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Empiric Treatment with a Fluoroquinolone Delays the Treatment for Tuberculosis and Is Associated with Poor Prognosis in Endemic Area

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Background: This study was conducted to evaluate the impact of empiric fluoroquinolone use on the timing of anti-tuberculous treatment and outcome of tuberculosis patients in an endemic area.

Methods: All culture-confirmed tuberculosis patients aged ≥ 14 years from July 2002 through December 2003 were included and their medical records were reviewed.

Results: Of the 548 tuberculosis patients, 79 (14.4%) received a fluoroquinolone (FQ group), 218 a non-fluoroquinolone (AB group) and 251 no antibiotics before anti-tuberculous treatment. Fifty-two (65.8%) experienced clinical improvement after fluoroquinolone use. In the FQ group, the median interval from initial visit to anti-tuberculous treatment was longer (41 *vs.* 16 *vs.* 7 days), and the prognosis was worse (hazard ratio 6.88 [1.84 – 25.72]). More patients in the FQ and AB groups were older than 65 years (53.2% and 61.0% *vs.* 31.5%), and had underlying disease (53.2% and 46.8% *vs.* 34.3%) and were hypoalbuminemic (67.2% and 64.9% *vs.* 35.1%). Of the 9 mycobacterial isolates obtained after fluoroquinolone use from 9 patients whose initial isolates were ofloxacin-susceptible, 1 (11.1%, after 7-day fluoroquinolone use) was ofloxacin-resistant. Independent poor prognostic factors included empiric fluoroquinolone use, age > 65, underlying disease, hypoalbuminemia, and lack of early anti-tuberculous treatment.

Conclusions: Of our tuberculosis patients, 14.4% received a fluoroquinolone before the diagnosis. With 34-day delay in anti-tuberculous treatment and more frequent coexistence of underlying disease and hypoalbuminemia, empiric fluoroquinolone therapy was associated with a poor outcome. *M. tuberculosis* isolates could obtain ofloxacin-resistance within 1 week.

The fluoroquinolones (FQs) were introduced into clinical practice in the 1980s. With broad-spectrum antimicrobial activity, they are recommended and widely used for the treatment of bacterial infections of the respiratory, gastrointestinal, and urinary tracts, as well as sexually transmitted diseases and chronic osteomyelitis.[1-4] In contrast to many other antibiotics used to treat bacterial infections, the FQs have excellent in vitro and in vivo activity against *Mycobacterium tuberculosis*.[5] [6] Recent study conducted in United States revealed that empiric FQ use was associated with a delay in the initiation of appropriate anti-tuberculous treatment.[7] However, this important issue had not been addressed in endemic area. It was also not clear whether the delay in anti-tuberculous treatment affected survival. Therefore, we conducted this study to evaluate the impact of empiric FQ use on the timing of anti-tuberculous treatment and outcome of tuberculosis (TB) patients in an endemic area.

MATERIALS AND METHODS

This retrospective study was conducted in a 1500-bed, tertiary-care referral center in northern Taiwan, where the incidence and mortality of TB in 2003 was 62.4 and 5.8 per 100,000, respectively.[8] We searched the records of the mycobacterial laboratory from July 2002 to December 2003 and found all of the newly diagnosed patients aged ≥ 14 years with culture-confirmed TB. Medical records (including pharmacy records and the interview records from TB case managers) of each patient were reviewed. Acid-fast smear (AFS), mycobacterial culture, and susceptibility test were performed as previously described.[9] The chest radiographs (CXRs) were reviewed by two pulmonary specialists independently. If discrepancy was noted between their interpretations, the image was further reviewed by one chest specialist blinded to the results.

