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# Relationship between chest radiographic characteristics, sputum bacterial load, and treatment outcomes in patients with extensively drug-resistant tuberculosis

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ABSTRACT

*Background:* Data about the relationship between chest radiographs and sputum bacillary load, with treatment outcomes, in patients with extensively drug-resistant tuberculosis (XDR-TB) from HIV/TB endemic settings are limited.
*Methods:* Available chest radiographs from 97 South African XDR-TB patients, at the time of diagnosis, were evaluated by two independent readers using a validated scoring system. Chest radiograph findings were correlated with baseline sputum bacillary load (smear-grade and culture time-to-positive in MGIT), and prospectively ascertained clinical outcomes (culture conversion and all-cause mortality).
*Results:* Radiographic bilateral lung disease was present in 75/97 (77%). In the multivariate analysis only a higher total radiographic score (95% CI) was associated with higher likelihood of death [1.16 (1.05–1.28) p = 0.003], and failure to culture convert [0.85 (0.74–0.97) p = 0.02]. However, when restricting analyses to HIV-infected patients, disease extent, cavitation, and total radiographic scores were not associated with mortality or culture-conversion. Finally, cavitary, disease extent, and total radiographic scores all positively correlated with bacterial load (culture time-to-positive).
*Conclusions:* In endemic settings, XDR-TB radiological disease extent scores are associated with adverse clinical outcomes, including mortality, in HIV uninfected persons. These data may have implications for clinical and programmatic decision-making and for evaluation of new regimens in clinical trials.


## Introduction

Tuberculosis (TB) remains a global health problem (Dheda et al., 2015). However, the advent of drug-resistant TB (DR-TB) threatens to reverse the gains made by national TB programs and is prohibitively expensive to treat (Pooran et al., 2013; WHO, 2015). There is also a growing epidemic of extensively drug-resistant TB (XDR-TB; defined as MDR-TB with resistance to a fluoroquinolone and either capreomycin, amikacin, or kanamycin) (WHO, 2006). It is estimated that ~10% of all MDR-TB patients have XDR-TB (WHO, 2015). Treatment-related outcomes in patients with XDR-TB who did not receive newer or repurposed drugs, like bedaquiline or linezolid, are extremely poor (Dheda et al., 2010). Indeed, in a long-term prospective cohort of 107 XDR-TB patients mortality was 78% and only 11% of patients had a favourable outcome at 60 months after diagnosis (Pietersen et al., 2014). Even with bedaquiline treatment, 30 month outcomes were sub-optimal with culture conversion rates of 62% (Pym et al., 2016).

Chest radiography is currently used for screening, diagnosis, and monitoring of response to anti-TB treatment (Rubin, 1995). Despite being limited by poor specificity and high inter-observer variability it remains a useful adjunct to clinical and microbiological tools. Several quantitative chest radiographic scoring systems have been developed and some have shown the potential to limit observer variability and increase the clinical value of the chest radiograph in TB (Pinto et al., 2013a; Ralph et al., 2010).

*Abbreviations:* BCH, Brooklyn Chest TB hospital; CD4, cluster of differentiation 4; CRRS, chest radiograph recording and reporting; CXR, chest radiography; DR-TB, drug-resistant tuberculosis; HIV, human immunodeficiency virus; ICC, intraclass coefficient; MDR-TB, multidrug-resistant tuberculosis; MGIT, mycobacteria growth indicator tube; PAS, *para*-aminosalicylic acid; PET-CT, positron emission tomography–computed tomography; TB, tuberculosis; TTP, time-to-positive; WHO, World Health Organisation; XDR-TB, extensively drug-resistant tuberculosis.

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In drug sensitive TB extent of lung disease and cavities on radiography at diagnosis are known to be associated with an increased sputum bacterial load (Perrin et al., 2010), delayed smear and culture conversion (Ralph et al., 2010; Ozsahin et al., 2011), and an increased risk of treatment failure (Hesseling et al., 2010; Singla et al., 2009). There is scanty data about chest radiographic findings in MDR-TB/HIV co-infected patients (Brust et al., 2013; Lessnau et al., 1994). Cavities on the baseline chest radiograph in MDR-TB may be an independent predictor of bacterial load, longer conversion times (Holtz et al., 2014) and poor outcomes (Jeon et al., 2009). However, there are hardly any data about chest radiographic findings in patients with XDR-TB (Cha et al., 2009), and how these relate to outcomes in XDR-TB (Jeon et al., 2009).

