Chest X-rays and associated clinical parameters in pulmonary tuberculosis cases from the National Tuberculosis Programme, Mumbai

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Abstract

The study was carried out in pulmonary tuberculosis (PTB) patients from the local Tuberculosis control programme, Mumbai, India. It examined features of chest X-rays and their correlation with clinical parameters for possible application in suspected multidrug resistant TB (MDRTB) and to predict outcome in new and treatment failure PTB cases. X-ray features (infiltrate, cavitation, miliary shadows, pleural effusion, mediastinal lymphadenopathy and extent of lesions) were analyzed to identify associations with biological/clinical parameters through univariate and multivariate logistic regression. Failures demonstrated associations between extensive lesions and high glycosylated hemoglobin (GHb) levels (P=0.028) and male gender (P=0.03). An association was also detected between cavitation and MDR (P=0.048). In new cases, bilateral cavities were associated with MDR (P=0.018) and male gender (P=0.01), low body mass index with infiltrates (P=0.008), and smoking with cavitation (P=0.0238). Strains belonging to the Manu1 spoligotype were associated with mild lesions (P=0.002). Poor outcome showed borderline significance with extensive lesions at onset (P=0.053). Furthermore, amongst new cases, smoking, the Central Asian Strain (CAS) spoligotype and high GHb were associated with cavitation, whereas only CAS spoligotypes and high GHb were associated with extensive lesions. The study highlighted associations between certain clinical parameters and X-ray evidence which support the potential of X-rays to predict TB, MDRTB and poor outcome. The use of X-rays as an additional tool to shorten diagnostic delay and shortlist MDR suspects amongst non-responders to TB treatment should be explored in a setting with limited resources coping with a high MDR case load such as Mumbai.

Introduction

Tuberculosis (TB) remains a public health concern. There were 9.2 million estimated new cases of TB in 2008 with 1.8 million deaths. India, China and Russia account for 60% of the global multidrug resistant (MDR) TB burden.[1] The HIV/ AIDS epidemic is reversing the gains achieved by efforts to control TB.

The Revised National Tuberculosis Control Programme (RNTCP) relies on sputum microscopy as the standard for diagnosis of pulmonary TB (PTB). Since it is performed on unconcentrated samples, the likelihood of false negatives and diagnostic delay remains high. Culture and drug susceptibility testing (DST) result in delayed detection of drug resistance.[2] The enhanced sensitivity of chest X-rays[3] allows their application in cases of suspected MDRTB,[4] reduces the need for microscopic screening[5] and makes diagnosis quicker. Furthermore, the Centers for Disease Control and Prevention (CDC) have established X-ray evaluation guidelines for HIV infected TB patients, due to their atypical radiographic manifestation.[6] The strategic use of X-rays could reduce the case detection gap of 40% and prevent wastage of resources.[7]

Several studies have compared the differences in clinical, X-ray and laboratory manifestations of PTB among young and elderly patients.[8] Various groups have reported associations between cavitation and, diabetes and MDR.[9,10] Such associations have also been studied in HIV positive TB patients.[11] An earlier publication by Chatterjee *et al.* reported the association between Central Asian Strains (CAS) and the presence of cavities, in new and treatment failure cases analyzed collectively.[12]

These reports have not generated information on in depth X-ray presentation and its association with a combination of demographic, clinical and biological parameters. This study was undertaken as part of a larger epidemiological investigation on MDRTB transmission in Mumbai. This analysis examines the influence of the biological characteristics (drug susceptibility and genotype) of the infecting strain, patient demographic and various clinical parameters on X-ray presentation in both new and 5-month treatment failure PTB cases from the RNTCP. Additionally, associations between X-ray evidence and treatment outcomes have been investigated. The study findings also served to assess the potential of X-rays as an adjunct to existing techniques for TB diagnosis, suspicion of MDRTB and prognosis of treatment efficacy.

Materials and Methods

Patient recruitment

This analysis is based on an epidemiological project on MDRTB transmission in Mumbai.[13] From April 2004 till September 2007, 2 groups of sputum positive PTB patients were screened: i) newly diagnosed patients at onset; and ii) treatment failures (sputum positive five months after commencing a regimen of two months of isoniazid (H), ethambutol (E), rifampicin (R) and pyrazinamide (Z) thrice weekly, and four months of H and R thrice weekly).