Respiratory symptoms were defined as any of the following: cough, dyspnea, pleuritic chest pain, and hemoptysis. Constitutional symptoms included fever, malaise, night sweat, or weight loss. Headache or consciousness change was considered as central nervous system (CNS) symptoms. Musculo-skeletal symptoms included arthralgia or backache. Abdominal symptoms were defined as abdominal pain or distention. Clinical improvement was defined as improvement of any of the presenting symptoms, CXR findings, and laboratory data.[7] Pulmonary TB that confined below the imaginary line traced across the midpoint of hila and including the parahilar regions on a chest radiograph was defined as lower-lung-field TB.[10] Disseminated TB was diagnosed if *M. tuberculosis* was isolated from blood, bone marrow, liver biopsy specimen, or ≥ 2 non-contiguous organs.[11] Chronic renal failure was defined as a serum creatinine level higher than 20 mg/L.[10] [12] Standard anti-tuberculous treatment consisted of isoniazid, rifampicin, ethambutol and pyrazinamide, and was modified according to the presence of concomitant hepatic and/or renal disease, adverse effects and to the results of the drug susceptibility testing after it became available. In patients with liver disease, pyrazinamide may be omitted. The anti-tuberculous treatment was considered early if it was started within 14 days after initial visit, and was judged as completed if fulfilling the definition of the World Health Organization (WHO).[13] All patients were followed until they were completely treated or until June 30, 2005.

Inter-group differences were analyzed using either independent-sample *t*-test or Mann-Whitney *U*-test for continuous variables, and *chi*-square test for categorical variables. Survival curves for each variable were generated using the Kaplan-Meier method and were compared using the log-rank test. If a significant difference ($p < 0.05$) was reached, the variables then entered the multivariate survival analysis using Cox regression to identify factors independently associated with mortality.

RESULTS

From July 2002 through December 2003, a total of 548 patients with newly diagnosed culture-confirmed TB were identified. Of them, pulmonary TB was diagnosed in 451 (82.3%) patients, including 38 (6.9%) who had concomitant pulmonary and extrapulmonary TB. The remaining 97 (17.7%) patients had only extrapulmonary involvement. Serostatus of *Human Immunodeficiency Virus* (HIV) were tested in 296 patients and was positive in 17. Of the 252 patients with unknown HIV serostatus, all were free of other acquired immunodeficiency syndrome (AIDS)-defined illness during follow-up. Of the 548 patients, 79 (14.4%) received a fluoroquinolone (FQ group) and 218 (39.8%) received non-FQ antibiotics (AB group) prior to the diagnosis of TB. Antibiotics, including FQs, were prescribed more than once in 65 patients. The FQ prescribed was ciprofloxacin in 42 patients, levofloxacin in 21, and moxifloxacin in the remaining 16, and the average duration of use was 9.5 days (SD: 6.0 days). The initial diagnosis was community-acquired pneumonia in 69 (87.3%) patients, septic arthritis in 4 (5.1%), bacterial peritonitis in 3 (3.8%), one (1.3%) each for urinary tract infection, meningitis, and fever of unknown origin. In 18 patients, *M. tuberculosis* isolates before and after the use of FQs were both preserved. Half of them had clinical specimens collected ≥ 7 days after the use of FQs (range: 7 – 18 days). All of the 36 isolates were ofloxacin-susceptible, except one from a patient after using a FQ for 7 days. The patient presented with right knee arthralgia for 1 week and had not taken any medication before coming to our hospital. Among the 469 patients without empiric FQ use, 177 had previously been treated by local doctors and 76 of them had received antibiotics (non-FQ antibiotics in 52, unknown in the remaining). Among the other 292 patients, 137 were not likely to have been treated due to a short duration of symptom (≤ 14 days).

The clinical characteristics of the 548 patients were summarized in Table 1. The age, presence of underlying disease, extrapulmonary involvement, respiratory or constitutional symptoms, duration of symptom, pulmonary cavitation, serum albumin level, and result of sputum AFS were significantly different among the three groups. Of the 50 asymptomatic patients, 24 (48%) had only one positive mycobacterial culture. Of them, 23 had pulmonary lesion which resolved after anti-tuberculous treatment. Only one (0.2%) with TB peritonitis had normal chest images.

