Clinical Infectious Diseases

MAJOR ARTICLE

Ultrasononography in Managing Extrapulmonary Tuberculosis: A Randomized, Controlled, Parallel, Superiority, Open-Label Trial

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Background. Patients with suspected extrapulmonary tuberculosis are often treated empirically. We hypothesized that extended focused assessment with sonography for human immunodeficiency virus (HIV) and tuberculosis (eFASH), in combination with other tests, would increase the proportion of correctly managed patients with suspected extrapulmonary tuberculosis.

Methods. This trial in adults with suspected extrapulmonary tuberculosis was performed in a rural and an urban hospital in Tanzania. Participants were randomized 1:1 to intervention or routine care, stratified by site and HIV status. All participants underwent clinical evaluation, chest radiography, and testing with sputum Xpert MTB/RIF and urine Xpert MTB/RIF Ultra assays. The intervention was a management algorithm based on results of eFASH plus microbiology, adenosine deaminase (ADA), and chest radiography. The primary outcome was the proportion of correctly managed patients. The presence of positive microbiological or ADA results defined definite tuberculosis. An independent end-point review committee determined diagnoses of probable or no tuberculosis. We evaluated outcomes using logistic regression models, adjusted for randomization stratification factors.

Results. From September 2018 to October 2020, a total of 1036 patients were screened and 701 were randomized (350 to the intervention and 351 to the control group). Of participants in the intervention group, 251 (72%) had a positive eFASH outcome. In 258 (74%) of the intervention and 227 (65%) of the control participants antituberculosis was initiated treatment at baseline. More intervention participants had definite tuberculosis (n = 124 [35%]), compared with controls (n = 85 [24%]). There was no difference between groups for the primary outcome (intervention group, 266 of 286 [93%]; control group, 245 of 266 [92%]; odds ratio, 1.14 [95% confidence interval: .60–2.16]; $P = .68$). There were no procedure-associated adverse events.

Conclusions. eFASH did not change the proportion of correctly managed patients but increased the proportion of those with definite tuberculosis.

Clinical Trials Registration. Pan African Registry: PACTR201712002829221.

Keywords. ultrasonography; FASH; extrapulmonary; tuberculosis; sub-Saharan Africa.

Tuberculosis is one of the main causes of ill health and death worldwide [1]. In low-income countries in 2020 diagnoses were microbiologically confirmed in only one-third of persons treated for tuberculosis, partly owing to limited access to diagnostics [1]. Furthermore, microbiological tests have a low sensitivity for extrapulmonary tuberculosis, and for pulmonary tuberculosis in both human immunodeficiency virus (HIV)–infected individuals and children [2–4]. Therefore, empirical treatment is routinely practiced [5–7]. This might lead to overtreatment among people who might not have the disease [8] and to a delay in the diagnosis of other conditions with similar clinical presentations as extrapulmonary tuberculosis.

Focused assessment with sonography for HIV and tuberculosis (FASH) is a ultrasonographic (US) protocol developed to detect signs of extrapulmonary tuberculosis, including pleural and pericardial effusion, enlarged intra-abdominal lymph nodes, splenic and hepatic abscesses, ascites, and abnormalities of the terminal ileum wall [9]. Previous studies have shown low to moderate diagnostic accuracy for abdominal US as a

Received 19 July 2022; editorial decision 28 October 2022; published online 4 November 2022

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Clinical Infectious Diseases® 2023;76(6):1013–21

https://doi.org/10.1093/cid/ciac871

stand-alone test for definite tuberculosis, although the presence of ≥3 US predictors increased the specificity to as high as 93% [10, 11]. In a previous study including HIV-positive and HIV-negative patients, we showed that the absence of FASH signs combined with a normal chest radiograph and absence of fever might exclude tuberculosis [12]. We expanded the FASH protocol by adding US of the chest, axillary and cervical lymph nodes, and the inferior vena cava diameter as a sign of heart failure, naming it extended FASH (eFASH)—an examination taking about 15 minutes [13].

We report results from a randomized controlled 2-center trial to assess the impact of eFASH on the correct management of persons with suspected extrapulmonary tuberculosis. We hypothesized that eFASH, compared with the standard of care, would lead to a higher proportion of participants with correct management.

METHODS

Trial Design

The current study was a randomized, controlled, parallel, superiority, open-label trial done at 1 rural and 1 urban hospital in the United Republic of Tanzania. In 2020 the national HIV prevalence was 4.6% [14] and the prevalence of multidrug-resistant tuberculosis was 0.3% (423/30 000 incident tuberculosis cases) [15]. The trial was approved by the institutional review board of the Ifakara Health Institute, Tanzania (Ifakara Health Institute/institutional review board no. 010–2018), the ethics committee of the National Institute for Medical Research, Tanzania (NIMR/HQ/R.8a/Vol.IX/2897), and the Ethikkomission Nordwest und Zentralschweiz, Switzerland (no. 2017–02220). Trial progress was monitored by an independent monitoring team of the Ifakara Health Institute.

