



Original Article

Microorganisms isolated at admission and treatment outcome in sputum smear-positive pulmonary tuberculosis[☆]



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ABSTRACT

Cured or completed cases in newly diagnosed sputum smear-positive pulmonary tuberculosis (TB) is 47.7% in Japan in 2016. Aging of TB patients and their underlying conditions could affect treatment outcome. We analyzed the association between the isolation of microorganisms from sputum at admission and the 180-day mortality rate of the sputum smear-positive pulmonary TB patients in Chiba-East Hospital in Japan. Total subjects were 761 (median age: 63 years). Sputum test for microorganisms was conducted in 708 patients. Microorganisms other than the normal oral flora were isolated in 128 cases (18.1%). Details of the isolated microorganisms were as follows: methicillin-resistant *Staphylococcus aureus* 23 cases, *Klebsiella pneumoniae* 17 cases, *Pseudomonas aeruginosa* 16 cases. Mortality was significantly elevated in the patients with those microorganisms than the others (39.8% vs. 10.2%) ($P < 0.01$). Fifty-one of 128 patients with those microorganisms died, and 10 of them died of infectious disease, which is the most frequent cause of deaths. The factors associated with the isolation of those microorganisms were as follows: respiratory failure (adjusted odds ratio (aOR):2.5 [95% confidence interval (CI) 1.3–4.7]), performance status 3 or 4 (aOR:2.9 [95% CI 1.6–5.4]), serum albumin <3.0 mg/dL (aOR:2.1 [95% CI 1.3–3.6]), age of 65 years or older (aOR:2.0 [95% CI 1.2–3.4]). Those strains were isolated from one of sixth patients. Patients with those microorganisms did not always develop infectious diseases; however, treatment outcomes were poor, with higher mortality. The isolations of microorganisms were associated with various underlying conditions, leading to death. Thus, attention should be paid to TB patients with the above factors.

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1. Introduction

The number of newly diagnosed tuberculosis (TB) patients was 17,625, and the TB notification rate was 13.9 per 100,000 persons in Japan in 2016. The notification rate has decreased since 1998. Aging of the TB patients has been progressive. The rate of patients aged 65 years or older has reached 66.6%. Because of the aging, the percentage of cured or completed smear-positive pulmonary tuberculosis (TB) is 47.7% in Japan in 2016.

Aged patients have some underlying conditions, which could affect the treatment outcome [1]. Diabetes mellitus, chronic renal failure, steroid therapy for underlying diseases, etc., were thought to be a kind of immunosuppressive conditions and risk factors for developing active TB from latent tuberculosis infection [2]. Some patients had been staying in hospitals or nursing care facilities for the treatment of underlying conditions when diagnosed as smear-positive pulmonary TB. Microorganisms often colonize in nasal cavities and respiratory tracts. The transmission of microorganisms, including drug-resistant microorganisms, was confirmed between a nursing home and a nearby hospital [3].

Colonization of methicillin-resistant *Staphylococcus aureus* (MRSA) in nasal cavity is the risk factor of bacteremia in geriatric hospitals and associated with higher mortality even in general populations [4,5]. The patients with underlying conditions were at

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higher risk of colonizing microorganisms. Then, we hypothesized that the conditions of the patients, in whose sputum microorganisms were isolated, would affect their TB treatment outcome.

2. Patients and methods

This study is a retrospective cohort analysis conducted on the population of our previous study at National Hospital Organization Chiba-East Hospital (CEH) in Chiba, Japan [1]. We analyzed the frequency of isolated microorganisms other than *Mycobacterium tuberculosis* (*M. tuberculosis*) and oral flora, and 180-day post-admission mortality rates. We also analyzed the risk of isolation of microorganisms associated with underlying conditions, as was analyzed in the former study [1].

Sputum smear-positive TB patients are recommended admission to TB treatment facilities for the prevention of *M. tuberculosis* transmission in accordance with the Japanese Infection Law. The subjects were hospitalized smear-positive pulmonary TB patients during the six years between 2007 and 2012. There were no multi-drug resistant TB patients newly diagnosed.