We could find no published data that examined the relationship between chest radiography and treatment-related outcomes in patients with XDR-TB from HIV and TB endemic settings where several factors including diagnostic delay, strain variability, and immunosuppression could potentially modulate radiographic findings. Moreover, the relationship between baseline chest radiography and bacterial load in XDR-TB has, hitherto, not been studied before. In this study we attempted to discern the relationship between baseline radiographic findings, bacterial load and treatment outcomes.

## Methods

### *Setting*

In this prospective outcomes-based cohort study available baseline chest radiographs (at the time of XDR-TB diagnosis) from patients admitted to Brooklyn Chest Hospital (BCH), Cape Town, South Africa, between October 2008 and June 2012 were evaluated. At the time of evaluation a limited number of radiographs were available at the study site because of transfer of patients to peripheral clinics where CXRs were not accessible and could not be removed from outlying health facilities. Patients were managed as in-patients for at least the duration of the intensive phase of treatment and discharged to clinic treatment and follow up after four consecutive negative cultures.

### *Study population*

222 patients with XDR-TB admitted to BCH during the period October 2008 to June 2012 were followed up. 97/222 available chest radiographs (CXR), dated within 3 months of XDR-TB diagnosis, were independently scored by two non-specialist medical doctors. In total, 125 CXRs were unavailable for study (13/125 were more than 3 months from the date of XDR-TB diagnosis, 109/125 unavailable as patients transferred out to peripheral clinics with their CXRs, and 3/125 were unreadable according to Chest Radiograph Recording and Reporting (CRRS) criteria) (Den Boon et al., 2005).

### *XDR-TB treatment regimen and outcomes*

Patients received a WHO approved, directly observed, regimen (WHO, 2016). Bedaquiline and linezolid were not available. Treatment outcomes were assigned at censor date (31st October 2013) and regarded as favourable (cure or treatment completion) or unfavourable (default, treatment failure and death). Treatment-related outcome definitions used were based on Laserson's classifications (Laserson et al., 2005).

### *Ethics statement*

Ethics approval was obtained from the University of Cape Town human research ethics committee.

### *Scoring of chest radiographs*

The two experienced primary care medical doctors attended a two day CRRS (Den Boon et al., 2005) chest radiology teaching course prior to the scoring of CXRs. To further establish consensus scoring both readers, pilot read consisting of 20 CXRs was done together with two specialist pulmonologists experienced in TB. Thus, criteria for calling cavities and disease extent were agreed on before independent scoring of the CXRs.

The scoring systems applied in this study (Figure 1) include two horizontal lines that were measured at the lower border of the 2nd and 5th anterior costochondral junctions resulting in 6 zones. Each of the 6 zones was given a numerical score for the extent of disease (disease extent score) and for the number and size of the cavities (cavity score) present. Any parenchymal or pleural abnormalities were regarded as diseased and the area involved was estimated as more than or less than 50% of the total area. Cavities were declared where there was clear visible ring like opacity of greater than 50% of the total circumference. Cavities less than 1 cm were not considered and scored as 'no cavitation'. A "total score" was derived by the sum of the total disease extent and total cavitation scores for all 6 zones.

### *Statistical analysis*

Factors (history of previous multi-drug-resistant, total number of drugs the organism was resistant to, weight under 50 kg, HIV status, and CD4 count) known to be associated with treatment outcomes (mortality and culture conversion) were tested for association using Wilcoxon-rank sum (for continuous variables) and Fisher's exact test (for discrete variables). Anti-retroviral therapy was not considered as all but 2 HIV-infected patients were on ARV treatment at the time of XDR-TB diagnosis. A univariate and multivariate Cox proportional hazards regression model was used to identify outcome predictors. Selected variables in the multivariate analysis included those with a p-value <0.1 in the univariate analysis. Culture conversion was assessed via a non-parametric competing risk model with death as the competing risk. We calculated medians and IQRs for continuous variables and frequency (percent) for categorical variables. Multivariate Cox proportional hazards models for mortality included variables that were significantly associated with outcome ($p < 0.1$) and the pre-specified variables (weight, diabetes, CXR scores, HIV). Statistical analysis was done in STATA version 13.