Inclusion criteria were: i) smear positivity; ii) age 15-69 years; iii) residency in Mumbai for at least three years before diagnosis and in the same area where treatment was sought. Patients with a history of TB or TB therapy or treatment interruption for more than two weeks (in treatment failures) were excluded. Patients were recruited after giving informed consent. Permission for the study was obtained from the Foundation for Medical Research (FMR) Institutional Ethics Committee (20.07.2001/01).

Demographic data (age, gender and smok-

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ing habits) were recorded. Age groups analyzed were 15-35 and 36-69 years. Body Mass Indices (BMI) below 18.5 were considered low.[14] At recruitment, patients were referred to private laboratories for hemoglobin (Hb) glycosylated hemoglobin (GHb) tests and chest X-rays and voluntary HIV counseling and testing. Hemoglobin was considered low if below 12 gm% for females and below 14 gm% for males.[15] A GHb level of 6.5% or under was considered normal.[16]

X-rays were first read by radiologists at the laboratories, and were then read again blinded by a chest physician (YD), who described them as:[17] i) normal: no lesions; ii) abnormal: shadows indicative of TB. If abnormal: a. whether cavitary or not; presence of infiltrates, miliary shadows, pleural effusion, mediastinal lymphadenopathy; b. the number of radiological zones involved; c. cavities were classified as: i) size (diameter in cm): small (<2), medium (2–4) and large (>4); ii) number: single, multiple; iii) position: unilateral, bilateral; d. extent of lesions: mild: no cavities and less than 3 radiological zones, moderate: 4-5 radiological zones or less than 3 radiological zones with cavities, extensive: more than 3 zones with cavities or 6 radiological zones.

Overall, 5% discordance was noted between the radiologists' and the chest physician's assessment. The physician's evaluation was more specific and detailed than the radiologists' reports and was, therefore, considered final.

Sample size

As for the overall study design, sample size for the failure and new cases was estimated at a minimum of 47 and 224, respectively.[13]

Drug susceptibility testing

Early morning sputum samples were tested using a radiorespirometric Buddemeyer assay.[13] Drug susceptibility testing (DST) interpretations were: MDR, resistance to at least H and R; monoresistance, resistance to only one drug; polyresistance, resistance to 2/3 drugs exclusive of the HR combination.

Spoligotyping

Spoligotyping was performed as described earlier.[12] A cluster was defined as two or more strains having an identical pattern.

Statistical analysis

Data was analyzed using SPSS 10.0 and EpiInfo 2002 using χ^2 tests. Cavity size was recoded into small *versus* medium and large; extent of lesions was recoded into mild *versus* moderate and severe. P<0.05 was considered significant. Multivariate analysis (MVA) was performed through binary logistic regression[18] using the Backward Wald method.

Results

Of the entire cohort, 68 treatment failures and 584 new cases for whom X-rays were available were analyzed. The demographic and clinical features of the patients are shown in Table 1. Fifty-six treatment failures and 529 new cases opted for HIV testing. Amongst both patient types, a majority were in the 15-35 years age group. The majority of the patients amongst both the treatment failures (66%) and new cases (62%) were males.

The DST and spoligotyping data of the entire cohort has been described earlier.[12,13] Briefly, the cohort of treatment failure and new cases revealed 17% and 35% of samples were sensitive, 41% and 24% were MDR, 26% and 20% were polyresistant, and 16% and 21% were monoresistant, respectively.[13] Spoligotyping showed 69% clustering of isolates from treatment failures, with Manu1 (n=14), CAS (n=8), Beijing (n=8), and East African Indian (EAI-5) (n=6) being the 4 major clusters. The isolates from new cases showed 71% clustering, with Manu1 (n=168), CAS (n=62), Beijing (n=22), and EAI-5 (n=30) forming the major clusters.[12]

Univariate analysis of X-ray features

Treatment failures

An association was noted between high GHb levels and extensive lesions on X-ray (χ^2=4.78, P=0.028). More patients with low hemoglobin levels also had extensive lesions on X-ray (73%) in comparison to those with normal hemoglobin (56%), but this was not significant (P=0.2). Additionally, male gender was associated with extensive lesions on X-ray (χ^2=4.67, P=0.03). Patients in the younger age group were found to show infiltrates (P=0.021). The presence of cavitation was associated with MDR (χ^2=3.9, P=0.048). As expected, HIV positivity was associated with mediastinal adenopathy but with borderline significance (P=0.053) (Table 2).

