http://dx.doi.org/10.5588/ijtld.15.0607

Clinical and molecular epidemiological features of tuberculosis after the 2011 Japan earthquake and tsunami

H. Kanamori,*†‡ T. Hatakeyama,§ B. Uchiyama,* D. J. Weber,‡ M. Takeuchi,* S. Endo,† Y. Hirakata,* M. Kaku†

***Miyagi Cardiovascular and Respiratory Center, Kurihara, Miyagi, †Department of Infection Control and Laboratory Diagnostics, Internal Medicine, Tohoku University Graduate School of Medicine, Sendai, Miyagi, Japan; ‡Division of Infectious Diseases, University of North Carolina School of Medicine, Chapel Hill, North Carolina, USA; §Department of Microbiology, Miyagi Prefectural Institute of Public Health and Environment, Sendai, Miyagi, Japan**

OBJECTIVE: To investigate clinical characteristics and prognosis in tuberculosis (TB) patients and the transmission dynamics of TB after the 2011 Japan earthquake and tsunami.

METHOD: This was a retrospective observational cohort study. Data were analyzed among 93 pulmonary TB patients (tsunami-affected areas 25, non-tsunami areas 68) hospitalized during March 2011–March 2012 with 1-year follow-up since treatment commencement. Variable number of tandem repeats (VNTR) typing was conducted for 38 TB strains (tsunami-affected areas 21, non-tsunami areas 17).

RESULTS: Patients from tsunami-affected areas were significantly more likely to be refugees (OR 12.8, 95%CI 2.45–67.20), receive oxygenation (OR 5.0, 95%CI 1.68–14.85), and have a unique VNTR (OR 4.6, 95%CI 1.14–18.41). Patients who died within 1 year were significantly more likely to be older (OR 9.8, 95%CI 1.85–180.26), partially dependent or dependent (OR 11.9, 95%CI 4.28–37.62), and to require oxygenation (OR 4.3, 95%CI 1.47–12.89), and had lower serum albumin levels (OR 11.1, 95%CI 2.97–72.32).

CONCLUSION: Risk factors for prognosis of TB after the earthquake were associated with advanced age, low serum albumin level, functional status at admission, and oxygen requirement. The VNTR results suggest that most of the cases with pulmonary TB experienced reactivation of latent tuberculous infection, likely due to the impact of the earthquake and tsunami.

KEY WORDS: disasters; clinical features; molecular epidemiology; risk factors; reactivation

MANY CRISES caused by natural disasters, armed conflict, or forced population displacement occur in areas or countries with a substantial tuberculosis (TB) burden.[1] TB is a leading health threat for populations affected by these crises, and people who are displaced after natural disasters are vulnerable to TB.[1,2] In the aftermath of the 2011 Great East Japan Earthquake, the occurrence and outbreaks of infectious diseases, including acute respiratory syndrome, influenza, norovirus gastroenteritis, legionellosis, and tetanus, were reported.[3] The occurrence of TB after the Japan earthquake was sporadic,[4] and the notification rates of TB disease after the Japan earthquake in the short term in the affected areas have been largely unchanged.[5] However, the clinical features of TB in the affected population and the impact of the Japan earthquake on TB transmission remains unclear. Although an industrialised country, Japan remains one of the middle TB burden countries. More generally, there is a lack of evidence regarding the TB burden after natural disasters, especially in industrialised countries with a low to middle TB burden. Crisis-associated risk factors, including malnutrition, overcrowding, disruption of health services, and human immunodeficiency virus (HIV) co-infection, could affect the incidence of new TB disease, reactivation of latent tuberculous infection (LTBI), and relapse of previously treated TB, thus increasing TB transmission and disease progression in both the short-term and long-term.[1]

In the present study, we investigated the clinical characteristics and prognosis of pulmonary TB (PTB) patients who were hospitalized after the earthquake and were followed until treatment completion after discharge. We also examined the transmission dynamics of TB strains after the Japan earthquake using molecular typing.

Correspondence to: Hajime Kanamori, Hospital Epidemiology, University of North Carolina Health Care, 1001 West Wing CB #7600, 101 Manning Drive, Chapel Hill, NC 27514, USA. Fax: (+1) 919 966 1451. e-mail: kanamori@med.unc.edu

Article submitted 12 July 2015. Final version accepted 25 October 2015.

MATERIALS AND METHODS

Miyagi Prefecture, in the Tohoku region of Japan, was the area most devastated by the 2011 earthquake, and the coastal area was heavily damaged by the subsequent tsunami. The Miyagi Cardiovascular and Respiratory Center (MCRC), a hospital with a 50-bed TB ward and a medical institution designated for TB in the Miyagi Prefecture, was also damaged,[6] but received the majority of hospitalized TB patients in the Miyagi Prefecture. TB patients from both coastal and inland areas throughout the prefecture after the Japan earthquake were referred to the MCRC and placed in a negative-pressure single room. Both tsunami-affected areas (Ishinomaki, Kesennuma, and Shiogama) and non-tsunami areas were determined based on maps of the area hit by the tsunami of 11 March 2011, which were provided by the Association of Japanese Geographers (Tokyo, Japan);[7] only TB patients from tsunami-affected areas were assigned to the tsunami group.