Participants

Eligible study participants included HIV-positive and HIV-negative patients aged ≥18 years presenting to the rural Saint Francis Referral Hospital, Ifakara, or to the urban Mwananyamala Regional Referral Hospital, Dar es Salaam, with clinical signs of extrapulmonary tuberculosis, with or without concomitant signs of pulmonary tuberculosis. Inclusion criteria were fever of any duration, night sweats within the last 3 weeks, or weight loss, plus ≥1 of the following nuchal, cervical, axillary or generalized lymphadenopathy, abdominal pain, ascites, neurological symptoms, hemoglobin level <8 g/dL in HIV-positive participants receiving antiretroviral therapy, skeletal or genitourinary disorders suggesting tuberculosis, or chest radiograph showing a miliary pattern, pleural or suspected pericardial effusion, upper lobe infiltrate, or a cavernous lesion. Pregnant women, patients on antituberculosis treatment, patients refusing participation or written informed consent, and those not available for follow-up were excluded [13].

Randomization

Eligible and consenting participants were randomly assigned in a 1:1 ratio to intervention or control using a list computer generated by the statistician, stratified by site and HIV status, with randomly varying block sizes of 4 and 6. Opaque, sealed envelopes were prepared by 2 persons not involved in study procedures. Randomization was performed by the study team using the envelopes sequentially.

Procedures

Participants underwent a clinical evaluation including an interview and physical examination, chest radiography, an HIV rapid test if the HIV status was unknown, and blood tests including hemoglobin, creatinine, and alanine aminotransferase [13]. We collected sputum for the Xpert MTB/RIF assay and culture for mycobacteria. The Xpert MTB/RIF assay for sputum was used because of its higher specificity compared with the Xpert MTB/RIF Ultra assay [2] and because it was the national standard for sputum samples during the study period. Sputum samples were decontaminated using cetylpyridinium chloride and N-acetyl-l-cysteine-sodium hydroxide and inoculated on Löwenstein-Jensen agar. Urine samples were analyzed with the Xpert MTB/RIF Ultra assay.

If sterile samples were obtained from pleural, ascitic, or pericardial fluids or from pus from lymph nodes, the Xpert MTB/RIF Ultra assay and liquid culture (mycobacteria growth indicator tube; BACTEC 960; BD Microbiology Systems) were performed. Adenosine deaminase (ADA) was measured in pleural and pericardial fluid and from ascites. Fine-needle aspiration biopsy specimens of lymph nodes were analyzed by means of Giemsa and Papanicolaou stains for cytomorphology, Ziehl-Neelsen stain, the Xpert MTB/RIF Ultra assay, and culture. Participants in the intervention group underwent eFASH evaluation according to a prespecified algorithm, while those in control group received the standard of care according to the attending clinician (Supplementary Figure 1).

eFASH results were considered positive if ≥1 of the following was present: (1) multiple hypoechogenic lesions in the spleen or the liver; (2) pericardial effusion without other clinical explanation; (3) pleural effusion and no clinical or US signs for heart failure (normal inferior vena cava); (4) subpleural granular artifacts together with B-lines; (5) abdominal, axillary, nuchal, or cervical lymph nodes >1.5 cm and no other explanation for them; (6) thickened ileum wall >4 mm and loss of wall architecture and at least another eFASH sign; or (7) ascites and ≥1 additional eFASH sign. In participants with ascites only, full abdominal US, and in those with suspected heart failure, echocardiography was done. In control patients, US could be used to guide invasive procedures or determine whether routine abdominal US was indicated.

In the intervention group, antituberculosis treatment was started if eFASH results were positive; if chest radiography

showed a miliary pattern, a cavernous lesion, or a upper lobe infiltrate; if any microbiology test result was positive; or if the ADA level was above the threshold. In the control group, antituberculous treatment was started according to the decision of the treating physician. In both groups, follow-up visits were done 2 and 6 months after enrollment, performing a clinical assessment in all patients and eFASH in the intervention group. If antituberculosis treatment was not administered at enrollment, additional follow-up visits were done at 2 and 4 weeks.

US was performed by 3 sonographers using Chison Sonobook 9 US machines equipped with a curved (C3-V) and a linear (L12-V) probe. Sonographers had a certificate in point-of-care US endorsed by the European Federation of Societies for Ultrasound in Medicine and Biology, and they received 2 hours of eFASH training before the study start. Baseline eFASH examinations were reviewed remotely by an independent board-certified sonographer.