## Results

### *Demographics and outcomes*

Patient characteristics are summarized in Table 1. A sensitivity analysis did not show any significant differences between the study group of 97 patients and the total group of 222 patients with respect to age, gender, HIV status and CD4 count.

Treatment-related outcomes were dismal: 4/97 (4%) XDR-TB patients cured and 86/97 (89%) had unfavourable treatment-related outcomes: 39/86 (45%) died, 40/86 (47%) treatment failed, and 7/86 (8%) defaulted. Treatment outcomes for 7/97 patients who transferred out are unclassified. All-cause mortality in the cohort was 64/97 (66%) however there was no difference in mortality in HIV-infected compared to non-infected patients [31/44 (71%) vs 33/53 (62%), $p = 0.53$)] (Table 2).

### *Chest radiograph findings*

Reliability between the two readers were tested and the Pearson intra-class coefficient (ICC) showed a "moderate"

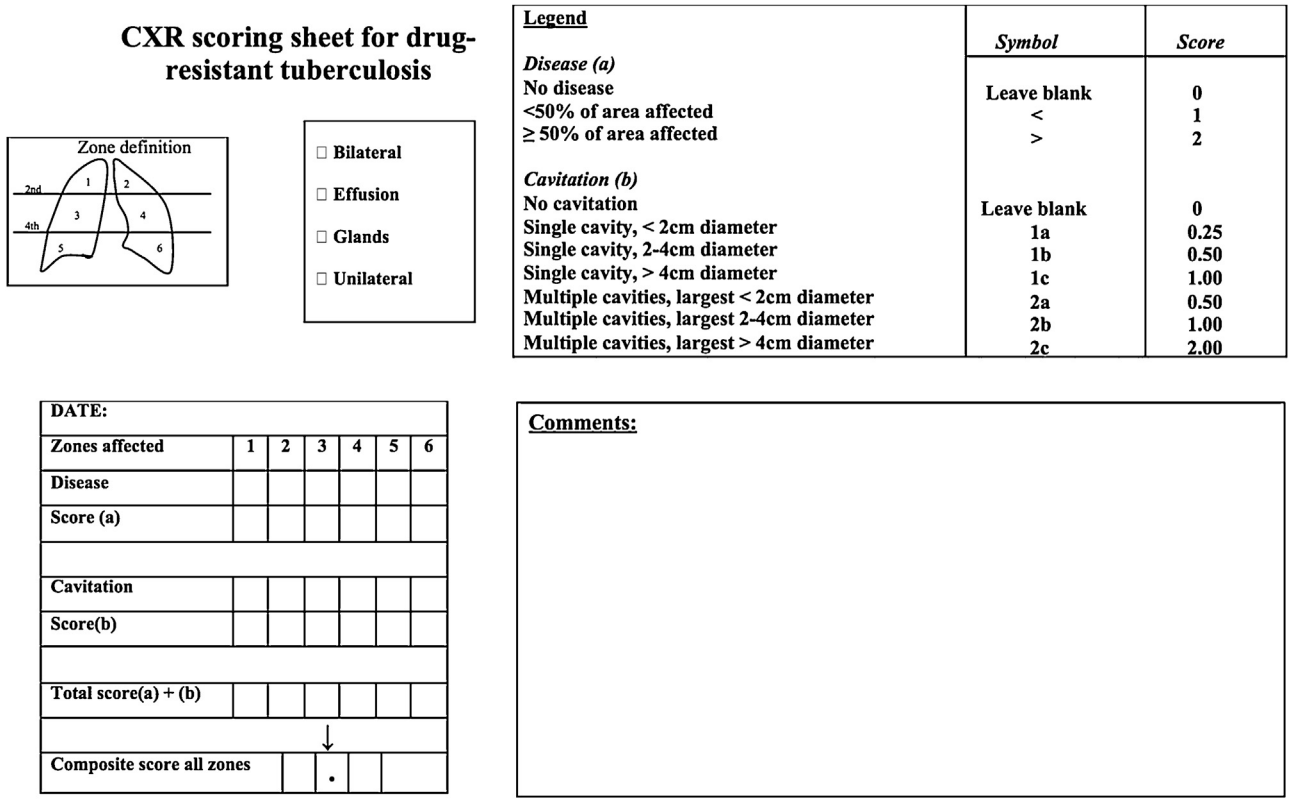


**Figure 1.** Chest X-ray scoring system.

correlation of 0.34 (95% CI 0.18–0.48) for cavity score and a "strong" correlation of 0.714 (0.62–0.79) for disease extent score.

75/97 (77%) patients, significantly more HIV-uninfected patients [49/53 (93%), p = < 0.0001)], had bilateral lung disease (Table 2). By contrast, significantly more HIV-uninfected patients had cavitation [37/53 (70%) vs 18/44 (41%)] and the median cavity score in HIV-uninfected patients was significantly higher compared to HIV-infected patients [1 (IQR 0–2) vs 0 (IQR 0–0.9)

**Table 1**
Clinical and radiographic characteristics of XDR-TB patients stratified by mortality and sputum culture conversion (data are shown as median (IQR) or n (%), unless otherwise stated).

| Clinical information | Total n = 97 | Alive 33/97 (34%) | Deceased 64/97 (66%) | p Value | Conversion 25/97 (26%) | No conversion 72/97 (74%) | p Value |
|---|---|---|---|---|---|---|---|