This was a retrospective observational cohort study. A total of 93 PTB patients (25 cases in the tsunami group and 68 cases in the non-tsunami group), including 84 sputum smear-positive cases, hospitalized during the 1-year period after the earthquake from 11 March 2011 to 31 March 2012, were analyzed using hospital databases and medical records. Laboratory examinations and chest radiography on admission were also evaluated. Data before admission and after discharge were collected from local public health centers. Sputum smear, sputum culture, and polymerase chain reaction (PCR) were performed following admission to diagnose *Mycobacterium tuberculosis*. Drug susceptibility testing (DST) was performed for eight drugs, including first- and second-line drugs. Functional status at admission was classified into three categories, 'independent,' 'partially dependent,' or 'dependent.' Delays in case finding were defined as follows: patient delay—the period between the time of symptom onset and the time of first visit to a medical institution; physician delay—the period between the time of first visit to a medical institution and the time of registration; and total delay—the period between the time of symptom onset and the time of registration. Patients were empirically treated with a regimen of isoniazid (INH), rifampin (RMP), and either ethambutol (EMB) or streptomycin (SM), with or without pyrazinamide (PZA). Other regimens were used for TB patients who developed adverse drug reactions, did not respond to initial treatment, or had drug resistance. Patients were discharged after sputum smears were repeatedly negative for acid-fast bacilli (AFB). Patients were followed up and continued to receive directly observed therapy (DOT) at regional out-patient clinics with the support of the public health centers. The treatment outcomes of the patients were evaluated within 1 year after treatment commencement.

Deletion targeted PCR was performed to identify strains in the Beijing or non-Beijing family.[8] Variable number of tandem repeats (VNTR) typing was conducted for 38 isolates available from 93 hospitalized PTB patients to assess the allelic profiles of TB strains after the earthquake. Tandem repeats, about 40–100 base pair (bp) DNA elements, are dispersed in the intergenic regions of the *M. tuberculosis* complex genome and evolve slowly in mycobacterial populations.[9] VNTR analysis was performed using 19 primers distinguishable within isolates belonging to the Beijing family (only 19/24 loci assessed), including 15 primers from the Japan Anti-Tuberculosis Association (JATA, Tokyo, Japan) (Mtub04, MIRU10, Mtub21, Mtub24, QUB11b, VNTR2372, MIRU26, QUB15, MIRU31, QUB3336, QUB26, QUB4156, VNTR1982, VNTR2163a, and ETR-A), obtained from the Research Institute of Tuberculosis,[10] and four primers (MIRU16, 23, 39, and 40) previously described by Supply et al.[11] Allele profiles were determined based on the size of the amplified products by each primer and were considered to have an identical genotype if their alleles matched at 18 loci or more.[12,13] The VNTR database in the Miyagi Prefecture from 2004 to 2011 was used for the comparison of VNTR results in this study. A geographic map was generated using MANDARA version 9.40, a geographic information system software (Figure).

Statistical significance was evaluated by the two-tailed Fisher's test or the χ^2 test according to sample size, and the Student's *t*-test was used for continuous variables. $P < 0.05$ was considered significant. Risk factors for the prognosis of TB patients were examined with the use of univariate and multivariate logistic regression. Factors with $P < 0.05$ in the univariate analysis, including age, functional status at admission, oxygen requirement on admission, and albumin level, were included in the multivariate analysis. All data were analyzed using JMP® 11 (Statistical Analysis System, Cary, NC, USA).

The study was approved by the ethics committee of the MCRC, Kurihara, Japan.

RESULTS

The clinical characteristics of 93 hospitalized PTB patients from tsunami-affected and non-tsunami areas after the Japan earthquake are summarized in Table 1. Nine (9.7%) persons had been forced to live in shelters, public or temporary housing before admission, and patients in the tsunami group were significantly more likely to have experienced living as a refugee (odds ratio [OR] 12.8, 95% confidence interval [CI] 2.45–67.20). Seventy-eight (83.9%) patients reported respiratory symptoms and 87