Outcomes

The primary outcome was the proportion of correctly managed participants at 6 months. A correctly managed participant was defined as a participant who was determined over the course of follow-up to have definite or probable tuberculosis and was treated with antituberculosis treatment at baseline or who was determined over the course of follow-up to not have tuberculosis and was not treated with antituberculosis treatment at baseline. A participant was defined as having definite tuberculosis if any microbiological test result was positive or if the ADA level was elevated (≥40 U/mL in pleural [16], ≥ 35 U/mL in ascitic [17], or ≥35 U/mL in pericardial fluid [18]).

An independent end-point review committee (ERC)—consisting of 3 clinical experts who see patients with tuberculosis in everyday practice in similar settings—reviewed end points in participants with probable or no tuberculosis. They were blinded to the final site diagnosis and used a predefined data listing (with clinical baseline and follow-up information and results from microbiology and additional tests). ERC members were instructed to use study definitions. In case of a discrepancy between an expert and a study physician, an additional expert was involved. For persisting discrepancies, the ERC chairperson decided on the final diagnosis.

Secondary outcomes included the proportions of asymptomatic participants at 2 and 6 months, the proportions of participants with alternative diagnoses and invasive procedures, and time to death. Defined safety outcomes were postintervention pneumothorax, major bleeding, and postexpansion pulmonary edema after pleural tapping, ascites puncture, or fine-needle aspiration biopsy.

Statistical Analysis

Based on the literature [5, 8, 19] and from an observational study performed in Ifakara [12], we anticipated that 85% and 73% of participants in the intervention and control groups, respectively, would be correctly managed. For a power of 95% with a 2-sided alpha value of .05, this yielded a sample size of 592 participants. Assuming a loss to follow-up of 10%, 650 participants were required. During the study, higher than anticipated numbers of loss to follow-up and deaths were noted and necessitated a protocol amendment to increase the sample size to 700 participants.

Outcome analyses were performed using the final tuberculosis status determined by the ERC, in the modified intention-to-treat population of participants in whom the status could be determined. We used logistic regression models adjusted for the randomization stratification factors of site and HIV status. For the primary outcome, we estimated risk differences between the groups using the marginal standardization technique, with 95% confidence intervals estimated using the delta method [20]. In predefined sensitivity analyses, we adjusted for covariates that appeared unbalanced between groups at baseline by visual inspection or were associated with missing primary outcome data, and we performed analyses using the clinical team (instead of ERC) determination of final tuberculosis status. We assessed effect modification by site and HIV status. We used Kaplan–Meier estimation and Cox proportional hazards models adjusted for the randomization stratification factors to analyze time to death.

We summarized the numbers and proportions of participants undergoing eFASH or other US procedures. Treatment completion was defined post hoc as receiving ≥154 days (6 months, with 2 week leeway) of antituberculosis treatment. We assessed the interrater reliability of eFASH findings at baseline between the first sonographer and an independent reviewer, reporting agreement and the Cohen κ value [21]. Analyses were done using Stata software (version 15) [22]. Data will be made available upon request (https://doi.org/10.5281/zenodo.6697574). The trial was registered with the Pan African Clinical Trials Registry (PACTR201712002829221).

RESULTS

From 26 September 2018 through 19 October 2020, 1036 individuals were screened, and 701 participants were enrolled and randomized, 350 to the intervention and 351 to the control group (Figure 1). The median age at enrollment was 39 years (interquartile range, 29–50 years), 415 participants (59%) were male, and 268 (38%) were HIV positive. Baseline characteristics were well balanced between groups, except for night sweats, abdominal signs, and an estimated glomerular filtration rate <50 mL/min (Table 1).

Follow-up lasted until 31 March 2021. Overall, 397 participants (57%) attended the 2-month and 331 (47%) the 6-month follow up visit. The primary outcome was determined in