| Age years (median, IQR) | 34 (27–42) | 34 (27–37) | 35 (27–45) | 0.25 | 36 (29–41) | 34 (25–43) | 0.51 |
| Gender (male) | 63/97 (65%) | 23/33 (70%) | 40/64 (62%) | 0.63 | 17/25 (68%) | 46/72 (64%) | 0.9 |
| Weight kg (median, IQR) | 50.3 (46–59) | 53.2 (48–60) | 50 (44–58) | 0.05 | 55.25 (52–63) | 49.7 (45–57) | 0.01 |
| Diabetes mellitus | 9/97 (9%) | 4/33 (12%) | 5/64 (8%) | 0.75 | 3/25 (12%) | 6/72 (8%) | 0.89 |
| HIV-infected | 44/97(45%) | 13/33(39%) | 31/64 (48%) | 0.53 | 15/25 (60%) | 29/72 (40%) | 0.14 |
| CD4 cells/mm$^3$ (median, IQR)[a] | 123 (70–266) | 122 (65–264) | 123 (72–266) | 0.91 | 119 (58–207) | 124 (92–306) | 0.34 |
| Previous DR-TB | 53/97 (55%) | 15/33 (45%) | 38/64 (59%) | 0.28 | 9/25 (36%) | 44/72 (61%) | 0.05 |
| Number of drugs resistant (median, IQR) | 11 (8–12) | 11 (9–12) | 11 (8–12) | 1 | 11.5 (11–12) | 10 (8–12) | 0.34 |
| Smear-positive | 42/97 (43%) | 10/33 (30%) | 32/64 (50%) | 0.03 | 5/25(20%) | 37/72 (51%) | 0.02 |
| Culture conversion | 25/97 (26%) | 20/33 (61%) | 5/64 (8%) | <0.0001 | | | |
| Time-to-positive (TTP) days (median, IQR) | 15 (11–22) | 16 (13–22) | 14 (10–21) | 0.08 | 18 (13–22) | 14 (10–21) | 0.03 |
| Treatment-related outcome: Unfavourable | 77/97(79%) | 22/33(67%) | 55/64(85%) | 0.03 | | | |
| Alive | – | – | – | – | 20/25 (80%) | 13/72 (18%) | <0.0001 |
| Died | – | – | – | – | 5/25(20%) | 59/72 (82%) | <0.0001 |
| X-ray | | | | | | | |
| Bilateral lung disease | 75/97 (77%) | 22/33 (67%) | 53/64 (83%) | 0.06 | 14/25 (56%) | 61/72 (85%) | <0.0001 |
| Cavity Score (median, IQR) | 0.5 (0–1) | 0.5 (0–1) | 0.5 (0–1.12) | 0.76 | 0 (0–0.5) | 1 (0–2) | <0.0001 |
| Disease extent score (median, IQR) | 7 (5–10) | 5 (5–7) | 9 (6–11) | <0.0001 | 5 (4–7) | 9 (6–11) | <0.0001 |
| Total Score (median, IQR)[b] | 8 (5.5–11.75) | 6 (5–8.5) | 10 (6–12) | <0.0001 | 5 (4–7) | 10 (6.38–12) | <0.0001 |