New cases

There was a significant association between a sensitive or monoresistant DST profile and unilateral cavities compared with an MDR profile with bilateral cavities (χ^2=5.58, P=0.018). Younger patients were more likely to have smaller cavities as compared to the older patients (χ^2=4.56, P=0.03) but were less likely to show mediastinal adenopathy (χ^2=3.74, P=0.053). Male gender was associated with both infiltration (χ^2=9.45, P=0.002) and bilateral cavitation (χ^2=6.62, P=0.01). A higher proportion of patients with a low BMI had infiltrates (χ^2=6.87, P=0.008) and bilateral cavities (χ^2=3.86, P=0.049) compared to those with normal BMI. Amongst the major clusters, the Manu1 cluster was associated with mild lesions (χ^2=9.36, P=0.002) and fewer strains showed cavitation (χ^2=6.59, P=0.01). In contrast, the CAS was associated with extensive lesions on X-ray (χ^2=15.17, P=0.00009) and a significantly higher number of CAS strains showed cavitation (χ^2=10.6, P=0.001). A similar association has been reported by Chatterjee *et al.* in a combined analysis of new and treatment failure cases.[12]

Miliary TB was more common amongst unique spoligotypes or minor clusters than the major clusters (P=0.033). Although there were only 2 Beijing strains showing a miliary pattern, within the major clusters, this cluster was more likely to be associated with miliary TB than the other major clusters (P=0.045). Smoking was associated with cavitation (χ^2=5.11, P=0.0238) (Table 2).

An adverse outcome such as failure was associated with extensive lesions on X-ray, but with borderline significance (χ^2=3.74, P=0.053). Furthermore, a follow up of the new patient cohort showed 166 of 550 (30%) to be smear positive at the 5th month of treatment. Of these, 106 (64%) showed cavitation at onset

Table 1. Sociodemographic. clinical and biological characteristics of patients.

		Treatment failures (n=68) n (%)	New cases (n=584) n (%)
Gender:	male	45 (66)	361 (62)
	female	23 (34)	223 (38)
Age:	15-35	55 (81)	515 (88)
	36-69	13 (19)	68 (12)
Smoking		18 (26)	93 (16)
Normal GHb		37 (54)	185 (32)
Normal Hb		16 (24)	70 (12)
Normal BMI		10 (15)	126 (22)
HIV positive		3 (4)	22 (4)
MDR*		95 (41)	117 (24)
Major clusters° (Manu1, CAS, Beijing, EAI-5)		36 (47)	282 (44)

Details on the larger cohort have been described earlier in *D'souza *et al.*[13] and °Chatterjee *et al.*[12]

(P=0.003) suggesting a strong association between cavitation at onset and smear positivity at 5th month of treatment.

Multivariate analysis of X-ray features

Treatment failures

Amongst failure cases, the association between cavitation and MDR (P=0.085) and extent of lesion and high GHb (P=0.139) or gender (P=0.183) did not remain significant.

New cases

If all the factors were analyzed in the MVA irrespective of their significance in the univariate analysis, cavitation was associated with high GHb (P=0.03), CAS (P=0.006) and smoking (P=0.011). Cavity size remained associated with younger age (P=0.02) and multiple cavities with smoking (P=0.015). The overall extent of lesions on X-ray were associated with CAS (P=0.0) and high GHb (P=0.02). Of the various X-ray features, cavity size remained a predictor for poor outcome but was not significant (P=0.053, OR = 2.338) (Table 3).

Discussion

Several studies have evaluated risk factors for recurrent TB, some of which are the severity of the X-ray manifestations of disease (presence of cavitation, extent of pulmonary involvement)[19] and microbial load at diagnosis.

We found MDR to be associated with cavitation in failure cases. Though cavitation was seen in only 56% of new cases, MDR was specifically associated with bilateral cavitation. Similar findings have been reported elsewhere, wherein the number of cavities and lobes containing small nodules were higher in MDR compared to sensitive patients.[4,20] This study corroborates reports that X-ray findings could be used for prognosis of MDRTB. Zahirifard *et al.* reported multiple cavities, especially in both lungs; and nodular and infiltrative lesions with pleural effusion as the main features of MDRTB in new cases.[21] These features could be used as indicators for suspicion of DR and need for further DST.