Sputum tests were performed to detect non-acid-fast bacteria when the smear-positive pulmonary TB patients were admitted to our hospital. Three consecutive sputum specimens were needed for the culture of *M. tuberculosis* at admission, and the first one was used for non-acid-fast bacterial examinations, semi-quantitative Gram stain and culture. A bacteria that is present in a moderate to heavy growth and as the predominant organism was defined as the isolated microorganism in this study. Whether the isolated microorganisms were normal oral flora or not were determined by the Clinical Laboratory Technicians certificated by the Ministry of Health, Labor and Welfare.

Clinical outcomes were judged by using the medical records in our hospital and public health center. A standardized data collection tool was utilized to collect case demographics and underlying medical conditions (cardiovascular disease, diabetes mellitus, malignancy, chronic liver disease, cerebrovascular disease, steroid therapy for underlying disease, chronic kidney disease (CKD) and performance status).

Anti-TB drugs were prescribed according to the Japanese standard regimen issued by the Japanese Ministry of Health, Labour and Welfare. There are two treatment regimens proposed. The first-choice regimen is a 6-month therapy using isoniazid (INH), rifampicin (RFP), ethambutol (EB), and pyrazinamide (PZA). EB and PZA are used only in the first two months, and streptomycin (SM) can be substituted for EB. The alternative regimen is a 9-month therapy using INH, RFP, and EB. EB is used only in the first two months, and EB can be replaced by SM. EB and PZA are prescribed three times a week for patients with advanced CKD and hemodialysis. If patients were not able to adhere to standard regimens owing to adverse events, underlying diseases and drug resistance, they were treated by using other anti-TB drugs.

The definition of CKD was defined as estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m² in this study. The definition of respiratory failure was O₂ saturation of <90% measured by pulse oximeter under breathing room air in this study. Hypertension without other heart disease or vascular disease was excluded from cardiovascular disease in this study. Performance status [6] 3 or 4 (PS 3 or 4) was used as an index for decreased ADL (activities of daily living). It was difficult to evaluate respiratory comorbidities, as pulmonary lesions were also affected by some pulmonary diseases other than pulmonary TB, such as COPD, bronchial ectasia and interstitial pneumonia, etc. Therefore, we used SpO₂ <90% as an index of severity of pulmonary lesions and respiratory failure. The duration of follow-up was 180 days after admission. Treatment outcome was estimated by calculating mortality by all causes and each direct cause.

Table 1
Characteristics of subjects.

	n (%)
Age, yr. median (IQR)	63 (48–79)
Male	549 (72.3)
Administration of antibiotics before TB diagnosis	154 (20.3)
Cigarette smoking	457 (60.2)
Alcohol daily use	422 (55.6)
Cavity in chest X-ray	511 (67.3)
Diabetes mellitus	201 (26.5)
Malignancy	54 (7.1)
Steroid therapy for underlying condition	45 (5.9)
Chronic liver disease	117 (15.4)
Chronic kidney disease ^a	60 (7.9)
Cerebrovascular disease	83 (10.9)
Respiratory failure ^b	64 (8.4)
Cardiovascular disease	77 (10.1)
PS 3 or 4	90 (11.9)

IQR, Interquartile Range; PS, Performance Status.

^a eGFR (estimated glomerular filtration rate) < 60 ml/min/1.73 m².

^b SpO₂<90% at admission under room air breathing.

2.1. Statistical analysis

The data were entered into Excel 2016 (Microsoft, Redmond, WA) and transferred to JMP[®] Pro 13.0.0 (SAS Institute Inc., Cary, NC, USA) for statistical analysis. Chi-square test or Fisher's exact test was used to compare categorical variables. Multivariate logistic regression modeling was employed to identify predictor variables that were significantly related to the likelihood of treatment outcome. Potential predictor variables for model entry were identified using univariate analysis, where a P-value <0.15 was used to determine entry into the models. Odds ratios (OR) and 95% confidence intervals (CI) were used for interpretation of the analysis. A P-value <0.05 was considered statistically significant. Results of logistic regression analysis were reported as adjusted OR with 95% CI. OR and 95% CI were used for interpretation of the analysis.