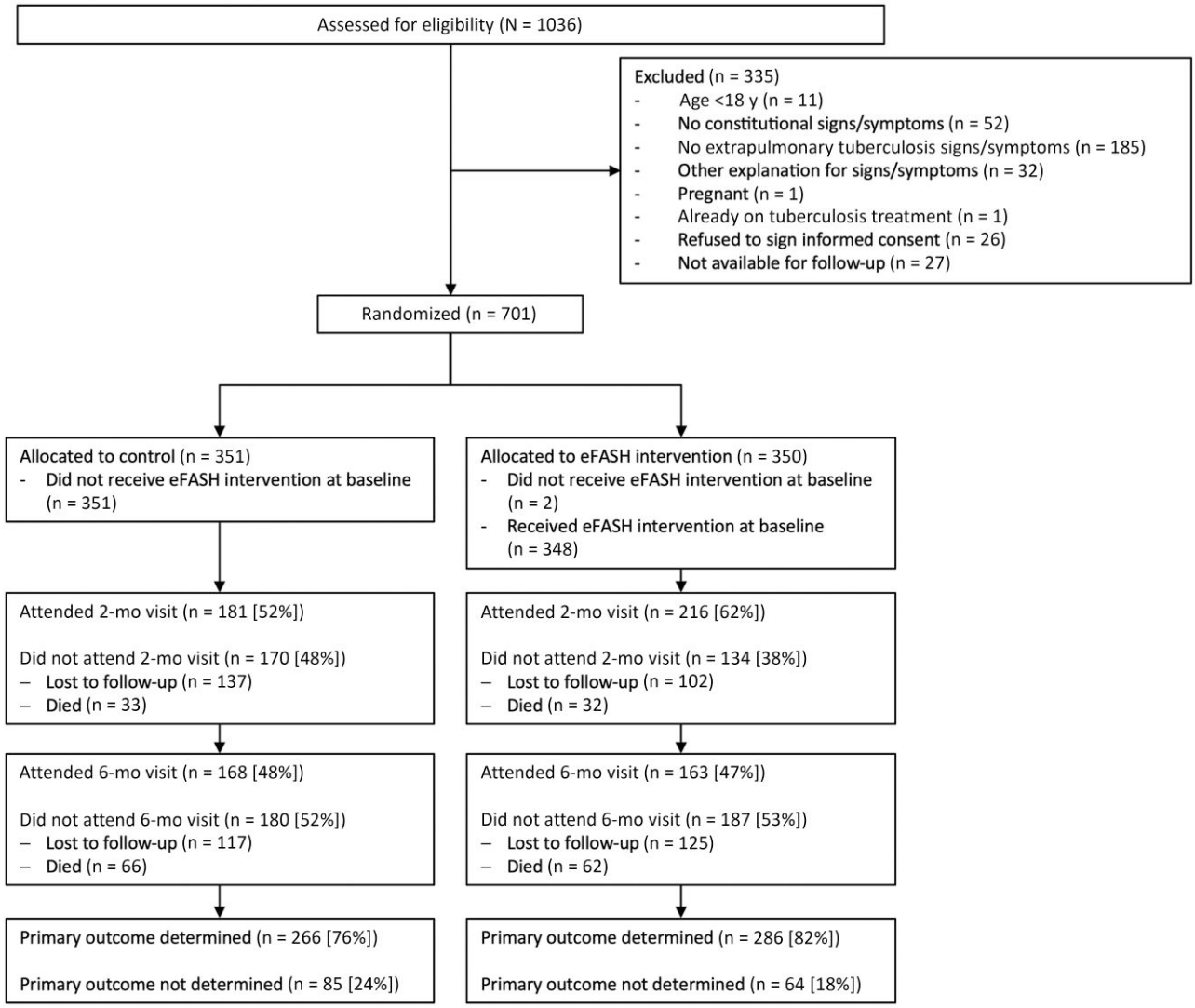

Figure 1. Study flow chart. Screened persons may have met >1 ineligibility criterion; 1 criterion was assigned to each person in the order hierarchy shown. The extended focused assessment with sonography for human immunodeficiency virus and tuberculosis (eFASH) results were lost in 1 participant, and 1 participant withdrew from the study during enrollment. The totals for participants who died (66 in the control and 62 in the intervention group) include those who died before the 2-month visit.

286 participants (82%) in the intervention versus 266 (76%) in the control group (Figure 1). Baseline characteristics were broadly similar between participants for whom the primary outcome was determined and those for whom it was not (Supplementary Tables 1 and 2).

At baseline, 348 participants (99%) in the intervention group underwent eFASH (vs none in the control group). Of these, 251 (72%) were eFASH positive. Pleural effusion was the most common finding (61%), followed by B-lines and subpleural granular artifacts (45%), ascites (32%), and enlarged para-aortic lymph nodes (20%) (Supplementary Table 3). The overall agreement for eFASH examinations between site investigator and reviewer was 94%, with a Cohen κ coefficient of 0.84 indicating strong agreement (Supplementary Table 4) [22]. Echocardiography was performed in 24 participants in the intervention and 25 in the control group. US protocols other than eFASH were performed in 54 participants (15%) in the intervention and 50 (14%) in the control group (Supplementary Table 5). Findings from these procedures revealed alternative diagnoses in 33 participants in the intervention and 22 in the control group (Supplementary Table 5).

At baseline, 258 participants (74%) in the intervention and 227 (65%) in the control group started treatment with antituberculosis drugs (Figure 2). Among participants who ever started treatment, 162 (60%) in the intervention versus 148 (62%) in the control group completed treatment (Supplementary Table 6).