In contrast, Balaji *et al.* reported no significant differences between sensitive and MDRTB on chest X-ray on initial presentation. This could be because they analyzed their MDR and extensively drug resistant (XDR) cohorts independently. The proportion of patients with cavitation in the MDR (42%) and XDR (47%) cohorts was higher than that in the sensitive cohort (29%).[9] The variation in X-ray manifestations across the studies could be a consequence of differential time intervals between disease onset and chest X-ray, which could have led to varied progression of X-ray manifestation.

Though our HIV seropositive cohort is small, our study revealed an association between mediastinal adenopathy and HIV seropositivity in treatment failures, as well as miliary TB and HIV seropositivity in new cases. The occurrence of these associations in immunocompromised patients has been reported previously.[22]

Studies involving patients with TB and diabetes mellitus have shown a greater incidence of cavitary disease.[10,23] Our study confirmed a significant association between high GHb and extensive lesions on X-ray in treatment failures. Even amongst our new cases with extensive lesions, 70% were diabetic, though this was not significant. In contrast to this, Morris *et al.*, reported multilobe involvement to be the predominant X-ray finding in both diabetic and non-diabetic PTB patients,[24] and Yurteri *et al.* found no difference in frequency of cavitary lesions between the diabetics and nondiabetics (67% *vs* 69%).[25] Control of diabetes through medication and the duration of diabetes before TB diagnosis could be responsible for the variation in these reports.

It has previously been shown that smokers are more likely to have cavitation[26] and similar findings have been noted in new cases in our study. This can be attributed to the immune suppression caused by nicotine thereby rendering smokers more susceptible to developing active

Table 2. Univariate analysis of the various X-ray features and clinical and biological parameters.

Characteristics	Infiltrate	Cavitation	Size	Cavity Number	Position	Pleural effusion	Miliary	Mediastinal adenopathy	Extent
Failures									
Age 15-39 yrs	0.323	0.406	0.286	0.29	1.0	1.0	0.49	1.0	0.76
Gender	0.29	0.107	1.0	0.19	0.66	1.0	1.0	0.34	0.03*
Low BMI	1.0	1.0	1.0	0.25	1.0	0.16	1.0	1.0	0.53
Low Hb	0.23	0.20	1.0	1.0	0.17	0.32	0.42	1.0	0.2
GHb≥6.5	1.0	0.61	0.72	0.54	1.0	0.4	0.5	1.0	0.03*
HIV positivity	1.0	0.55	0.53	0.23	1.0	0.25	1.0	0.053*	0.55
MDR	0.63	0.048*	1.0	0.92	0.12	1.0	1.0	0.38	0.15
Major cluster	1.0	0.72	0.25	0.46	0.7	0.67	0.24	0.49	0.72
CAS	1.0	0.14	1.0	1.0	0.18	1.0	1.0	1.0	0.14
Manu1	0.17	0.24	0.53	1.0	0.52	0.55	0.49	1.0	0.24
Beijing	1.0	0.37	0.5	0.62	1.0	0.54	0.045*	1.0	0.37
Smoking	0.28	0.35	1.0	0.72	0.21	1.0	1.0	1.0	0.35
Poor outcome	0.62	0.1	0.15	0.75	0.69	0.64	0.18	0.43	0.1
New cases									
Age 15-39 yrs	1.0	0.11	0.03*	0.33	0.22	0.5	0.68	0.053*	0.15
Gender	0.002*	0.58	0.164	0.07	0.01*	0.918	0.71	0.25	0.32
Low BMI	0.008*	0.26	0.80	0.09	0.049*	0.93	0.19	0.37	0.13
Low Hb	0.7	0.62	0.66	0.85	0.56	0.58	1.0	1.0	0.95
GHb≥6.5	0.38	0.1	0.81	0.91	0.51	0.85	0.22	0.98	0.13
HIV positivity	1.0	0.72	0.49	0.08	0.14	0.7	0.19	0.6	0.38
MDR	0.75	0.81	0.36	0.15	0.02*	0.94	0.63	0.29	0.85
Major cluster	0.42	0.91	0.53	0.72	0.46	0.36	0.03*	0.42	0.38
CAS	0.59	0.001*	0.78	0.09	0.12	1.0	-	1.0	0.00009*
Manu1	0.15	0.01*	0.42	0.58	0.63	0.47	-	0.41	0.002*
Beijing	1.0	0.52	0.68	0.74	1.0	0.29	-	0.17	0.85
Smoking	0.49	0.0238*	0.83	0.12	0.15	0.84	1.0	0.22	0.11
Poor outcome	0.63	0.036*	0.09	0.39	0.67	0.77	1.0	0.23	0.053*

disease[27] and exacerbated X-ray presentation.