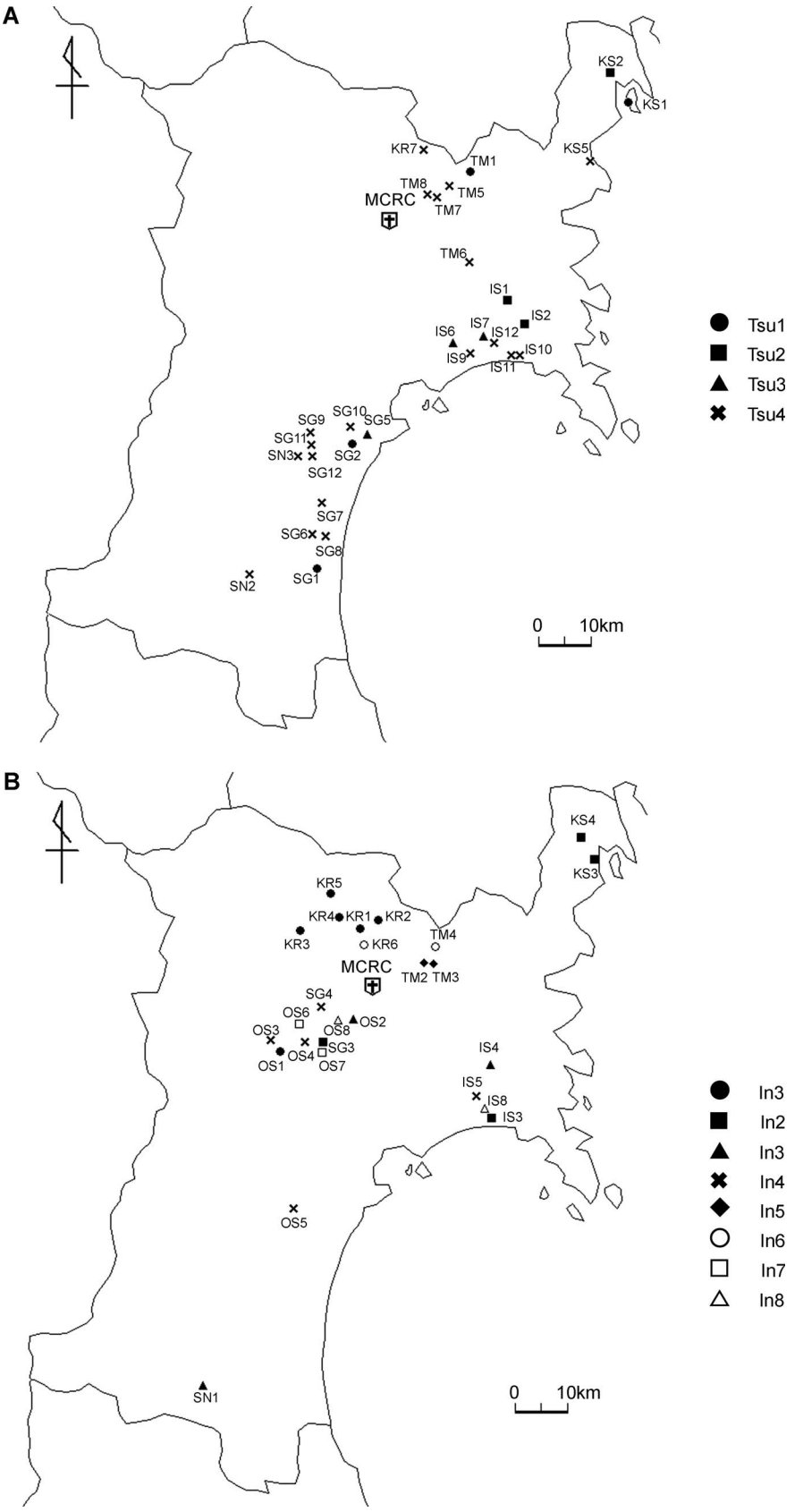

Figure Geographic distribution of tuberculosis using VNTR in **A)** tsunami-affected areas and **B)** inland areas of the Miyagi Prefecture after the 2011 Great East Japan Earthquake, showing the geographic areas of the patients in each cluster. Of the clustered cases, 15 strains from this study and 40 strains from the existing VNTR database in the Miyagi Prefecture during 2004–2011 are shown. Each case in this map corresponds to a case described in Table 5. MCRC = Miyagi Cardiovascular and Respiratory Center; Tsu = clustered cases in tsunami-affected areas; In = clustered cases in inland areas (non-tsunami areas); VNTR = variable number of tandem repeats.

Table 1 Clinical characteristics of hospitalized patients with pulmonary tuberculosis after the 2011 Great East Japan Earthquake

	Overall ($n = 93$)	Tsunami group ($n = 25$)	Non-tsunami group ($n = 68$)	OR (95%CI)	*P* value
Age, years, mean ± SD	72.9 ± 17.96	77.0 ± 17.01	71.5 ± 18.19		0.193
Sex					
Female*	37	14	23	1	
Male	56	11	45	0.4 (0.16–1.02)	0.061
Nationality					
Japanese*	92	24	68	1	
Foreign	1	1	0	NA	0.269
Case finding					
Health examination*	8	1	7	1	
Clinics/hospitals	85	24	61	2.8 (0.32–23.59)	0.678
Shelter, public or temporary housing					
No*	84	18	66	1	
Yes	9	7	2	12.8 (2.45–67.20)	0.001
Symptoms in case finding					
Respiratory symptoms					
No*	15	3	12	1	
Yes	78	22	56	1.6 (0.40–6.11)	0.752
Any symptoms					
No*	6	1	5	1	
Yes	87	24	63	1.9 (0.21–17.16)	1
Source of infection known					
No*	86	25	61	1	
Yes	7	0	7	0	0.183
Comorbid conditions					
Malignancy					
No*	70	18	52	1	
Yes	23	7	16	1.3 (0.45–3.57)	0.787
Diabetes					
No*	75	22	53	1	
Yes	18	3	15	0.5 (0.13–1.83)	0.380
Cardiac disease					
No*	73	18	55	1	
Yes	20	7	13	1.7 (0.57–4.76)	0.398
Extra-pulmonary tuberculosis					
No*	73	19	54	1	
Yes	20	6	14	1.2 (0.41–3.62)	0.778
Functional status at admission					
Independent*	57	13	44	1	
Partially dependent or dependent	36	12	24	1.7 (0.67–4.29)	0.338
Oxygen requirement on admission					
No*	75	15	60	1	
Yes	18	10	8	5 (1.68–14.85)	0.006
Sputum smear					
Negative*	9	2	7	1	
Positive	84	23	61	1.3 (0.26–6.82)	1
Chest X-ray					
Bilateral					
No*	32	10	22	1	
Yes	61	15	46	0.7 (0.28–1.85)	0.623
Cavity					
No*	64	19	45	1	
Yes	29	6	23	0.6 (0.22–1.76)	0.454
BMI, kg/m^2, mean ± SD ($n = 82$)	19.4 ± 3.13	19.8 ± 3.90	19.3 ± 2.88		0.579
Albumin, g/dl, mean ± SD	3.2 ± 0.83	2.9 ± 0.95	3.3 ± 0.75		0.034
Aspartate aminotransferase, U/l, mean ± SD	33.2 ± 25.23	35.0 ± 28.37	32.6 ± 24.17		0.685
BUN/creatinine ratio, mean ± SD	24.3 ± 9.93	26.9 ± 10.40	23.3 ± 9.65		0.120
CRP, mg/dl, mean ± SD (24 vs. 67, $n = 91$)	4.9 ± 5.15	5.8 ± 5.90	4.6 ± 4.85		0.293
Hemoglobin, g/dl, mean ± SD	12.0 ± 1.82	11.7 ± 1.75	12.1 ± 1.85		0.403
White blood cell count, /μl, mean ± SD	6990 ± 2865.8	6496 ± 1976.6	7172 ± 3123.0		0.316
Neutrophil count, /μl, mean ± SD (25 vs. 67, $n = 92$)	5343 ± 2150.0	5222 ± 2032.9	5387 ± 2205.3		0.745
Lymphocyte count, /μl, mean ± SD (25 vs. 67, $n = 92$)	1140 ± 1280.2	876 ± 519.3	1239 ± 1457.8		0.228
Platelet count, 10^3 /μl, mean ± SD	261 ± 93.3	230 ± 67.8	272 ± 99.0		0.048
Treatment					
Initial treatment*	79	21	58	1	
Retreatment	14	4	10	1.1 (0.31–3.90)	1