A greater proportion of participants in the intervention group had definite tuberculosis diagnosed (124 [35%] vs 85 [24%] in the control group) (Table 2). Overall, 12% of

Table 1. Baseline Characteristics by Group

Characteristic	Participants, No. (%)[a]		
	Control Group (n = 351)	Intervention Group (n = 350)	Total (N = 701)
Site			
Ifakara	163 (46)	163 (47)	326 (47)
Mwananyamala	188 (54)	187 (53)	375 (53)
HIV status			
Positive	135 (38)	133 (38)	268 (38)
Negative	216 (62)	217 (62)	433 (62)
Sex			
Male	205 (58)	210 (60)	415 (59)
Female	146 (42)	140 (40)	286 (41)
Age, median (IQR), y	38 (30–49)	39 (29–50)	39 (29–50)
Symptoms			
Fever of any duration	274 (78)	277 (79)	551 (79)
Night sweats	156 (44)	180 (51)	336 (48)
Weight loss	327 (93)	323 (92)	650 (93)
Medical history			
Previous pulmonary tuberculosis[b]	35 (10)	32 (9)	67 (10)
Previous extrapulmonary tuberculosis[c]	9 (3)	7 (2)	16 (2)
Other disease[b,d]	16 (5)	23 (7)	39 (6)
Comedication at enrollment			
Anti-infective drugs	99 (28)	109 (31)	208 (30)
ART drugs[e]	57 (42)	63 (47)	120 (45)
Isoniazid preventive treatment	1 (0)	0 (0)	1 (0)
NCD drugs	32 (9)	24 (7)	56 (8)
Steroids	7 (2)	6 (2)	13 (2)
Other	55 (16)	56 (16)	111 (15)
Unknown	1 (0)	2 (1)	3 (0)
Clinical signs			
Fever (temperature ≥38°C)	54 (15)	49 (14)	103 (15)
Systolic BP, median (IQR), mm Hg[f]	115 (101–131)	114 (100–130)	114 (101–130)
Diastolic BP, median (IQR), mm Hg[f]	78 (68–88)	77 (67–87)	77 (67–88)
Weight, median (IQR), kg[f]	51 (46–59)	51 (45–58)	51 (45–58)
BMI, median (IQR)[f,g]	20 (18–22)	20 (18–22)	20 (18–22)
BMI <18.5[f,g]	119 (34)	110 (32)	229 (33)
Physical examination			
Pulmonary signs[f]	272 (77)	273 (78)	545 (78)
Cardiac signs[f]	70 (20)	63 (18)	133 (19)
Abdominal signs[f]	144 (41)	169 (48)	313 (45)
Neurological signs[f]	7 (2)	10 (3)	17 (2)
Lymphadenopathy[f]	132 (38)	128 (37)	260 (37)
Blood laboratory results			
Median value (IQR)			
Hemoglobin, g/L[h]	11 (9–12)	11 (9–12)	11 (9–12)
ALT, IU/L	19 (12–34)	21 (13–34)	20 (12–34)
Creatinine, μmol/L[i]	67 (54–86)	71 (55–96)	69 (54–90)
eGFR, mL/min[i]	88 (63–116)	86 (59–111)	87 (60–113)
eGFR <50 mL/min[i]	53 (15)	66 (19)	119 (17)
Hospitalization[f]	67 (19)	73 (21)	140 (20)
Among those HIV positive	n = 135	n = 133	n = 268
CD4 cell count, median (IQR), cells/μL[j]	176 (41–335)	115 (44–252)	144 (42–292)
CD4 cell count <200 cells/μL	37 (58)	44 (67)	81 (62)

Abbreviations: ALT, alanine aminotransferase; ART, antiretroviral therapy; BMI, body mass index; BP, blood pressure; eGFR estimated glomerular filtration rate; HIV, human immunodeficiency virus; IQR, interquartile range; NCD, noncommunicable diseases.

[a]Data represent No. (column % of those with nonmissing data) unless otherwise specified.

[b]Missing information in 3 participants in each group.

[c]Missing information in 4 participants in control and 3 in intervention group.

[d]Comorbid conditions reported by the participant at enrollment.

[e]Percentage refers to total number of HIV-positive patients.

[f]Missing for 1 participant in intervention group (dropout during enrollment).

[g]BMI calculated as weight in kilograms divided by height in meters squared.

[h]Missing for 2 participants in each group.

[i]Missing for 6 participants in control and 4 in intervention group.

[j]Missing for 71 participants in control and 67 in intervention group.