X-ray manifestation could also serve as a means to predict poor outcomes. An association between unfavorable outcome and cavitation or extensive lung involvement has been reported in treatment failures.[28,29] Surprisingly, our analysis showed an association between poor outcome and cavitation and extensive lesions on X-ray in our new cases at diagnosis. Such an association at onset of treatment should be investigated to assess its potential for predicting poor outcome.

Patients with cavities on X-ray are typically more infectious than patients with non-cavitary disease.[30] Several studies report cavitary lesions on X-ray to be associated with increased risk of a positive acid fast bacilli (AFB) smear at onset in adults.[31] Our study detected an association between cavitation at onset and smear positivity at 5th month of follow up, supporting the use of X-ray as an adjunct to smear microscopy not only for diagnosis, but also for monitoring therapy.

Contrasting data has emerged from studies which investigated the relationship between the infecting strain and its X-ray presentation. An association between the Beijing strain and widespread cavitation and multiple zone involvement has been reported.[32] However, our findings are similar to reports in which the Beijing genotype is not associated with a different X-ray presentation.[33,34] Instead, we found CAS to be associated with extensive lesions on X-rays, and Manu1 associated with less cavitation compared to the other major clusters. We, therefore, hypothesize that the association between X-ray manifestations and the infecting strain could be local strain specific, predetermined by the virulence and other properties of the dominant strain, if any.

While our study has highlighted various clinical parameters and their correlation to X-ray features and consequently outcomes, the occurrence of certain radiological patterns in different locales may also vary due to specific characteristics of host defence mechanisms.[35] This may explain the variation between associations observed in our study and those of others.

Our study has 3 limitations, one of which is the small number of both the treatment failures and HIV positive patients. Secondly, the disproportionate distribution of strain clusters may have led to biased findings. Lastly, since X-rays were taken only at recruitment for both the treatment failures and new cases, there was no opportunity to study the progression of X-ray manifestations during treatment.

Overall, the study has confirmed the correlation between various clinical parameters and chest X-ray manifestations. The use of X-rays for diagnosis has been established in certain locales through the use of a standardized reading methodology using reference X-rays, and a system of accreditation for readers.[34] The findings support their possible use as a means to shorten the interval between patient presentation and diagnosis. Furthermore, their potential as an additional tool in suspicion of MDRTB and as predictor of treatment outcomes[36] should be explored. This would ensure prudent prioritization of funds in settings with limited resources, improved patient management and thus a positive impact on TB control programs.

Table 3. Multivariate analysis for various X-ray features.

X-ray characteristics	P value	OR	Confidence interval
Failures			
Cavitation			
GHb ≥6.5	0.085	0.081	0.005-1.41
MDR	0.243	4.40	0.37-53.06
Extent			
Gender	0.139	0.15	0.01-1.84
GHb ≥6.5	0.183	0.17	0.01-2.32
New cases			
Cavitation			
GHb ≥6.5	0.03*	2.06	1.07-3.95
CAS	0.006*	4.67	1.56-13.97
Smoking	0.011*	3.22	1.30-7.95
Cavity Size			
Age 15-35 yrs	0.02*	3.16	1.19 -8.34
Gender	0.14	2.07	0.78-5.47
HIV positivity	0.10	4.22	0.74-24.02
Cavity number			
Smoking	0.015*	3.08	1.24-7.63
GHb ≥6.5	0.12	0.49	0.20-1.21
Pleural effusion			
GHb ≥6.5	0.003*	0.17	0.05-0.552
Beijing	0.059	5.88	0.94-36.83
MDR	0.096	0.14	0.015-1.408
Extent			
CAS	0.00*	4.85	2.14-11.01
GHb ≥6.5	0.02*	2.17	1.13-4.18
Age 15-35 yrs	0.08	1.93	0.93-4.02

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