Table 1 (continued)

	Overall ($n = 93$)	Tsunami group ($n = 25$)	Non-tsunami group ($n = 68$)	OR (95%CI)	*P* value
HRZE/S treatment in patients aged <80 years ($n = 49$)					
No*	14	4	10	1	
Yes	35	7	28	0.6 (0.15–2.60)	0.706
Drug resistance ($n = 91$)					
All susceptible*	75	18	57	1	
Resistant to one or more drugs	16	7	9	2.5 (0.80–7.56)	0.129
Outcome in hospital					
Hospital days	59.3 ± 31.27	54.4 ± 24.21	61.1 ± 33.48		0.364
Discharged alive*	84	22	62	1	
Died in hospital	9	3	6	1.5 (0.32–6.12)	0.698
Outcome on directly observed therapy					
Completed alive*	66	16	50	1	
Died within 1 year	27	9	18	1.6 (0.59–4.16)	0.442
VNTR ($n = 38$)					
Cluster*	15	5	10	1	
Unique	23	16	7	4.6 (1.14–18.41)	0.046

* Referent group.
OR = odds ratio; CI = confidence interval; SD = standard deviation; NA = not available; BMI = body mass index; BUN = blood urea nitrogen; CRP = C reactive protein; H = isoniazid; R = rifampin; Z = pyrazinamide; E = ethambutol; S = streptomycin; VNTR = variable number of tandem repeats.

(93.5%) reported any symptoms. Comorbidities included 23 (24.7%) cases with malignancy, 20 (21.5%) cases with cardiac disease, and 18 (19.4%) cases with diabetes mellitus. No case with human immunodeficiency virus (HIV) infection was reported. Thirty-six patients (38.7%) were classified as 'partially dependent' or 'dependent' functional status at admission. Oxygenation was required for 18 (19.4%) patients on admission; patients in the tsunami group were significantly more likely to need oxygenation due to respiratory failure (OR 5.0, 95%CI 1.68–14.85). Chest radiography showed bilateral infiltration in 61 (65.6%) cases and cavitation in 29 (31.2%) cases. Serum albumin in patients from tsunami-affected areas was significantly lower than in patients from non-tsunami-affected areas ($P = 0.034$). Of the 91 isolates available for DST, 16 (17.6%) demonstrated resistance to ⩾1 drug and patients were treated based on DST results. One (1.1%) strain showed multidrug-resistant TB (MDR-TB), and one (1.1%) strain demonstrated extensively drug-resistant TB (XDR-TB). Patients in the tsunami group were significantly more likely to be unique on VNTR (OR 4.6, 95%CI 1.14–18.41). Of the 93 patients, respectively 9 (9.7%) and 27 (29.0%) died in hospital or within 1 year after treatment began. The mortality rates for the tsunami vs. the non-tsunami group both in hospital (OR 1.4, 95%CI 0.32–6.12) and at year 1 (OR 1.6, 95%CI 0.59–4.16) were higher, but the difference did not reach statistical significance.

Patients who died within 1 year after beginning treatment were significantly more likely to be older (OR 9.8, 95%CI 1.85–180.26), partially dependent or dependent on admission (OR 11.9, 95%CI 4.28–37.62), and to require oxygenation on admission (OR 4.3, 95%CI 1.47–12.89) (Table 2). Four (44.4%) of the nine persons who were forced to live in shelters, public or temporary housing died. Three (8.6%) of the 35 patients aged <80 years who were treated with INH, RMP, PZA, and either EMB or SM died; 6 (42.9%) of the 14 patients who were treated without PZA died (OR 0.13, 95%CI 0.02–0.58). Laboratory data on admission from patients who died showed that the albumin level was significantly lower (OR 11.1, 95%CI 2.97–72.32), whereas the blood urea nitrogen/creatinine ratio tended to be higher. Multivariate logistic regression analysis indicated that functional status at admission (dependent) and albumin level (<2.1 g/dl) were independent predictors for the prognosis of hospitalized patients with PTB (Table 3).

The frequency of patients aged ⩾65 years in this study was 79.6%; in addition, these patients were significantly more likely to be older (OR 2.5, 95%CI 1.53–4.19) than subjects in the national database (Table 4). There was a significant delay in case finding (⩾2 months) between symptom onset and first visit to a medical institution (OR 1.7, 95%CI 1.04–2.89), but there was no significant delay (⩾1 month) between first visit to a medical institution and diagnosis, compared with the national data. In this study, 41/70 patients (58.6%) who were newly registered smear-positive cases successfully completed DOT, but 18/70 patients (25.7%) died within 1 year after treatment started.

All of the 38 isolates analyzed in this study were assigned to the Beijing family. Of the 38 isolates, 15 (39.5%) were classified into 12 clustered VNTR patterns (Tsu1-4 and In1-8) using the past database in the Miyagi Prefecture (Table 5, Figure). The remaining 23 isolates (60.5%) exhibited unique VNTR patterns. The cluster sizes ranged from 2 to 19, and identical VNTR patterns ranged from 0 to 7 years.