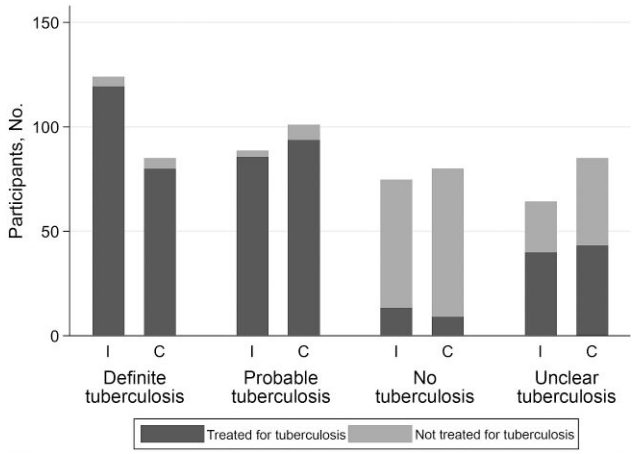

Figure 2. Management by tuberculosis status, as determined by the end of follow-up. Treatment status represents that at baseline. Participants were determined to have met the primary outcome of correct management if they had definite or probable tuberculosis and were treated, or did not have tuberculosis and were not treated. It was not possible to determine the primary outcome among those with unclear tuberculosis status. The intervention group (I; n = 350) included 124 participants (35%) with definite tuberculosis, 88 (25%) with probable tuberculosis, 74 (21%) with no tuberculosis, and 64 (18%) with unclear tuberculosis. The control group (C; n = 351) included 85 (24%), 101 (29%), 80 (23%), and 85 participants (24%), respectively, in the same categories.

participants tested positive with the Xpert MTB/RIF assay in sputum, 12% by culture in sputum, 8% with the Xpert MTB/RIF Ultra assay in urine, and 17% with the Xpert MTB/RIF assay in either sputum or urine (Supplementary Table 7). Overall, 19 participants (16 in the intervention and 3 in the control group) were classified as having definite tuberculosis based on an elevated ADA level alone. Multidrug-resistant tuberculosis was identified in 3 participants. According to both site and ERC assessments, smaller proportions of participants were determined to have probable tuberculosis in the intervention than in the control group (Table 2 and Supplementary Table 8).

There was no difference in the primary outcome between the 2 groups; a high proportion of participants were correctly managed: 266 of 286 (93%) in the intervention versus 245 of 266 (92%) in the control group (adjusted odds ratio, 1.14 [95% confidence interval: .60–2.16]; $P = .68$) (Table 3). Results were robust to sensitivity analyses (Supplementary Table 9). Reclassifying participants with only an elevated ADA level from definite to probable tuberculosis did not change the primary outcome (Supplementary Table 10). Among participants who started antituberculosis therapy and were gaining weight, 98% were correctly managed (Supplementary Table 11).

There was no difference in secondary outcomes between the 2 groups, except that a greater proportion of participants in the intervention group, compared with the control group, underwent an invasive procedure (202 [58%] vs 18 [5%], respectively; adjusted odds ratio, 25.6 [95% confidence interval: 15.2–43.1]; $P < .001$) (Table 3 and Supplementary Table 12). None of the predefined safety outcomes occurred in either group. A total of 138 (39%) and 159 (45%) participants in the intervention and control groups, respectively, received a diagnosis other than tuberculosis (including concomitant diagnoses in those with definite and probable tuberculosis) by the end of follow-up. In total, pulmonary diseases were diagnosed in 45 (13%) and 50 (14%) of the participants in the intervention and control groups, respectively, cardiac diseases in 48 (14%) and 57 (16%), and cancer in 30 (9%) and 26 (7%) (Supplementary Table 13). In both groups, 26% of participants died (Table 3 and Supplementary Figure 2). Of 181 deaths, 46 (25%) were attributed to tuberculosis, and 73 (40%) to other diseases—for example, cancer (n = 24), heart failure (n = 17), or liver disease (n = 10). In 62 participants (34%), the cause of death remained unknown.

DISCUSSION

In this randomized controlled trial evaluating the effect of eFASH in the management of persons suspected to have extrapulmonary tuberculosis, we did not find differences in the correct management, absence of symptoms or mortality rates among participants randomized to the intervention compared with the standard of care. We did find a significant difference between groups in the proportion of participants with definite tuberculosis.

The greater proportion of definite tuberculosis in the intervention group (35%) versus the control group (24%) was primarily due to a higher proportion of invasive procedures with positive microbiological findings or elevated ADA levels, mostly from pleural fluid and lymph node fine-needle aspirations. In other studies, proportions of patients with definite extrapulmonary tuberculosis were lower at 4%–24% [6, 7]. The absence of complications after invasive procedures in our and other studies [23–26] motivates the use of US-guided invasive procedures to increase the proportion of patients with definite tuberculosis. This is of epidemiological importance, especially in the context of drug resistance, and is associated with higher survival rates in HIV-positive patients with extrapulmonary tuberculosis [6].

Our hypothesis that overtreatment of tuberculosis could be reduced by the intervention was not confirmed. While observational studies have shown an association of FASH with tuberculosis [10–12], the diagnostic accuracy of US was low in a 2019 Cochrane review [10]. The high morbidity among included participants and the resulting high eFASH positivity rate of 72% in the intervention group could be a reason for similar outcomes in both groups. Owing to the lack of appropriate diagnostics, other causes of pleural effusion could not be ascertained [27].

