and more extensive abdominal involvement. Ultrasound features are thus more likely to be present in patients with more advanced immunosuppression.

We identified 4 PoCUS predictors (lowest positive threshold) with significant univariable association with tuberculosis (any pericardial effusion, ascites, any splenic lesion, and any intra-abdominal lymphadenopathy). Our results can be compared with ultrasound predictors that were significantly associated with tuberculosis in 4 other studies: multiple splenic lesions (2–15 mm) and abdominal lymphadenopathy.

| Predictor Variable | B     | Standard Error | Wald P | Odds Ratio (95% CI) | –2 Log Likelihood |
|--------------------|-------|----------------|--------|---------------------|-------------------|
| Univariable association |       |                |        |                     |                   |
| Ascites            | 1.388 | 0.317          | 0.000  | 4.01 (2.15 to 7.46) | 540.923           |
| Intra-abdominal lymph nodes (any size)* | 1.599 | 0.292          | 0.000  | 4.95 (2.08 to 5.06) | 528.036           |
| Intra-abdominal lymph nodes (≥5 mm)* | 1.571 | 0.292          | 0.000  | 4.81 (2.71 to 8.53) | 529.482           |
| Intra-abdominal lymph nodes (≥10 mm)* | 1.407 | 0.371          | 0.000  | 4.08 (1.97 to 8.46) | 545.892           |
| Pericardial effusion (any size)† | 0.948 | 0.213          | 0.000  | 2.58 (1.70 to 3.92) | 541.806           |
| Pericardial effusion (≥5 mm)‡ | 0.984 | 0.231          | 0.000  | 2.68 (1.70 to 4.21) | 543.443           |
| Pleural effusion (any) | 0.415 | 0.260          | 0.111  | 1.52 (0.91 to 2.52) | 559.497           |
| Any splenic lesion (any size)† | 1.096 | 0.234          | 0.000  | 2.99 (1.89 to 4.74) | 539.380           |

| Predictor Variable | B     | Standard Error | Wald P | Adjusted Odds Ratio (95% CI) | –2 Log Likelihood |
|--------------------|-------|----------------|--------|-----------------------------|-------------------|
| Univariable association§ |       |                |        |                             |                   |
| Intra-abdominal lymph nodes (any size)* | 1.313 | 0.304          | 0.000  | 3.7 (2.0–6.7)               | 506.150           |
| Ascites            | 1.086 | 0.334          | 0.001  | 3.0 (1.5–5.7)               |                   |
| Pericardial effusion (any size)† | 0.642 | 0.228          | 0.005  | 1.9 (1.2–3.0)               |                   |
| Constant            | −0.927| 0.140          | 0.000  |                             |                   |

*Number of suboptimal views included as negative feature = 46.
†Number of suboptimal views included as negative feature = 3.
‡Number of suboptimal views included as negative feature = 8.
§Ultrasound predictors with the lowest positive threshold were included, where different thresholds for positivity were used.
(>15 mm) in an Indian study, 22 pleural effusion, abdominal lymph nodes (>15 mm), and hepatomegaly in a Tanzanian study 41; lymph nodes (≥10 mm), hypoechoic splenic lesions, splenomegaly (≥110 mm), and abdominal/pleural/pericardial effusion in a South African study, and splenic lesions, ascites, pericardial effusion, and lymphadenopathy (>10 mm) in another South African study. 10 Three of these studies used a less robust composite reference standard than in our study, 10,22,41 while 2 also included HIV-negative or HIV-unknown participants. 10,41

In our study ascites, pericardial effusion and any size intra-abdominal lymphadenopathy were independent predictors of tuberculosis after multivariable logistic regression. Independent predictors in other studies were multiple intra-abdominal lymph nodes (≥12 mm), abdominal lymph nodes (≥10 mm), hypoechoic splenic lesions, 34 and abdominal/pleural/pericardial effusion. 34 Both these studies used a robust reference standard, and formal ultrasound examinations were performed in radiology departments.

Our study has limitations. First, PoCUS might not be applied to all participants in real-life scenarios as patients with a clear nontuberculosis diagnosis after the clinical examination (eg, pneumonia) will be managed accordingly. Second, PoCUS examinations were performed by a single, experienced operator. A second reviewer and or sonographer would have enhanced the generalizability of the features. The main strength of our study is the robust microbiologic reference standard applied. It was a pragmatic study as PoCUS was performed under routine conditions experienced in the emergency center.

Our study suggests that ultrasound for the diagnosis of HIV-associated tuberculosis can be used at the point of care. PoCUS is limited by moderate sensitivity, and care must be taken to not rule tuberculosis out after a negative PoCUS examination. The presence of 2 or more independent PoCUS predictors suggests that PoCUS can be used as a rule-in tuberculosis test in emergency centers in high-burden settings. Further research needs to be performed to externally validate the findings, particularly to assess its performance in settings with different prevalences of tuberculosis and alternative diagnoses. Finally, the impact on outcomes of integrating PoCUS into tuberculosis diagnostic algorithms needs to be assessed.