Table 2 Univariate regression analysis of risk factors for the prognosis of hospitalized patients with pulmonary tuberculosis

Factors on admission	Dead ($n = 27$)	Alive ($n = 66$)	OR (95%CI)	*P* value
Age, years				
<65*	1	18	1	
⩾65	26	48	9.8 (1.85–180.26)	0.004
Sex				
Female*	7	30	1	
Male	20	36	2.4 (0.92–6.77)	0.075
Case finding				
Health examination*	1	7	1	
Clinics/hospitals	26	59	3.1 (0.51–59.17)	0.246
Tsunami-affected area				
No*	18	50	1	
Yes	9	16	1.6 (0.57–4.13)	0.375
Shelter, public or temporary housing				
No*	23	61	1	
Yes	4	5	2.1 (0.49–8.71)	0.301
Symptoms in case finding				
Respiratory symptoms				
No*	5	10	1	
Yes	22	56	0.8 (0.25–2.76)	0.692
Any symptoms				
No*	1	5	1	
Yes	26	61	2.1 (0.32–41.87)	0.468
Source of infection known				
No*	25	61	1	
Yes	2	5	1.0 (0.13–4.86)	0.978
Comorbid conditions				
Malignancy				
No*	18	52	1	
Yes	9	14	1.9 (0.67–5.01)	0.227
Diabetes				
No*	19	56	1	
Yes	8	10	2.4 (0.80–6.88)	0.119
Cardiac diseases				
No*	18	55	1	
Yes	9	11	2.5 (0.88–7.04)	0.084
Extra-pulmonary tuberculosis				
No*	19	54	1	
Yes	8	12	1.9 (0.66–5.32)	0.233
Functional status at admission				
Independent*	6	51	1	
Partially dependent or dependent	21	15	11.9 (4.28–37.62)	<0.0001
Oxygen requirement on admission				
No*	17	58	1	
Yes	10	8	4.3 (1.47–12.89)	0.008
Sputum smear				
Negative*	4	5	1	
Positive	23	61	0.5 (0.12–2.05)	0.301
Chest X-ray				
Bilateral				
No*	6	26	1	
Yes	21	40	2.3 (0.85–6.88)	0.105
Cavity				
No*	21	43	1	
Yes	6	23	0.5 (0.18–1.45)	0.224
BMI, kg/m^2 ($n = 82$)				
⩾18.5*	12	37	1	
<18.5	8	25	1.0 (0.34–2.74)	0.980
Albumin, g/dl				
⩾3.5*	2	31	1	
<3.5	25	35	11.071 (2.966–72.315)	<0.0001
BUN/creatinine ratio				
⩽20*	8	33	1	
>20	19	33	2.375 (0.937–6.465)	0.069

Table 2 (continued)

Factors on admission	Dead ($n = 27$)	Alive ($n = 66$)	OR (95%CI)	*P* value
Treatment				
Initial treatment*	22	57	1	
Retreatment	5	9	1.439 (0.405–4.662)	0.557
Drug resistance ($n = 91$)				
All susceptible* ($n = 75$)	21	54	1	
Resistant to one or more drugs ($n = 16$)	4	12	0.857 (0.220–2.783)	0.806
HRZE/S treatment in patients aged <80 years ($n = 49$)				
No* ($n = 14$)	6	8	1	
Yes ($n = 35$)	3	32	0.125 (0.022–0.577)	0.008
VNTR ($n = 38$)				
Cluster* ($n = 15$)	5	10	1	
Unique ($n = 23$)	8	15	1.067 (0.272–4.416)	0.927

* Referent group.
OR = odds ratio; CI = confidence interval; BMI = body mass index; BUN = blood urea nitrogen; CRP = C reactive protein; H = isoniazid; R = rifampin; Z = pyrazinamide; E = ethambutol; S = streptomycin; VNTR = variable number of tandem repeats.

Respectively five (SG2, KS2, SG5, SG8, and IS12) and 10 clustered cases lived in tsunami-affected areas and inland areas (non-tsunami-affected areas). OS1 and TM3 were an acquaintance of a family with a history of TB and a neighbor with a history of TB, respectively. Six patients had strains with genotypes identical to strains that had emerged more than 2 years earlier (OS1, KS2, OS2, SN1, OS7, and OS8). Five clustered groups were detected during this study period (a, b, c, d, and e).

DISCUSSION

In this study, older people accounted for most of the TB cases hospitalized after the Japan earthquake and tsunami. Approximately 90% of patients reported symptoms, and approximately 20% had comorbidities such as malignancy, cardiac disease, and/or diabetes. Older PTB patients had fewer clinical symptoms (e.g., fever, sweating, and hemoptysis), worse laboratory data (e.g., serum albumin and blood leukocyte levels), and less typical radiological patterns (e.g., cavities), but had more frequent dyspnea, comorbid conditions, and poor prognosis.[14–16]

Univariate logistic analysis in this investigation revealed that advanced age, lower serum albumin level, poorer functional status at admission, and oxygen requirement were key risk factors for the prognosis of in-patients with PTB; in multivariate logistic analysis, dependent status and severe hypoalbuminemia were strongly prognostic. This finding bolstered the TB prognostic score with four factors—including age, serum albumin level, activity of daily living, and oxygen requirement—among in-patients with smear-positive PTB without MDR-TB or HIV infection, recently developed by Horita et al.[16] Our study showed that older TB patients presented with worse laboratory data on admission (e.g., hypoalbuminemia) from tsunami-affected areas. Hypoalbuminemia was significantly associated with poor

Table 3 Multivariate logistic regression analysis of risk factors for the prognosis of hospitalized patients with pulmonary tuberculosis

Factors on admission	Dead ($n = 27$)	Alive ($n = 66$)	OR (95%CI)	*P* value
Age, years				
<65*	1	18	1	
65–74	3	16	1.5 (0.11–36.49)	0.775
75–84	15	13	3.6 (0.38–79.41)	0.275
⩾85	8	19	0.7 (0.05–18.62)	0.812
Functional status at admission				
Independent*	6	51	1	
Partially dependent	4	10	2.2 (0.32–16.12)	0.428
Dependent	17	5	10.6 (1.50–102.04)	0.017
Oxygen requirement on admission				
No*	17	58	1	
Yes	10	8	1.1 (0.18–5.66)	0.936
Albumin, g/dl				
⩾3.5*	2	31	1	
2.8–3.4	7	22	1.7 (0.20–15.71)	0.626
2.1–2.7	9	13	3.5 (0.39–38.44)	0.260
<2.1	9	0	55 896 398 (4.36–)	0.004

* Referent group.
OR = odds ratio; CI = confidence interval.