Table 2. Final Diagnosis of Tuberculosis by Group According to Site and End-Point Review Committee

Final Diagnosis[a]	Diagnosis by Site, No. (%)[b]		Diagnosis by ERC, No. (%)[b]	
	Control Group (n = 351)	Intervention Group (n = 350)	Control Group (n = 351)	Intervention Group (n = 350
Definite tuberculosis	85 (24)	124 (35)		
Pulmonary only	13 (15)	8 (6)	…	…
Extrapulmonary only	28 (33)	60 (48)		
Pulmonary and extrapulmonary	44 (52)	56 (45)		
Probable tuberculosis	104 (30)	93 (27)	101 (29)	88 (25)
Pulmonary only	6 (6)	3 (3)	…	…
Extrapulmonary only	91 (88)	83 (89)		
Pulmonary and extrapulmonary	7 (7)	7 (8)		
No tuberculosis	98 (28)	79 (23)	80 (23)	74 (21)
Unclear tuberculosis	64 (18)	(54 (15)	85 (24)	64 (18)
Determination of definite tuberculosis[c,d]				
Positive Xpert TB/RIF assay results at baseline	61 (72)	73 (58)	…	…
Culture positive	51 (60)	68 (55)		
ADA positive[e]	4 (5)	24 (19)		
AFB positive[f]	3 (4)	3 (1)		
Histologically positive[g]	1 (1)	0		
Cytologically positive[h]	0	15 (12)		
Microbiologically positive at follow-up	0	0		

Abbreviations: ADA, adenosine deaminase; AFB, acid-fast bacilli; ERC, end-point review committee.

[a]If B-lines together with subpleural granular artifacts were present and the chest radiograph was normal or showed a miliary pattern, the participant was classified as having extrapulmonary tuberculosis. If infiltrates were present, the participant was classified as having pulmonary tuberculosis.

[b]Data represent no. (column % [% of those randomized and for type of tuberculosis, % of those with definite or probable tuberculosis]). Not all tests were done in all participants.

[c]Including samples from sputum, urine, other body fluids, and lymph nodes.

[d]Some participants met >1 criterion.

[e]Performed in 40 control and 120 intervention group participants.

[f]Performed in 3 control and 3 intervention group participants.

[g]Performed in 1 control and 1 intervention group participant.

[h]Performed in 1 control group (negative) and 48 intervention group (15 positive, 31 negative, 2 inconclusive) participants.

Our study has strengths: First, it was the first randomized trial evaluating the effect of a diagnostic algorithm including eFASH on the management of extrapulmonary tuberculosis that included a large number of participants. Second, there was a strong agreement on eFASH signs between the study physician and an independent board-certified sonographer. This is comparable to a study on a short course of FASH in South Africa documenting excellent agreement [28], and it speaks to the operational feasibility of point-of-care US in routine care. Third, all outcomes were clinically relevant. Other outcomes such as weight gain or quality of life would be less feasible.

There are important limitations to the current study. First, in 24% of participants in the control and 18% in the intervention group, we failed to determine whether or not tuberculosis was present owing to high rates of early deaths and loss to follow-up. The reported loss to follow-up in tuberculosis was 15%–22% in urban tuberculosis programs [29] and higher in rural settings with lack of transport, migrating populations [30], advanced disease and high early mortality [31]. We have addressed this issue by extensive tracking activities. Second, almost one-third of participants had probable tuberculosis, leaving uncertainty about the correct diagnosis and management, despite the fact that probable tuberculosis is an accepted standard in similar settings [32] and despite establishment of an independent ERC. Third, we classified participants with only an elevated ADA level as having definite tuberculosis because of the high sensitivity and specificity of this marker [16, 17, 33]. Reclassification of these cases as probable tuberculosis did not change the primary outcome. Fourth, the unavailability of the sputum Xpert TB/RIF Ultra assay and urine lipoarabnomannan might have lowered the number of definite tuberculosis diagnoses. Fifth, to confirm diagnoses others than tuberculosis, our diagnostic tools were limited. Sixth, the study was conducted during the first 2 waves of the coronavirus disease 2019 pandemic, leading to interruption of recruitment and follow-up visits from March to June 2020 and possibly increasing loss to follow-up and mortality Seventh, 15% of control participants underwent US, possibly decreasing the difference in the primary outcome. Finally, findings might not be generalizable to other settings and populations with a lower morbidity.