Anti-tuberculous treatment was started within 14 days after initial visit in 249 (45.4%) patients, including 9 (11.4%) in the FQ group, 90 (41.3%) in the AB group, and 150 (59.8%) in the control group. In comparison with patients in the other two groups, those in the FQ group were delayed studied ($p = 0.037$ for non-FQ antibiotic group; $p = 0.040$ for no antibiotic group) and treated ($p < 0.001$ for both groups) for TB, and had a worse prognosis ($p < 0.001$ for no antibiotic group) (Table 2). For the patients with smear-negative specimens, those in the FQ group were treated 42 days after the initial visit in median, 31 days after mycobacterial culture was ordered, while in the other two group, patients were treated 27 and 13 days after the initial visit, only 16 and 1 days after mycobacterial culture was requested, respectively ($p < 0.001$ for both groups). In the FQ group, 52 (65.8%) patients experienced clinical improvement of symptoms (40 patients), CXR findings (19 patients) or laboratory data (14 patients) within 4 days after empiric FQ use on average (range: 1 – 14 days).

Of the 12 patients in the FQ group who died of TB (Table 2), the cause of death was septic shock without any bacteriologic evidence other than *M. tuberculosis* infection in 8, and respiratory failure due to extensive pulmonary inflammation in 3

and sputum impaction in the remaining one. No events of sudden death due to prolongation of the corrected QT interval (QTc) were noted. In the other two groups, fifteen patients died of septic shock without any evidence of concomitant bacterial infection other than *M. tuberculosis*. Another 8 patients in the other two groups died of respiratory failure, with 7 due to severe caseous pneumonia and 1 due to sputum impaction. A total of 45 patients, including 13 in the FQ group, 30 in the AB group, and 2 in the control group, died within 3 months after initial visit. At the terminal stage, ciprofloxacin-resistant bacteria were isolated in 8 (61.5%), 8 (26.7%), and 1 (50.0%) of the three groups, respectively ($p = 0.090$). Among them, multidrug resistant (MDR) *Pseudomonas aeruginosa* or *Acinetobacter baumannii*, defined as resistance to ≥ 2 classes of anti-pseudomonal agents,[14] were isolated in 4, 2, and 1, respectively ($p = 0.052$). One patient in the FQ group, two in the non-FQ antibiotic group, and 5 in the no antibiotic group died after TB was completely treated.

In order to identify factors which could be associated with the obvious different prognosis among the three groups, survival analysis was performed on the 11 variables with significant inter-group differences, as well as the factor "empiric antibiotic use" itself. Multivariate survival analysis for the 548 patients revealed that the poor prognostic factors including empiric FQ use (HR: 2.39 [1.20 – 4.76]), age > 65 (HR: 4.13 [2.3 – 7.42]), presence of underlying disease (HR: 2.79 [1.61 – 4.84]), serum albumin level < 3.5 g/dL (HR: 3.14 [1.73 – 5.71]), and lack of anti-tuberculous treatment within 14 days after initial visit (HR: 2.04 [1.18 – 3.57]). Because a patient with underlying disease is more likely to have a low level of serum albumin and empiric treatment with a FQ is more likely for an acute illness, we then excluded this subgroup and analyzed the prognostic impact of empiric antibiotic use in the 318 patients without underlying disease (Table 3). From table 2, it appears that empiric antibiotic use (including FQs and non-FQ antibiotics) is associated with increased mortality in univariate analysis but that after adjustment for confounders, the effect of non-FQ antibiotics is not significantly different from no antibiotics, whereas the increased mortality with respect to FQs remains strong and significant. Other independent poor prognostic factors included age > 65, hypoalbuminemia, and lack of early anti-tuberculous treatment.