Table 4 Delay in case finding before admission and outcome of DOT after discharge among patients with pulmonary tuberculosis

	This study *n/N* (%)	Overall Japan in 2011 (reference)* *n/N* (%)	OR (95%CI)	*P* value†
Age ⩾65 years	74/93 (79.57)	13 756/22 681 (60.65)	2.5 (1.53–4.19)	0.0002
Delay in case finding				
⩾1 months between symptom onset and first visit to a medical institution	34/74 (46.0)	2 862/8 763 (32.7)	1.8 (1.11–2.77)	0.018
⩾2 months between symptom onset and first visit to a medical institution	21/74 (28.4)	1 629/8 763 (18.6)	1.7 (1.04–2.89)	0.036
⩾1 month between first visit to a medical institution and diagnosis	14/88 (15.9)	2 843/12 540 (22.7)	0.7 (0.36–1.14)	0.159
⩾3 months between symptom onset and diagnosis	21/74 (28.4	1 717/8 837 (19.4)	1.6 (0.99–2.73)	0.056
Outcome of DOT for newly registered smear-positive cases				
Successfully completed	41/70 (58.6	4 288/8 242 (52.0)	1.3 (0.81–2.10)	0.283
Died	18/70 (25.7	1 711/8 242 (20.8)	1.3 (0.77–2.26)	0.302

* Retrieved from the website of the Tuberculosis Surveillance Center in Japan.[5]
† Two-tailed, Fisher's exact test.
DOT = directly observed therapy; OR = odds ratio; CI = confidence interval.

prognosis among our TB cases. Previous studies have shown that malnutrition or hypoalbuminemia affect mortality due to TB.[16,17] A systematic review demonstrated the importance of ensuring adequate nutritional intake for TB prevention and control in crisis settings.[1] Assessment and improvement of nutritional status in older TB patients after natural disasters may be necessary as well as the appropriate use of anti-tuberculosis drugs and supportive care, although the role of nutrition as an adjuvant to treatment remains undetermined.

The Japan earthquake and tsunami increased functional disability in older people, especially those in coastal areas severely affected by the disaster.[18] In this study, functional status on admission of TB patients from tsunami-affected areas was likely to be worse and was significantly associated with the prognosis. Liu et al. described the great need for the prevention of immobilization and the important role of rehabilitation support after the earthquake.[19] Rehabilitation from the early phase may help older TB patients maintain functional ability after a natural disaster. Moreover, our data support the view that oxygen requirement (respiratory failure) among PTB in-patients is associated with mortality,[17] suggesting the importance of respiratory care for patients with severe PTB as well.

Patient delay was significantly longer than in a historic control study from Japan, which included more elderly patients aged >65 years, and which found that elderly TB patients often presented with atypical clinical examination. Patients in the active phase of the disease may present with or no mild symptoms, thus impairing the ability of the patients and families to seek a medical evaluation. Poor access to medical institutions in affected areas may also delay consultation. Physician delay tended to be shorter than for the rest of Japan, although this difference did not reach statistical significance. Physicians were able to suspect TB because patients had clear clinical manifestations or when their status became severe and they had to be hospitalized after delaying consultation. Improving the health concerns of the general public through educational efforts is necessary in affected areas. In addition, continuous medical education and training are important for visiting physicians, as many came from different parts of the country and the world.[20] Improving people's awareness and promoting education among health care personnel would allow rapid diagnosis and treatment of TB in elderly patients. Mitigating overcrowding and dealing with displacement (refugees) are also essential for TB prevention and control in crisis settings.[1]

It is to be noted that approximately 60% of TB cases in this study successfully completed DOT, which compares favorably with the national average for the same year. Impaired health care services and access after a natural disaster can lead to poor treatment adherence, disease relapse, and the development of MDR-TB.[1] We have described several TB contact investigations showing successful adherence rates for LTBI treatment, related to the Japan earthquake.[20–22] Successful completion of DOT in natural disaster settings may be attributed to a resilient health care infrastructure as well as the efforts of the health care personnel in cooperating with people in affected areas. In contrast, the case-fatality rate (deaths among in-patients) within 1 year after treatment commencement was high, at approximately 30%, despite appropriate treatment, although similar to the national average.

Clustered cases with geographic links to the same areas and neighboring regions during the same period (a, b, c, d, and e) suggest that direct transmission between patients and clonal expansion of TB occurred in some affected areas. Patients are at greatest risk for progression to disease in the first 2 years after infection, and approximately 5% are at risk during their lifetime.[23] However, 5/15 clustered

Table 5 Tuberculosis strains clustered using VNTR after the 2011 Great East Japan Earthquake

Cluster ID	VNTR database*								VNTR of samples from patients hospitalized after the earthquake in this study, March 2011–March 2012	Comments
	2004	2005	2006	2007	2008	2009	2010	2011		
Tsu1 ($n = 4$)						SG1, KS1		TM1a	SG2a	a: clustered cases in 2011
In1 ($n = 6$)		KR1, KR2, KR3, KR4		KR5					OS1	Family members or acquaintances
Tsu2 ($n = 3$)	IS1	IS2							KS2	
In2 ($n = 4$)	KS3			KS4			IS3		SG3	
In3 ($n = 3$)						IS4			OS2b, SN1b	b: clustered cases in 2011
In4 ($n = 5$)				IS5		SG4	OS3	OS4c	OS5c	c: clustered cases in 2011
In5 ($n = 2$)							TM2		TM3	Neighbors
In6 ($n = 2$)								TM4d	KR6d	d: clustered cases in 2011
In7 ($n = 2$)			OS6						OS7	
Tsu3 ($n = 3$)							IS6, IS7		SG5	
In8 ($n = 2$)						IS8			OS8	
Tsu4 ($n = 19$)		IS9 TM5			SG6	SG7 IS10, SG9 KS5	SG10, SG11, SG12, IS11 KR7, TM6	SN2e, SN3e TM7e	SG8e IS12 TM8e	A major clustered group within three different broad areas; e: clustered cases in 2011

* VNTR database in Miyagi prefecture, 2004–2011, was used for comparison of cases clustered using VNTR typing in this study. Five clustered groups (a, b, c, d, and e) show clustered cases in 2011.
VNTR = variable number of tandem repeats; Tsu = tsunami-affected areas; In = inland areas (non-tsunami areas).

strains (33.3%) re-emerged more than 2 years after the earthquake (In1, Tsu2, In3, In7, and In8). In contrast, 60.5% (23/38) of the isolates tested had unique VNTR patterns, with a particularly high frequency of unique patterns in the tsunami group. Patients in the tsunami group were also significantly likely to be refuge dwellers, and have poor functional status at admission, low albumin level, and respiratory failure. Our data suggest that most of the study PTB cases were caused by LTBI reactivation due to the impact of the natural disaster rather than by direct transmission.