Table 3. Primary and Secondary Outcomes

Outcome	Participants, No. With Outcome/Total No. (%)			
	Control Group (n = 351)	Intervention Group (n = 350)	OR (95% CI)[a]	*P* Value[b]
Primary outcome: correct management[c]	245/266 (92)	266/286 (93)	1.14 (.60–2.16)	.68
Effect modification of primary outcome				
Site				
Ifakara (rural)	98/107 (92)	115/124 (93)	1.18 (.45–3.08)	.94
Mwananyamala (urban)	147/159 (92)	151/162 (93)	1.12 (.48–2.62)	
HIV status				
Positive	84/91 (92)	100/108 (93)	1.05 (.36–3.01)	.84
Negative	161/175 (92)	166/178 (93)	1.20 (.54–2.68)	
Secondary outcomes				
Free of symptoms at 2 mo	80/183 (44)	79/216 (37)	0.77 (.50–1.17)	.22
Free of symptoms at 6 mo	124/168 (74)	114/163 (70)	0.84 (.51–1.37)	.49
Diagnosis other than tuberculosis at 6 mo[d]	159/351 (45)	138/350 (39)	0.78 (.57–1.05)	.11
Underwent an invasive procedure	18/351 (5)	202/350 (58)	25.6 (15.2–43.1)	<.001
Any safety outcome[e]	0	0	NA	NA
Death	90/351 (26)	91/350 (26)	HR: 0.91 (.67–1.23)	.54

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; HR, hazard ratio; NA, not applicable; OR, odds ratio.

[a]Results are intervention effects reported as ORs from logistic regression models, except for the result for death, reported as HR from Cox proportional hazards models, adjusted for the randomization stratification factors of site and HIV status.

[b]*P* values represent the intervention effect, except for the analysis of effect modification of the primary outcome, where the *P* values represent effect modification.

[c]Correct management was defined as initiating antituberculosis treatment at baseline with probable or definite tuberculosis determined by 6 months, or not initiating antituberculosis treatment at baseline and the absence of tuberculosis determined by 6 months. Tuberculosis status results are according to assessment by an independent end-point review committee; results correspond to a rate ratio of 1.01 (95% CI: .96–1.06) and risk difference of 0.009 (−.03 to .05), with standard errors estimated using the delta method.

[d]Including concomitant second diagnoses in participants with definite, probable, unclear, or no tuberculosis.

[e]Predefined as pneumothorax during thoracentesis, major bleeding during puncturing, or postexpansion pulmonary edema.

In conclusion, eFASH did not lead to improved correct management of tuberculosis in a population of HIV-positive and HIV-negative patients with a high morbidity. However, it did increase the proportion of definite tuberculosis diagnoses by means of uncomplicated invasive tests.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Acknowledgments. We thank George Sikalengo, US-AID, Tanzania, Andrew Katende, Ifakara Health Institute, Tanzania, and Ngisi Masawa, Catholic University of Health and Allied Sciences, Mwanza, Tanzania, for being members of the independent end-point review committee. We also thank Roland Stieger, Kantonsspital Baden, Switzerland, for reviewing extended focused assessment with sonography for human immunodeficiency virus and tuberculosis (eFASH) examinations

Author contributions. Conceptualization of trial: R. N., O. N., F. M., K. R., M. B., D. H. P., M. W., and M. R. Funding acquisition: D. H. P., M. W., and M. R. Supervision: F. M., D. H. P., M, W., and M. R. Project administration: R. N., O. N., and M. R. Investigation, data curation, and resources: R. N., O. N., F. B., Y. T., H. W., J. H., M. S., D. M., N. K., H. H., J. W., H. M., I. B. K., and F. M. Interpretation of data: F. V., W. G., K. R., M. B., D. H. P., M. W., and M. R. Formal analysis and visualization: F. V., M. W., and M. R. Drafting of manuscript: R. N., O. N., M. W., and M. R. All authors reviewed and edited the draft manuscript, approved the final version, agreed to be accountable for all aspect of the published work, and are responsible to appropriately resolve and investigate all questions related to the accuracy or integrity of the published work.

Disclaimer. The funders of the study had no role in study design, data collection, data analysis, data interpretation, manuscript writing, or in the decision to submit the report for publication.

Financial support. This work has been supported by the Rudolf Geigy Foundation, Basel, Switzerland, and the Gottfried und Julia Bangerter-Rhyner Foundation, Basel, Switzerland (salary support to F. V. through her employer, Swiss Tropical and Public Health Institute). N. K. and J. W. report the following support for this work: sample processing, manuscript writing, and manuscript review (N.K and J. W were supported by their employer, the Ifakara Health Institute).

Potential conflicts of interest. K. R. reports grants or contracts unrelated to this work from Botnar Research Centre for Child Health/European and Developing Countries Clinical Trials Partnership: MistraL Outreach. K. R. also reports unpaid participation on a data safety monitoring board or advisory board for evaluation of new diagnostics and field evaluation of point-of-care triage tests for active tuberculosis. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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