[a] CD4 cells of the HIV-infected subgroup.
[b] Total score = disease extent score plus cavitation score.

**Table 2**
Clinical and radiological characteristics of XDR-TB patients stratified by HIV status [data are shown as median (IQR) or n (%), unless otherwise stated].

| Clinical | Total n = 97 | HIV-infected n = 44 (45%) | HIV-uninfected n = 53 (55%) | p Value |
|---|---|---|---|---|
| Age years (median, IQR) | 34 (27–42) | 36 (32–41) | 33 (24–45) | 0.17 |
| Gender male | 63/97 (65%) | 24/44 (55%) | 39/53 (74%) | 0.08 |
| Weight kg (median, IQR) | 50 (46–59) | 54 (46–63) | 50 (46–55) | 0.22 |
| Diabetes mellitus | 9/97 (9%) | 6/44 (14%) | 3/53(6%) | 0.32 |
| CD4 106 cells/mm$^3$ (median, IQR) | | | | |
| Previous DR-TB | 53/97 (55%) | 22/44 (50%) | 31/53 (59%) | 0.53 |
| Number of drugs resistant (median, IQR) | 11(8–12) | 11.5 (11–12) | 9.5 (8–12) | 0.15 |
| Smear-positive | 42/97 (43%) | 18/44 (41%) | 24/53 (45%) | 0.78 |
| Culture conversion | 25/97 (26%) | 15/44 (34%) | 10/53 (19%) | 0.14 |
| Time-to-positive (TTP) days (median, IQR) | 15 (11–22) | 15 (11–23) | 15 (11–20) | 0.54 |
| Treatment-related outcome: Unfavourable | 86/97 (89%) | 40/44 (91%) | 46/53 (87%) | 0.12 |
| Died | 64/97 (66%) | 31/44 (71%) | 33/53 (62%) | 0.53 |
| X-ray | | | | |
| Bilateral lung disease | 75/97 (77%) | 26/44 (59%) | 49/53 (93%) | <0.0001 |
| Cavity Score (median, IQR) | 0.5 (0–1) | 0 (0–0.9) | 1 (0–2) | <0.0001 |
| Disease extent score (median, IQR) | 7 (5–10) | 6 (4–10) | 8 (6–10) | 0.08 |
| Total Score[a] (median, IQR) | 8 (6–12) | 7 (4–11) | 9 (6–12) | 0.02 |

[a] Total score = disease extent score plus cavitation score.

p = < 0.0001)] (Table 2). Patients with a history of previous DR-TB were more likely to have bilateral lung disease (p = 0.026) but there was no significant difference in disease extent (p = 0.68) or cavity scores (p = 0.42). The respective median total scores, indicating extent of lung disease and cavitation, and cavity scores were significantly lower in XDR-TB HIV-infected patients [7 (IQR 4–11) vs 9 (IQR 6–12), p = 0.02] and [0 (IQR 0–0.9) vs 1 (IQR 0–2); (p = < 0.0001) (Table 2).

*Chest radiographs related to conversion*

XDR-TB patients who failed to sputum culture convert did significantly worse and more had a history of previous DR-TB [44/72 (61%) vs 9/25 (36%) p = 0.05], smear positive sputum [37/72 (51%) vs 5/25 (20%) p = 0.02], a shorter time-to-positive (days) sputum culture [14 (IQR 10–21) vs 18 (IQR 13–22) p = 0.03], bilateral lung disease [61/72 (85%) vs 14/25 (56%) p = < 0.0001] and death [59/72 (82%) vs 5/25 (20%) p = < 0.0001] (Table 1).