In conclusion, this is the first observational study of clinical and molecular epidemiological characteristics of PTB after the 2011 Great East Japan Earthquake. Studies on populations affected by natural disasters are sparse, as data collection and research in the post-disaster phase are generally difficult. If studies are implemented, comparison with other natural disasters may also be difficult because of the variations in severity, disruptions in underlying health infrastructure, and level of TB burden. In this study, a potential sampling bias for VNTR typing may have been a limitation. Our study demonstrated risk factors (e.g., age, serum albumin level, functional status at admission, and oxygen requirement) for prognosis of hospitalized PTB patients after the Japan earthquake and tsunami. This natural disaster may have facilitated progression from LTBI to TB disease. Further molecular epidemiologic investigations are needed to clarify the impact of the natural disaster on the development from LTBI to TB disease and the TB burden over a long-term period.

Acknowledgements

The authors thank N Aso and H Saito at Miyagi Cardiovascular and Respiratory Center for their contributions to patient management, T Kanno at the Miyagi Cardiovascular and Respiratory Center for his assistance with data collection, and the health care personnel at the Miyagi Cardiovascular and Respiratory Center and Public Health Centers in the Miyagi Prefecture, who contributed to patient care and management.

Part of this work was presented at the IDWeek 2013, San Francisco, CA, USA, October 2013 (Presentation number: 1635).

This work was supported by internal funding and a grant from the Daido Life Welfare Foundation, Tokyo, Japan.

Conflicts of interest: none declared.

References

1 Kimbrough W, Saliba V, Dahab M, Haskew C, Checchi F. The burden of tuberculosis in crisis-affected populations: a systematic review. Lancet Infect Dis 2012; 12: 950–965.

2 World Health Organization. Tuberculosis care and control in refugee and displaced populations. An interagency field manual. 2nd ed. WHO/HTM/TB/2007.377; WHO/CDS/DCE/2007.2. Geneva, Switzerland: WHO, 2007. http://whqlibdoc.who.int/publications/2007/9789241595421_eng.pdf. Accessed December 2015.

3 National Institute of Infectious Diseases. Infectious disease outbreaks related to the March 11 Great East Japan Earthquake in 2011 and infection control measures taken. Infect Agents

Surveill Rep 2011; 32: S1. http://idsc.nih.go.jp/iasr/32/32s/me32s1.html Accessed December 2015.
4 Mori T. The East Japan earthquake and tsunami disaster and tuberculosis. Kekkaku 2011; 86: 933–943. [Japanese]
5 Tuberculosis Surveillance Center. Statistics of TB. Tokyo, Japan: Research Institute of Tuberculosis, http://www.jata.or.jp/rit/ekigaku/en/annual-reports Accessed December 2015.
6 Kanamori H, Aso N, Weber D J, et al. Latent tuberculosis infection in nurses exposed to tuberculous patients cared for in rooms without negative pressure after the 2011 great east Japan earthquake. Infect Control Hosp Epidemiol 2012; 33: 204–206.
7 Association of Japanese Geographers. Maps of the area hit by the tsunami of 11 March 2011, Northeast Japan. Tokyo, Japan: Association of Japanese Geographers, 2011. http://danso.env.nagoya-u.ac.jp/20110311/map/index_e.html Accessed December 2015.
8 Warren R M, Victor T C, Streicher E M, et al. Patients with active tuberculosis often have different strains in the same sputum specimen. Am J Respir Crit Care Med 2004; 169: 610–614.
9 Supply P, Mazars E, Lesjean S, Vincent V, Gicquel B, Locht C. Variable human minisatellite-like regions in the *Mycobacterium tuberculosis* genome. Mol Microbiol 2000; 36: 762–771.
10 Murase Y, Mitarai S, Sugawara I, Kato S, Maeda S. Promising loci of variable numbers of tandem repeats for typing Beijing family *Mycobacterium tuberculosis*. J Med Microbiol 2008; 57: 873–880.
11 Supply P, Lesjean S, Savine E, Kremer K, van Soolingen D, Locht C. Automated high-throughput genotyping for study of global epidemiology of *Mycobacterium tuberculosis* based on mycobacterial interspersed repetitive units. J Clin Microbiol 2001; 39: 3563–3571.
12 Savine E, Warren R M, van der Spuy G D, et al. Stability of variable-number tandem repeats of mycobacterial interspersed repetitive units from 12 loci in serial isolates of *Mycobacterium tuberculosis*. J Clin Microbiol 2002; 40: 4561–4566.
13 Supply P, Allix C, Lesjean S, et al. Proposal for standardization of optimized mycobacterial interspersed repetitive unit-variable-number tandem repeat typing of *Mycobacterium tuberculosis*. J Clin Microbiol 2006; 44: 4498–4510.
14 Pérez-Guzmán C, Vargas M H, Torres-Cruz A, Villarreal-Velarde H. Does aging modify pulmonary tuberculosis? A meta-analytical review. Chest 1999; 116: 961–967.
15 Kwon Y S, Chi S Y, Oh I, et al. Clinical characteristics and treatment outcomes of tuberculosis in the elderly: a case control study. BMC Infect Dis 2013; 13: 121.
16 Horita N, Miyazawa N, Yoshiyama T, et al. Development and validation of a tuberculosis prognostic score for smear-positive in-patients in Japan. Int J Tuberc Lung Dis 2013; 17: 54–60.
17 Rao V K, Iademarco E P, Fraser V J, Kollef M H. The impact of comorbidity on mortality following in-hospital diagnosis of tuberculosis. Chest 1998; 114: 1244–1252.
18 Tomata Y, Kakizaki M, Suzuki Y, Hashimoto S, Kawado M, Tsuji I. Impact of the 2011 Great East Japan Earthquake and Tsunami on functional disability among older people: a longitudinal comparison of disability prevalence among Japanese municipalities. J Epidemiol Community Health 2014; 68: 530–533.
19 Liu M, Kohzuki M, Hamamura A, et al. How did rehabilitation professionals act when faced with the Great East Japan earthquake and disaster? Descriptive epidemiology of disability and an interim report of the relief activities of the ten rehabilitation-related organizations. J Rehabil Med 2012; 44: 421–428.
20 Kanamori H, Aso N, Tadano S, et al. Tuberculosis exposure among evacuees at a shelter after earthquake, Japan, 2011. Emerg Infect Dis 2013; 19: 799–801.
21 Kanamori H, Uchiyama B, Hirakata Y, Chiba T, Okuda M, Kaku M. Lessons learned from a tuberculosis contact investigation associated with a disaster volunteer after the 2011 Great East Japan Earthquake. Am J Respir Crit Care Med 2013; 187: 1278–1279.
22 Kanamori H, Kimura R, Weber D J, et al. Lessons learned from earthquake-related tuberculosis exposures in a community shelter, Japan, 2011. Am J Infect Control 2014; 42: 246–248.
23 American Thoracic Society; Centers for Disease Control and Prevention; Infectious Diseases Society of America. American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America: controlling tuberculosis in the United States. Am J Respir Crit Care Med 2005; 172: 1169–1227.