CONCLUSION

We identified independent PoCUS predictors (intra-abdominal lymphadenopathy, ascites, and pericardial effusion) for diagnosing tuberculosis in HIV-positive patients presenting to the emergency center. Although the presence of at least 2 independent PoCUS predictors had better specificity than the FASH protocols, it only had moderate discrimination. Further refinement and possible inclusion of other clinical features should be investigated. These findings could contribute to the development of a clinically orientated point-of-care algorithm to expedite the diagnosis of tuberculosis and initiation of antituberculosis therapy in acute care settings in regions with a high burden of HIV-associated tuberculosis.

ACKNOWLEDGMENTS

The authors acknowledge the valuable contribution of Rene Goliath (research clinical site coordinator, Institute of Infectious Disease & Molecular Medicine, University of Cape Town), the staff of the National Health Laboratory Service (NHLS), and the staff and administration of the Western Cape Department of Health.

REFERENCES

1. World Health Organization. Global Tuberculosis Report 2019. Geneva, Switzerland: World Health Organization; 2019. Available at: https://www.who.int/tb/publications/global_report/en/. Accessed November 25, 2019.
2. Dawson R, Masuka P, Edwards DJ, et al. Chest radiograph reading and recording system: evaluation for tuberculosis screening in patients with advanced HIV. Int J Tuberc Lung Dis. 2010;14:52–58.
3. Horne DJ, Kohli M, Zifodya JS, et al. Xpert MTB/RIF and Xpert MTB/RIF Ultra for pulmonary tuberculosis and rifampicin resistance in adults. Cochrane Database Syst Rev. 2019;CD009593. DOI: 10.1002/14651858.CD009593.pub4.
4. Steingart KR, Ng V, Henry M, et al. Sputum processing methods to improve the sensitivity of smear microscopy for tuberculosis: a systematic review. Lancet Infect Dis. 2006;6:664–674.
5. Palmieri F, Girardi E, Pellicelli AM, et al. Pulmonary tuberculosis in HIV-infected patients presenting with normal chest radiograph and negative sputum smear. Infection. 2002;30:68–74.
6. Abiri MM, Kirpekar M, Abiri S. The role of ultrasonography in the detection of extrapulmonary tuberculosis in patients with acquired immunodeficiency syndrome (AIDS). J Ultrasound Med. 1985;4:471–473.
7. World Health Organization. Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection: Recommendations for a Public Health Approach. 2nd ed. Geneva, Switzerland: WHO Press; 2016. Available at: https://www.who.int/hiv/pub/avt_arv-2016/en/. Accessed November 6, 2019.
8. Heller T, Gobhrirsch S, Bahlas S, et al. Diagnostic value of FASH ultrasound and chest X-ray in HIV-co-infected patients with abdominal tuberculosis. Int J Tuberc Lung Dis. 2013;17:342–344.
9. Giordani MT, Brunetti E, Binazzi R, et al. Extrapulmonary mycobacterial infections in a cohort of HIV-positive patients: ultrasound experience from Vicenza. Italy Infect. 2013;41:409–414.
10. Patel MN, Beningfield S, Burch V. Abdominal and pericardial ultrasound in suspected extrapulmonary or disseminated tuberculosis. South Afr Med J. 2011;101:39–42.
11. Hunter L, Bélard S, Janssen S, et al. Miliary tuberculosis: sonographic pattern in chest ultrasound. Infection. 2016;44:243–246.
12. Heller T, Wallrauch C, Lessells RJ, et al. Short course for focused assessment with sonography for human immunodeficiency virus/ tuberculosis: preliminary results in a rural setting in South Africa with high prevalence of human immunodeficiency virus and tuberculosis. Am J Trop Med Hyg. 2010;82:512–515.
13. Heller T, Wallrauch C, Gobhrirsch S, et al. Focused assessment with sonography for HIV-associated tuberculosis (FASH): a short protocol and a pictorial review. Crit Ultrasound J. 2012;4:21.
14. Agarwal D, Narayan S, Chakravarty J, et al. Ultrasoundography for diagnosis of abdominal tuberculosis in HIV infected people. Indian J Med Res. 2010;132:77–80.
15. Spalgais S, Agarwal U, Sarin R, et al. Role of routine abdominal ultrasonography in intensified tuberculosis case finding algorithms at HIV clinics in high TB burden settings. BMC Infect Dis. 2017:17:351.
16. Sinkala E, Gray S, Zulu I, et al. Clinical and ultrasonographic features of abdominal tuberculosis in HIV positive adults in Zambia. BMC Infect Dis. 2009;9:44.
17. Heller T, Mtemang’ombe EA, Huson MAM, et al. Ultrasound for patients in a high HIV/tuberculosis prevalence setting: a needs assessment and review of focused applications for Sub-Saharan Africa. Int J Infect Dis. 2017;56:229–236.
18. Bobbio F, Di Gennaro F, Marotta C, et al. Focused ultrasound to diagnose HIV-associated tuberculosis (FASH) in the extremely resource-
limited setting of South Sudan: a cross-sectional study. BMJ Open. 2019; 9:e027179.