DISCUSSION

Our findings confirmed the important practical concern that the empiric antibiotic use, especially fluoroquinolones, for presumed bacterial infection could delay the treatment for TB, especially in patients with smear-negative specimens.[7 15-18] Our results also showed that patients who received a FQ, but not non-FQ antibiotics, prior to the standard anti-tuberculous treatment had poor prognosis, most likely due to the emergence of drug-resistant bacteria and the association with aging, underlying disease, malnutrition, and delayed treatment. With empiric FQ use for 1-3 weeks, 11.1% of the *M. tuberculosis* isolates become ofloxacin-resistant.

In the study conducted in Baltimore, where the incidence of TB is relative low, empiric FQ use was given in 16 TB patients within 40 months, and was associated with a significant delay in the anti-tuberculous treatment (21 days *vs*. 5 days).[7] Though the proportion of TB patients who received FQs in our study was less than that in Baltimore (14.4% *vs*. 48%), our study showed that the impact of widespread FQ use was greater in an endemic area of TB, since there were 79 TB patients within 18 months receiving empiric FQ therapy who were significantly delayed treated (Table 2). Most of this delay occurred from the time that the bacteriologic tests were ordered until the anti-tuberculous medications were started. Yet the time required for the mycobacterial isolates to grow was similar for the three groups. The proportion of patients who received TB study at initial visit was not significantly different, but the time from initial visit to ordering TB studies was significantly longer in the FQ group. Two reasons were probably responsible for these findings. First, with the excellent in vivo activity of FQs against *M. tuberculosis*,[5 6] about two third of our TB patients who had received a FQ had clinical improvement. For them, laboratory studies for TB were often not ordered until a later date (17.5 vs. 11.4 day, though statistically insignificant). Even if they were performed, with a partly improved clinical course and low index of suspicion, anti-tuberculous treatment would not be started until culture became positive and *M. tuberculosis* was identified. Second, more patients receiving a FQ were elderly and hypoalbuminemic, and had underlying co-morbid conditions, implying poor general condition. They might be too weak to expectorate adequate sputum specimens for TB studies. This could lead to low smear-positive rate and delayed treatment in the FQ group.

Our analysis revealed that empiric FQ use itself was independently associated with poor prognosis, most likely due to the emergence of the ciprofloxacin-resistant isolates and MDR *P. aeruginosa* or *A. baumannii*, which had been documented to increase the infection-related mortality and deteriorate the survival.[14 19] In addition, inappropriate use of FQs can result in the development of FQ resistance in *M. tuberculosis*.[20-22] Although we were unable to verify the previous medication history, our finding was consistent with the case reported by Ginsburg *et al* who described that FQ resistance can develop after only 13 days of exposure, and suggested that the mycobacterial resistance to FQ could potentially occur during the short treatment course for a common bacterial infection. The treatment delay resulted from empiric FQ use further increased the morbidity and deteriorated the survival of TB patients.[23-25] In consistent with previous study,[10] our survival analysis revealed that the mortality of TB was significantly affected by the presence of conditions that would alter cell-mediated immunity, including aging,[26] underlying systemic diseases such as diabetes mellitus,[27] malignancy,[28] and chronic renal insufficiency,[29] and low serum albumin level,[30] further emphasizing the importance of cell-mediated immunity in the defense from TB infection.

We also found that empiric use of non-FQ antibiotics was associated with a delay in anti-TB treatment, but not ordering TB studies, suggesting that the delay was due to the time inherent in taking a course of antibiotics and waiting to see if there is a clinical response.[18] Like patients in the FQ group, those in the non-FQ antibiotic group were older and poorer nourished, more often had underlying diseases, presented acutely with constitutional symptoms and lower-lobe infiltrates (Table 1) than those who had no previous antibiotics. Thus they tended to have an initial diagnosis of acute pneumonia, which contributed to the delay of anti-tuberculous treatment. Yet the delay in this group was less in magnitude, compared with the FQ group, probably because the progressively deteriorating disease raised the suspicion of tuberculosis and prompted the anti-tuberculous therapy. Patients in the FQ group, on the other hand, could become improved with the use of FQ, which masked the presence of TB and markedly delayed the diagnosis. Although patients in the FQ and non-FQ antibiotic group were similar in being old, malnourished with underlying disease, those in the non-FQ group who died tended to die earlier than in the FQ group (Table 2), probably because the bactericidal effect of the FQ on *M. tuberculosis* partially alleviated the progression and prevented early mortality.