XDR-TB patients who achieved sputum culture conversion had a significantly lower median total score [5 (IQR 4–7) vs 10 (IQR 6.38–12), (p = < 0.0001)] and essentially no cavitation [0 (IQR 0–0.5) vs 1 (IQR 0–2) p = < 0.0001] (Table 1). In a multivariate analysis the total score was found to be inversely associated with conversion and time to conversion with mortality as a competing risk factor (0.85 (95% CI 0.74–0.97) p = 0.02) (Table 3). In HIV-infected patients cavity and total scores did not independently predict the likelihood of culture conversion.

**Table 3**
Multivariate Cox proportional hazards model of clinical and radiographic factors in the full cohort associated with culture conversion in the presence of the competing risk of death.

| | Full cohort HR (95% CI) | p Value |
|---|---|---|
| Age (years) | 0.99 (0.95–1.04) | 0.79 |
| Weight (kg) | 1.03 (0.99–1.07) | 0.15 |
| Diabetes mellitus | 0.65 (0.14–2.98) | 0.58 |
| HIV-infected | 1.33 (0.50–3.50) | 0.57 |
| Previous DR-TB | 0.36 (0.15–0.91) | 0.03 |
| X-ray: Total Score[a] | 0.85 (0.74–0.97) | 0.02 |

[a] Total score = disease extent score plus cavitation score.

*Chest radiographs related to mortality*

XDR-TB patients who died were more likely to have smear positive sputum (p = 0.03) (Table 1). There was no difference between those alive and deceased with regards time-to-positive sputum conversion (p = 0.08), cavitation (p = 0.76) and bilateral lung disease (p = 0.06) (Table 1). However, XDR-TB patients who died had a significantly higher lung disease extent score [9 (IQR 6–11) vs 5 (IQR 5–7) p = < 0.0001] and total score [10 (IQR 6–12) vs 6 (IQR 5–805) p = < 0.0001]. The total score was independently associated with death in those with XDR-TB [1.16 (95% CI 1.05–1.28) p = 0.003] (Table 4).

*Chest radiographs related to bacterial load*

There was no difference between HIV-infected and uninfected XDR-TB patients with regards to time-to-positive sputum (Table 2). Smear status was not significantly associated with disease extent (p = 0.23) or cavity scores (p = 0.76). Disease extent and cavity scores were however associated with time-to-positive (TTP) (both p = < 0.0001). There was a correlation between the cavity score and TTP (p = 0.038), and the total score and TPP (p = 0.039) but not between disease extent and TTP (p = 0.071) although a trend was evident (Figure 2).

## Discussion

The key findings of this study in patients with XDR-TB were that: (i) there was a clear independent correlation between radiological disease extent and culture conversion; (ii) total radiological score (disease extent plus cavitation scores) strongly predicted the risk of death, and (iii) baseline (at diagnosis) cavitation and disease extent scores correlated with bacterial load. Both cavity and total scores were significantly lower in HIV-infected patients and did not independently predict the likelihood of culture conversion or death in that sub-group. Furthermore, we have demonstrated the utility of a validated and reliable chest radiograph scoring system in patients with XDR TB, as we have documented the inter-reader variability but more importantly demonstrated biological meaningfulness and relevance given the correlation with disease outcomes and bacterial load. There are several implications, which include using the chest radiograph for

**Table 4**
Multivariate Cox proportional hazards model of clinical and radiographic factors associated with risk of death in HIV-infected and uninfected XDR-TB patients.

| | Full cohort HR (95%CI) | p Value | HIV COHORT HR (95%CI) | p Value |
|---|---|---|---|---|
| Weight (kg) | 0.98 (0.95–1.01) | 0.13 | – | – |
| Diabetes mellitus | – | – | 0.23 (0.05–1.02) | 0.05 |
| Previous MDR-TB | – | – | 1.89 (0.80–4.45) | 0.15 |
| Sputum culture conversion | 0.11 (0.03–0.37) | <0.0001 | 0.21 (0.05–0.93) | 0.04 |
| TTP(days) | 0.99 (0.95–1.04) | 0.79 | – | – |
| Diagnosis to treatment(days) | 1.00 (1.00–1.00) | 0.67 | 0.99 (0.98–1.01) | 0.31 |
| X-ray | | | | |
| Unilateral disease | 2.05 (0.82–5.14) | 0.13 | 1.26 (0.34–4.67) | 0.73 |
| Disease extent score | – | – | 1.19 (0.95–1.48) | 0.13 |
| Total radiographic score[a] | 1.16 (1.05–1.28) | 0.003 | – | – |

Dashes = factors not incorporated in the model as the p value was <0.1 in the univariate analysis.
[a] Total score = disease extent score plus cavitation score.