19. Barreiros AP, Braden B, Schieferstein-Knauer C, et al. Characteristics of intestinal tuberculosis in ultrasonographic techniques. Scand J Gastroenterol. 2008;43:1224–1231.

20. Kaneria MV, Yeole S, Patil S. Splenic microabscesses in HIV infection. A marker of disseminated tuberculosis? Acta Anaesthesiol Ital. 2009;60:20–30.

21. Monill-Serra JM, Martinez-Noguera A, Montserrat E, et al. Abdominal ultrasound findings of disseminated tuberculosis in AIDS. J Clin Ultrasound. 1997;25:1–6.

22. Weber SF, Saravu K, Heller T, et al. Point-of-care ultrasound for extrapulmonary tuberculosis in India: a prospective cohort study in HIV-positive and HIV-negative presumptive tuberculosis patients. Am J Trop Med Hyg. 2018;98:266–273.

23. Dominguez-Castellano A, Yáñez P, Muniaín MA, et al. The usefulness of abdominal echography in the diagnosis of extrapulmonary tuberculosis in patients with HIV infection. Enferm Infecc Microbiol Clin. 1998;16:61–65.

24. Roever L. Types of bias in studies of diagnostic test accuracy. Evid Based Med Pract. 2016;2:1–2.

25. van Hoving DJ, Griesel R, Meintjes G, et al. Abdominal ultrasound for diagnosing abdominal tuberculosis or disseminated tuberculosis with abdominal involvement in HIV-positive individuals. Cochrane Database Syst Rev. 2019;CD012777. DOI: 10.1002/14651858.CD012777.pub2.

26. Thom A. W. Cape Plots HIV Rates by District. Health-e News. Available at: https://health-e.org.za/2004/10/07/w-cape-plots-hiv-rates-by-district/. Accessed October 7, 2004.

27. Janssen S, Schutz C, Ward AM, et al. Hemostatic changes associate with mortality in hospitalized patients with HIV-associated tuberculosis: a prospective cohort study. J Infect Dis. 2004;199:427–434.

28. Hunter LD, Lahri S, van Hoving DJ. Case mix of patients managed in the resuscitation area of a district-level public hospital in Cape Town. Afr J Emerg Med. 2017;7:19–23.

29. World Health Organization. Systematic Screening for Active Tuberculosis: Principles and Recommendations. Geneva, Switzerland: World Health Organization; 2015. Available at: https://www.who.int/tb/tscreening/en/. Accessed April 30, 2019

30. Van Hoving DJ, Lahri S, Lategan HJ, et al. Brief report: real-world performance and interobserver agreement of urine lipoarabinomannan in diagnosing HIV-associated tuberculosis in an emergency center. J Acquir Immune Defic Syndr. 2019;81:e10–e14.

31. Atkinson P, Bowra J, Lambert M, et al. International federation for emergency medicine point of care ultrasound curriculum. CJEM. 2015; 17:161–170.

32. Caremani M, Occhini U, Caremani A, et al. Focal splenic lesions: US findings. J Ultrasound. 2013;16:65–74.

33. Jung HO. Pericardial effusion and pericardiocentesis: role of echocardiography. Korean Circ J. 2012;42:725–734.

34. Griesel R, Cohen K, Mendelson M, et al. Abdominal ultrasound for the diagnosis of tuberculosis among human immunodeficiency virus-positive inpatients with world Health organization danger signs. Open Forum Infect Dis. 2019;6:ofz094.

35. Sculier D, Vannarith C, Pe R, et al. Performance of abdominal ultrasound for diagnosis of tuberculosis in HIV-infected persons living in Cambodia. JAIDS J Acquir Immune Defic Syndr. 2010;55:500–502.

36. Lawn SD, Kerkhoff AD, Burton R, et al. Diagnostic accuracy, incremental yield and prognostic value of Determine TB-LAM for routine diagnostic testing for tuberculosis in HIV-infected patients requiring acute hospital admission in South Africa: a prospective cohort. BMC Med. 2017;15:67.

37. Peduzzi P, Concato J, Kemper E, et al. A simulation study of the number of events per variable in logistic regression analysis. J Clin Epidemiol. 1996;49:1373–1379.

38. Collett D. Modelling Binary Data. 2nd ed. New York, NY: Chapman and Hall/CRC; 2002.

39. Hosmer DW, Lemeshow S, Sturdivant RX. Applied Logistic Regression. Hoboken, NJ: John Wiley & Sons, Inc; 2013.

40. Steyerberg EW, Harrell FE, Borsboom GIJM, et al. Internal validation of predictive models. J Clin Epidemiol. 2001;54:774–781.

41. Ndege R, Weisser M, Elzi L, et al. Sonography to rule out tuberculosis in sub-Saharan Africa: a prospective observational study. Open Forum Infect Dis. 2019;6:ofz154.