Our study was limited by the possible bias in patient selection because the study was conducted in a tertiary-care referral center and only culture-confirmed cases of TB were included. Another major limitation was the unavailability of the previous medication history since most of the patients without empiric FQ use could possibly have received FQs before coming to our hospital. However, our analysis showed that the widespread use of FQs for the treatment of bacterial infection had resulted in delay in the treatment of TB and a worse outcome in endemic area. Our data revealed that 14.4% of our TB patients received FQs prior to the diagnosis of TB. By causing the emergence of resistant bacteria, a significant delay in the initiation of anti-tuberculous treatment, and associating with conditions that compromise cellular immunity, empiric FQ use in TB patients was associated with poor outcome. In addition, the *M. tuberculosis* isolates could obtain ofloxacin-resistance within merely one week. Therefore in endemic area of TB, a high index of suspicion is required. *M. tuberculosis* should be considered as a possible causative pathogen in every infectious disease whether clinical improvement is noted after the use of a FQ or not, and appropriate bacteriologic and histopathologic studies for TB should be performed as early as possible.

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Table 1. Characteristics of the 548 patients with culture-confirmed tuberculosis

Characteristic	Empiric antibiotic use		
	FQ (*n* = 79)	Others (*n* = 218)	No (*n* = 251)
Age > 65 years	42 (53.2%)†	133 (61.0%)‡	79 (31.5%)
Male sex	49 (62.0%)	150 (68.8%)	163 (64.9%)
Underlying disease	42 (53.2%)†	102 (46.8%)‡	86 (34.3%)
Diabetes mellitus	20 (25.3%)	51 (23.4%)	50 (19.9%)
Malignancy	13 (16.5%)	29 (13.3%)	24 (9.6%)
Chronic renal insufficiency*	8 (10.1%)	30 (13.8%)	7 (2.8%)
Receiving steroid	5 (6.3%)	6 (2.8%)	11 (4.4%)
AIDS	5 (6.3%)	10 (4.6%)	5 (2.0%)
Liver cirrhosis	2 (2.5%)	5 (2.3%)	6 (2.4%)
Alcoholism	0	1 (0.5%)	3 (1.2%)
Smoking			
Current smoker	17 (21.5%)	62 (28.4%)	72 (28.3%)
Ex-smoker	14 (17.7%)	27 (12.4%)	25 (10.0%)
Extrapulmonary TB	20 (25.3%)	72 (33.0%)‡	43 (17.1%)
TB pleurisy or peritonitis	11 (13.9%)	43 (19.7%)	22 (8.8%)
Musculo-skeletal TB	4 (5.1%)	9 (4.1%)	7 (2.8%)
TB lymphadenopathy	0 (0%)	6 (2.8%)	8 (3.2%)
Urogenital TB	1 (1.3%)	10 (4.6%)	3 (1.2%)
TB meningitis	1 (1.3%)	1 (0.5%)	3 (1.2%)
Disseminated TB	3 (3.8%)	3 (1.4%)	0
Symptom at presentation			
Respiratory symptoms	52 (65.8%)	127 (58.3%)‡	177 (70.5%)
Constitutional symptoms	41 (51.9%)†	103 (47.2%)‡	60 (23.9%)
CNS symptoms	4 (5.1%)	14 (6.4%)	7 (2.8%)
Neck mass	0	5 (2.3%)	6 (2.4%)
Dysuria	0	3 (1.4%)	2 (0.8%)
Musculo-skeletal symptoms	2 (2.5%)	5 (2.3%)	6 (2.4%)
Abdominal symptoms	2 (2.5%)	10 (4.6%)	8 (3.2%)
No (incidental finding)	4 (5.1%)	17 (7.8%)	29 (11.6%)
Symptom > 14 days	46 (58.2%)†	122 (56.0%)‡	193 (76.9%)
Ordering CXR at initial visit in PTB	69 (87.3%)	174 (79.8%)	194 (77.3%)
CXR finding			
Pattern			
Fibronodular infiltrates	25 (31.6%)	66 (30.3%)	84 (33.5%)
Alveolar consolidation	33 (41.8%)	86 (39.4%)	77 (30.7%)