The study was approved by the CEH Research Ethics Committee (ID 1714) and was conducted in accordance with the principles of the Declaration of Helsinki.

3. Results

There were 759 patient admissions (males/females: 548/211, median age (year): 63, inter-quartile range: 48–79). Two of the

Table 2
Microorganisms isolated from sputum in smear-positive pulmonary tuberculosis patients.

Microorganisms isolated at admission	n (%)
MRSA	23 (3.0)
<i>Klebsiella pneumoniae</i>	17 (2.2)
<i>Pseudomonas aeruginosa</i>	16 (2.1)
MSSA	14 (1.8)
Coagulase negative staphylococci	14 (1.8)
<i>Enterobacter cloacae</i>	7 (0.9)
Gram negative rod	7 (0.9)
<i>Streptococcus agalactiae</i>	5 (0.7)
<i>Escherichia coli</i>	4 (0.5)
<i>Stenotrophomonas maltophilia</i>	4 (0.5)
Other	17 (2.2)
No growth	580 (76.2)
Not conducted	53 (7.0)
Total	761

MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*; ESBL, extended spectrum β-lactamase.

There was 1 case with multi-drug resistant *Pseudomonas aeruginosa*, 1 case with ESBL-productive *Escherichia coli*, and 1 case with ESBL-productive *Proteus mirabilis*.

Table 3
Univariate analysis of factors associated with the isolation of microorganisms.

Factors		n	isolation of microorganism	(%)	P value ^a
Age of 65 years or older	yes	350	96	(27.4)	<0.01
	no	358	32	(8.9)	
Male	yes	513	89	(17.3)	ns
	no	195	39	(20.0)	
serum albumin <3.0 mg/dL	yes	316	92	(29.1)	<0.01
	no	392	36	(9.2)	
PS 3 or 4	yes	84	47	(56.0)	<0.01
	no	626	81	(12.9)	
Some symptoms at diagnosis	yes	594	113	(19.0)	ns
	no	114	15	(13.2)	
Diagnosed by periodic medical checkup	yes	119	8	(6.7)	<0.01
	no	589	120	(20.4)	
Administration of antibiotics before TB diagnosis	yes	141	41	(29.1)	<0.01
	no	567	87	(15.3)	
Cavity in chest X-ray	yes	479	74	(15.4)	0.01
	no	229	54	(23.6)	
Diabetes mellitus	yes	190	34	(17.9)	ns
	no	518	94	(18.1)	
Malignancy	yes	52	14	(26.9)	ns
	no	656	114	(17.4)	
Steroid therapy for underlying condition	yes	38	8	(21.1)	ns
	no	670	120	(17.9)	
Chronic liver disease	yes	114	20	(17.5)	ns
	no	594	108	(18.2)	
Chronic kidney disease ^b	yes	60	31	(51.7)	<0.01
	no	648	97	(15.0)	
Cerebrovascular disorder	yes	78	28	(35.9)	<0.01
	no	630	100	(15.9)	
Respiratory failure ^c	yes	60	31	(51.7)	<0.01
	no	648	97	(15.0)	
Cardiovascular disease	yes	73	24	(32.9)	<0.01
	no	635	104	(16.4)	
Cigarette smoking	yes	429	67	(15.6)	ns
	no	268	57	(21.3)	
Daily alcohol use	yes	392	51	(13.0)	<0.01
	no	305	73	(23.9)	

TB, tuberculosis; ns, no significant difference; PS, Performance Status.

^a P-value was analyzed between yes and no.

^b eGFR (estimated glomerular filtration rate) < 60 ml/min/1.73 m².

^c SpO₂ < 90% at admission under room air breathing.

patients were infected with HIV. The characteristics of the subjects are shown in Table 1. Sputum test results were available for 708 patients, for a screening rate of 93.1%. The microorganisms excluding normal oral flora and acid-fast bacillus were isolated from 128 patients, 16.6% of the total patients (Table 2).