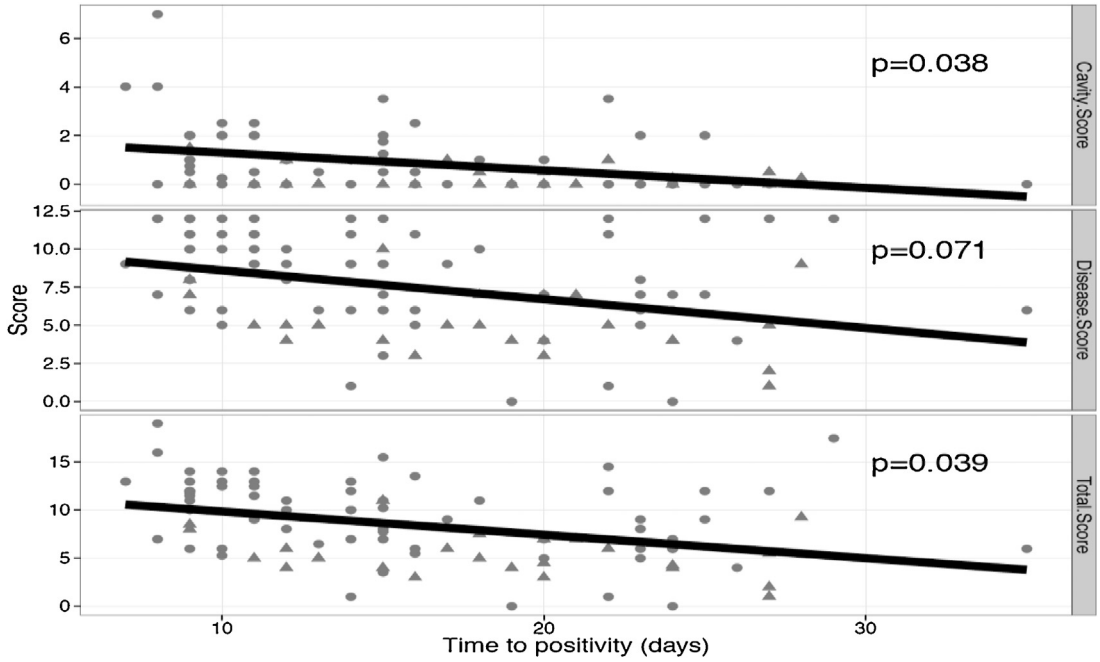


**Figure 2.** Scatter plot of chest radiographic scores (cavity, disease extent, and total) and sputum culture time-to-positive (days). Linear regression line for each scatter plot added to indicate direction of trend. P-value reports results of test for non-zero correlation coefficient.

regimen selection (decision-making when deciding to use more aggressive regimens and potent drugs including bedaquiline and linezolid), prognosis, and treatment monitoring. Furthermore, its prognostic value may facilitate the evaluation and pre-selection of new immunotherapeutic interventions for MDR-TB (conventional trials can take 5 to 10 years to complete). Indeed, better prognostic markers are urgently needed to facilitate evaluation studies of new drugs. PET-CT has recently shown promise as a marker of outcomes in patients with MDR-TB (Chen et al., 2014; Stelzmueller et al., 2016). However, this is an expensive and poorly accessible technology and more data are required to study the utility of a simple chest X-ray.