Multiple nodules or mass	9 (11.4%)	20 (9.2%)	44 (17.5%)
Fibrotic change	5 (6.3%)	15 (6.9%)	12 (4.8%)
Miliary shadowing	1 (1.3%)	8 (3.7%)	10 (4.0%)
No parenchymal lesion	6 (7.6%)	23 (10.6%)	24 (9.6%)
Lower-lung-field TB	18 (22.8%)	47 (21.6%)‡	36 (14.3%)
Cavity	9 (11.4%)	21 (9.6%)‡	43 (17.1%)
Albumin (g/dL)			
< 35 / ≥ 35	43 (67.2%) / 21†	113 (64.9%) / 61‡	54 (35.1%) / 100
Mean (SD)	31.7 (6.2)†	32.2 (6.1)‡	37.4 (6.4)
Sputum AFS(+) in PTB	8 (12.1%)#†	53 (24.3%)	65 (25.9%)
Anyone-drug resistance	20 (25.3%)	48 (22.0%)	73 (29.1%)
Multidrug resistance	10 (12.7%)	17 (7.8%)	29 (11.6%)

AFS = acid-fast smear; AIDS = acquired immunodeficiency syndrome; CNS = central nervous system; CXR = chest radiograph; PTB = pulmonary tuberculosis; TB = tuberculosis;

* Chronic renal insufficiency was defined as a serum creatinine level > 20 mg/L.[12]

# $p < 0.05$ for comparing FQ group and other antibiotic group.

† $p < 0.05$ for comparing FQ group and no antibiotic group.

‡ $p < 0.05$ for comparing other antibiotic group and no antibiotic group.

Table 2 Management and outcome

Characteristic	Empiric antibiotic use			
	FQ (*n* = 79)	FQ, no underlying disease (*n* = 37)	Others (*n* = 218)	No (*n* = 251)
Initial visit to ordering TB studies (days)*	6 (0 – 173)#†	6 (1 – 173)	5 (0 – 163)	5 (0 – 272)
AFS (+) (*n* = 126)	9 (1 – 173)	4 (1 – 173)	3 (0 – 78)	3 (0 – 112)
AFS (-) (*n* = 422)	6 (0 – 159)	6 (1 – 61)	5 (0 – 163)	5 (0 – 272)
TB study to anti-TB treatment (days)*	25 (-3 – 231)#†	31 (-3 – 73)	7 (-35 – 143)‡	0 (-114 – 146)
AFS (+) (*n* = 123)	5 (1 – 21)†	4 (2 – 9)	2 (-16 – 98)‡	-1 (-35 – 55)
AFS (-) (*n* = 363)	31 (-3 – 231)#†	33 (-3 – 73)	16 (-35 – 143)‡	1 (-114 – 146)
Initial visit to anti-TB treatment (days)*	41 (6 – 233)#†	38 (6 – 175)	16 (0 – 198)‡	7 (0 – 286)
AFS (+) (*n* = 123)	15 (8 – 175)#†	10 (8 – 175)	6 (0 – 105)‡	3 (0 – 123)
AFS (-) (*n* = 363)	42 (6 – 233)#†	39 (6 – 96)	27 (0 – 198)‡	13 (0 – 286)
Ordering TB study at initial visit	53 (67.1%)	26 (70.3%)	163 (74.8%)	179 (71.3%)
TB study to identification available (days)*	63 (37 – 85)	64 (55 – 82)	62 (36 – 92)	62 (35 – 121)
AFS (+) (*n* = 126)	63 (57 – 73)	60 (57 – 62)	63 (36 – 78)	63 (50 – 77)
AFS (-) (*n* = 422)	63 (37 – 85)	64 (55 – 82)	62 (54 – 92)	62 (35 – 121)
Outcome	†		‡	
Completed treat	41 (51.9%)	23 (62.2%)	133 (61.0%)	198 (78.9%)
Ongoing treat	0	0	1 (0.5%)	4 (1.6%)
Not treated	2 (2.5%)	2 (5.4%)	5 (2.3%)	1 (0.4%)
Loss	13 (16.5%)	7 (18.9%)	34 (15.6%)	33 (13.1%)
Mortality	23 (29.1%)	5 (13.5%)	45 (20.6%)	15 (6.0%)
Die of TB	12	3	22	1
Die with TB	11	2	23	14
Survival (days)*	85.5 (18 – 448)†	59 (26 – 448)	55 (1 – 708)‡	249 (23 – 902)