Details of the isolated microorganisms were as follows: MRSA 23 (3.0%), *Klebsiella pneumoniae* (*K.pneumoniae*) 17 (2.2%), *Pseudomonas aeruginosa* (*P.aeruginosa*) 16 (2.1%), methicillin-sensitive *Staphylococcus aureus* (MSSA) 14 (1.8%), coagulase negative staphylococcus (CNS) 14 (1.8%), etc. (Table 2). Multi-drug resistant *P. aeruginosa* (MDRP) was isolated in one patient. Extended-spectrum β-lactamase (ESBL)-producing Gram-negative bacillus were isolated in two patients (*Escherichia coli* (*E.coli*) and *Proteus mirabilis* (*P.mirabilis*), respectively).

We analyzed the underlying conditions and comorbidities associated with the isolation of microorganisms (Table 3). The frequency of the isolation of microorganisms significantly increased in the patients who had received antibiotics before admission to our hospital for the tentative diagnosis of pneumonia. Other significant factors were age of 65 years or older, serum albumin <3.0 mg/dL, PS 3 or 4, CKD, cerebrovascular disease, respiratory failure, and cardiovascular disease. The frequency of the isolation of microorganisms was lower in the patients with cavity formation on chest X-ray and daily alcohol use. The variables with univariate P less than 0.15 were included in the multivariate logistic analysis. Respiratory

failure, PS 3 or 4, serum albumin <3.0 mg/dL and age of 65 years or older were selected as independent risk factors for the isolation of microorganisms (Table 4).

Overall mortality at 180 days after admission was 110 (15.5%) (Table 5). Mortality with and without microorganisms was 39.8% and 10.2%, respectively, a significant difference ($P < 0.01$). Kaplan-Meier survival curve is shown in Fig. 1. The direct causes of death are shown in Table 5. Deaths occurred owing to TB itself, malignancy, infectious disease, cardiovascular disease, and respiratory failure. Mortality of the patients with microorganisms was significantly higher than that of the others. The details of infectious diseases were pneumonia in 18 cases and sepsis in four cases, one of which was pneumonia complicated by sepsis.

Table 4

Multivariate logistic analysis of factors associated with the isolation of microorganisms.

Factors	aOR [95% CI]	P value
Respiratory failure ^a	2.5 [1.3–4.7]	<0.01
PS 3 or 4	2.9 [1.6–5.4]	<0.01
serum albumin <3.0 mg/dL	2.1 [1.3–3.6]	<0.01
Age of 65 years or older	2 [1.2–3.4]	<0.05

aOR, adjusted odds ratio; CI, confidence interval; PS, Performance Status.

^a SpO₂<90% at admission under room air breathing.

Table 5
Causes of deaths within 180 days of admission in smear-positive pulmonary tuberculosis.

	All cases	Isolation of the microorganisms		P value ^a
	(n = 708) (%)	yes (n = 128) (%)	no (n = 580) (%)	
Total Death	110 (15.5)	51 (39.8)	59 (10.2)	<0.01
Details of causes of death				
Tuberculosis	22 (3.1)	10 (7.8)	12 (2.1)	
Malignancy	22 (3.1)	8 (6.3)	14 (2.4)	
Infectious disease	21 (3.0)	11 (8.6)	10 (1.7)	
Cardiovascular disease	8 (1.1)	5 (3.9)	3 (0.5)	
Respiratory failure	7 (1.0)	4 (3.1)	3 (0.5)	
Other	10 (1.4)	7 (5.5)	3 (0.5)	
Unknown	20 (2.8)	6 (4.7)	14 (2.4)	

^a P-value was analyzed between with and without pathogenic microorganism isolation.