Long-term treatment related outcomes were poor with high mortality and treatment failure (Pietersen et al., 2014), and in this cohort 89% of XDR-TB patients had died or failed treatment at the censor date. Similar to previous studies (Pietersen et al., 2014; Holtz et al., 2014) we found initial culture conversion to independently predict the risk of death in all XDR-TB patients. However, cavitary disease also had prognostic value. Cavitation was first shown to be an independent predictor of time-to-culture conversion in 167 patients with MDR-TB (Holtz et al., 2014) and an independent risk factor for poor outcomes in Korean XDR-TB patients who were HIV-uninfected (Jeon et al., 2009). Our findings are similar; in the multivariate analysis total radiographic disease score (disease extent plus cavitation scores) predicted culture conversion and time-to-culture conversion with death as a competing risk. We also found that the total score (disease extent plus cavity scores) strongly predicted risk of death.

The TTP of *Mycobacterium tuberculosis* is a more sensitive indicator of bacterial load than smear status (Epstein et al., 1998). Patients with more extensive disease and cavitation on chest radiograph are known to have higher bacillary burdens and shorter TTPs (Ralph et al., 2010; Perrin et al., 2010). Indeed, we have shown an inverse relationship between extent of lung disease, cavity scores, and TTP (Figure 1). Patients who experienced culture conversion had significantly longer median TTP at diagnosis. However, in the multivariate analysis TTP did not independently predict culture conversion. Thus, TTP is likely to be a less powerful indicator of treatment response in XDR-TB than in drug sensitive

TB (Hesseling et al., 2010) or MDR-TB (Holtz et al., 2014) presumably because of several modulating factors including fitness, strain variability, higher grade resistance, and possibly greater pre-existing lung damage in XDR TB.

We found no association between baseline chest radiography and conversion or mortality in HIV-infected patients with XDR-TB. The sample size is small but several other factors may explain this including more likely death from non-TB related causes (amplified by delayed diagnosis), and that advanced immunosuppression is associated with less fibrosis and cavitation on the chest radiograph (despite the higher pulmonary bacterial load) (Long et al., 1991). Similarly, we found lower chest radiographic scores in HIV-infected compared to uninfected patients, and limited value to predict risk of death. Nevertheless, the extent of lung disease was substantial and in keeping with a group of patients with MDR-TB (88% HIV-infected) from Tugela Ferry Kwa-Zulu Natal (Brust et al., 2013).

We highlight the importance of quantitative radiological analysis as a factor in predicting treatment response and prognosis in XDR-TB. Indeed, a recent systematic review found that most chest radiograph scoring systems combine clinical and radiological data to inform respiratory isolation in a hospital setting (Pinto et al., 2013b). Pinto et al. (2013a) developed a numerical scoring system based on CRRS (Den Boon et al., 2005) with a high negative predictive value in smear negative, smear positive, and HIV-infected patients as a rule out test where TB is clinically suspected. However, there is a need for a more simple and standardized radiological scoring system, irrespective of a clinical profile, that is suitable for use in HIV-infected and uninfected patients. We evaluated a user friendly and basic zonal scoring system that generates a numerical score, and found it to be a reliable tool. This has promise as a chest radiograph scoring system for use in clinical out-patient settings and for future research.

Our study has several limitations. The retrospectively collected chest X-rays and large number of patients who transferred out to clinics limited the proportion of patients whose radiographs were analysed. It is possible therefore that the study group included a greater proportion of patients with more advanced disease who remained hospitalised. However, for regulatory (Provincial study approval structure), resource-based and logistical reasons we were unable to access the chest radiographs from peripheral clinics, and a sensitivity analysis showed that the excluded population had similar characteristics to those included in the study with respect to age, gender, HIV status and CD4 count. Chest X-rays done closer to the date of diagnosis may have improved the overall accuracy of this study. Lastly, evidence of extra pulmonary TB was not included in the multivariate analysis.

In conclusion, we have shown that quantitative baseline chest radiographic analysis in XDR-TB was independently associated with bacterial load and treatment response (culture conversion and survival). Quantitative chest radiography remains relevant in the clinical management of HIV-uninfected patients with XDR-TB, and has implications for the development of a prognostic bio-clinical score for tuberculosis that could be useful for the evaluation of new interventions for MDR-TB.

## Conflict of interest

There are no conflicts of interest to declare for any authors.

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No specific funding was used to perform this study since CXRs, clinical and mycobacterial analysis were all performed as part of routine care.

## Ethical approval

Ethics approval was obtained from the University of Cape Town human research ethics committee.

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