AFS = acid-fast smear; TB = tuberculosis;

* noted as "median (range)".

# $p < 0.05$ for comparing FQ group and other antibiotic group.

† $p < 0.05$ for comparing FQ group and no antibiotic group.

‡ $p < 0.05$ for comparing other antibiotic group and no antibiotic group.

Table 3. Survival analysis for the 318 patients who did not have underlying disease

	Patient No.	Mortality (%)	Hazard ratio	
			univariate	multivariate*
Empiric antibiotic use				
Fluoroquinolone	37	5 (13.5%)	6.88 (1.84 – 25.72)	4.22 (1.01 – 11.82)
Others	116	14 (12.1%)	5.19 (1.71 – 15.79)	1.36 (0.33 – 5.56)
No	165	4 (2.4%)		
Age				
> 65 years	131	19 (14.5%)	7.08 (2.41 – 20.81)	6.43 (1.37 – 30.29)
≤ 65 years	187	4 (2.1%)		
Involvement of tuberculosis				
Extrapulmonary	81	8 (9.9%)	1.38 (0.58 – 3.26)	
Pure pulmonary	237	15 (6.3%)		
Respiratory symptoms				
Yes	224	10 (4.5%)	0.34 (0.15 – 0.77)	0.66 (0.20 – 2.16)
No	94	13 (13.8%)		
Constitutional symptoms				
Yes	105	12 (11.4%)	2.25 (0.99 – 5.10)	
No	213	11 (5.2%)		
Duration of symptoms				
> 14 days	217	10 (4.6%)	0.31 (0.13 – 0.70)	0.74 (0.26 – 2.10)
≤ 14 days	101	13 (12.9%)		
Lower-lung-field tuberculosis				
Yes	61	4 (6.6%)	0.89 (0.30 – 2.62)	
No	257	19 (7.4%)		
Cavity on chest radiograph				
Yes	42	3 (7.1%)	1.03 (0.31 – 3.47)	
No	276	20 (7.2%)		
Albumin (g/dL)				
< 35	76	15 (19.7%)	15.07 (3.44 – 66.05)	8.85 (1.96 – 39.94)
≥ 35	119	2 (1.7%)		
Sputum acid-fast smear				
positive	61	2 (3.3%)	0.38 (0.09 – 1.64)	
Negative	257	21 (8.2%)		
Anti-tuberculous treatment				
≤ 14 days after initial visit	162	7 (4.3%)	0.37 (0.15 – 0.91)	0.70 (0.51 – 0.97)
> 14 days after initial visit	156	16 (10.3%)		

* Multivariate survival analysis was performed for the 195 patients with complete data.