OBJECTIF : Rechercher les caractéristiques cliniques et le pronostic des patients tuberculeux après le tremblement de terre et le tsunami du Japon en 2011 et les dynamiques de transmission de la tuberculose (TB).
METHODE : Etude rétrospective d'observation de cohorte. Les données ont été analysées pour 93 patients atteints de TB pulmonaire (25/68 zones affectées/non affectées par le tsunami) hospitalisés entre mars 2011 et mars 2012 avec 1 an de suivi à partir de la mise en route du traitement. Un typage d'un nombre variable de répétitions en tandem (VNTR) a été réalisé pour 38 souches tuberculeuses (21/17 zones affectées/non affectées par le tsunami).
RÉSULTATS : Les patients des zones affectées par le tsunami ont été significativement plus susceptibles d'être des réfugiés (OR 12,8 ; IC95% 2,45–67,20), de recevoir de l'oxygène (OR 5,0 ; IC95% 1,68–14,85), et d'avoir un VNTR unique (OR 4,6 ; IC95% 1,14–18,41). Les patients qui sont décédés dans l'année étaient généralement plus âgés (OR 9,8 ; IC95% 1,85–180,26), dépendants partiellement ou totalement (OR 11,9 ; IC95% 4,28–37,62), avaient plus souvent besoin d'oxygène (OR 4,3 ; IC95% 1,47–12,89) et avaient un taux d'albumine plus faible (OR 11,1 ; IC95% 2,97–72,32).
CONCLUSION : Les facteurs de risque en termes de pronostic de la TB après le tremblement de terre ont été un âge avancé, un faible taux sérique d'albumine, un statut fonctionnel médiocre à l'admission et le besoin d'oxygène. Les résultats du VNTR ont suggéré que la majorité des cas de TB pulmonaire étaient des réactivations d'une infection tuberculeuse latente probablement dues à l'impact de la catastrophe.

OBJETIVO: Investigar las características clínicas y el pronóstico de los pacientes aquejados de tuberculosis (TB) después del terremoto y tsunami del 2011 en el Japón y evaluar la dinámica de la transmisión de la enfermedad.
MÉTODO: Fue este un estudio retrospectivo de observación de cohortes. Se analizaron los datos de 93 pacientes con diagnóstico de TB pulmonar (25 de los cuales provenían de las zonas afectadas por el tsunami y 68 de otras zonas), hospitalizados de marzo del 2011 a marzo del 2012 y con un seguimiento de 1 año después de haber comenzado el tratamiento. Se practicó la genotipificación con marcadores de secuencias repetitivas en tándem de número variable (VNTR) de 38 cepas de *Mycobacterium tuberculosis* (21 provenientes de zonas afectadas por el tsunami).
RESULTADOS: Fue más probable que los pacientes provenientes de las zonas afectadas por el tsunami fueran refugiados (OR 12,8; IC95% 2,45–67,20), recibieran oxigenoterapia (OR 5,0; IC95% 1,68–14,85) y presentaran un perfil único de la VNTR (OR 4,6; IC95% 1,14–18,41). Los pacientes que fallecieron durante el año de seguimiento eran con mayor frecuencia mayores (OR 9,8; IC95% 1,85–180,26), parcialmente dependientes o dependientes (OR 11,9; IC95% 4,28–37,62), habían necesitado oxigenoterapia (OR 4,3; IC95% 1,47–12,89) y presentaron una albuminemia más baja (OR 11,1; IC95% 2,97–72,32).
CONCLUSIÓN: Los factores de riesgo de un pronóstico desfavorable de la TB después de un terremoto se asociaron con la ancianidad, una baja albuminemia, el estado funcional en el momento de la hospitalización y la necesidad de oxigenoterapia. Los resultados de la genotipificación mediante la técnica VNTR indican que la mayoría de los casos de TB pulmonar consistieron en reactivaciones de una infección tuberculosa latente ocasionadas por el desastre.