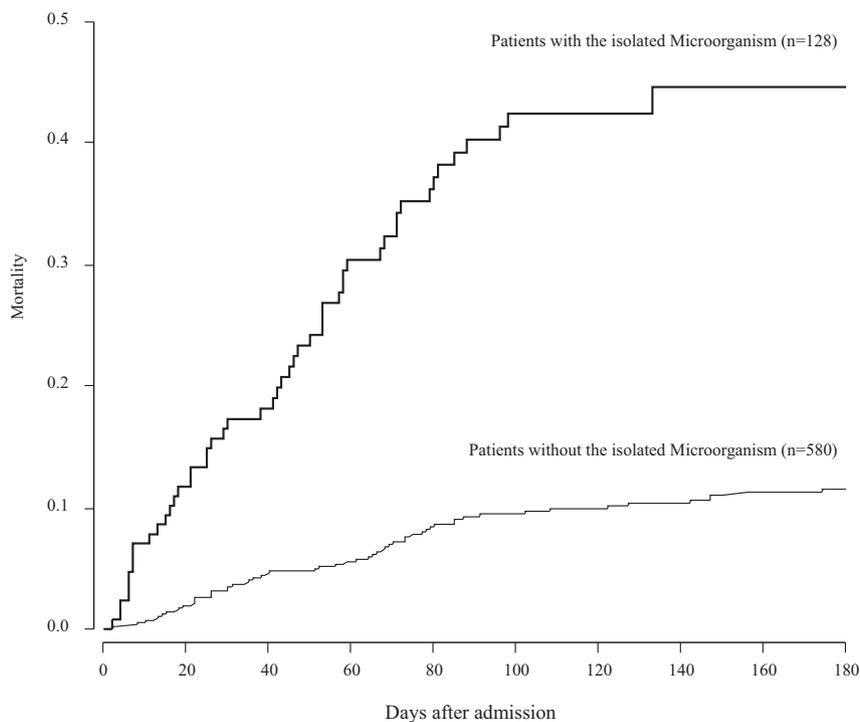


Fig. 1. The mortality of sputum smear-positive pulmonary tuberculosis patients at 180 days after admission. Mortality after admission was analyzed by Kaplan-Meier method. Total 708 sputum smear-positive pulmonary tuberculosis patients were classified into two groups by sputum examination except for mycobacteria. One-hundred one patients died within 180 days after admission. There was a significant difference in death between patients with and without microorganisms isolated at admission. (Log-rank test, $P < 0.01$).

4. Discussion

Microorganisms other than normal oral flora were concurrently isolated from sputum in 16.8% of TB patients, in addition to *M. tuberculosis*. The species of microorganisms, in order of frequency, were MRSA, *K. pneumoniae* and *P. aeruginosa*, MSSA, and so on. Those microorganisms are frequently isolated in hospital-acquired pneumonia (HAP) and healthcare-associated pneumonia (HCAP) [7–15]. Although the numbers were small, MDRP, ESBL productive *E. coli*, and *P. mirabilis* were isolated at admission to the TB ward. Those antibiotic-resistant microorganisms can cause infectious diseases, such as pneumonia and sepsis, and result in death. Therefore, health care workers should conduct infection control to prevent those infectious diseases.

The isolation of microorganisms, which can cause HAP and HCAP, was associated with certain factors. Univariate analysis identified several significant factors, such as age of 65 years or older, CKD, PS 3 or 4, cerebrovascular disorder, respiratory failure, and

cardiovascular disease. After multivariate logistic analysis, respiratory failure, PS 3 or 4, respiratory failure and age of 65 years or older were selected as independent factors associated with the isolation of microorganisms. The number of registered Japanese TB patients in 2016 was 17,625. The percentage of TB patients ≥ 70 years old increased yearly to 59.0%. Japan is the top aging country in the world, and therefore TB patients with co-morbidities (NCDs) were also increasing [16]. Impaired ADL is associated with aging and shown to be a risk factor for MRSA isolation [17]. Respiratory failure, PS 3 or 4, serum albumin < 3.0 mg/dL (as an index of malnutrition) and age 65 years or older would be factors leading to impaired ADL. Thus, attention should be paid to TB patients with the above conditions because of isolating those microorganisms and their expected poor treatment outcome.

Co-infection of *M. tuberculosis* and other microorganisms have been reported in HIV/AIDS patients [18]. However, there are a few reports regarding of co-infection of *M. tuberculosis* and other microorganisms in non-HIV patients [19]. In our study, no patients

were given antibiotics in addition to *anti*-TB drugs at admission. It was because that those patients had been given antibiotics for tentative pneumonia diagnosis before admission to our hospital, although in vain. The isolation of some microorganisms, which means whether there is infection or colonization, can result in poor outcome. For instance, colonization of MRSA in the nasal cavity was associated with higher mortality even in general populations [5]. Thus, we hypothesized that the conditions of the patients, in whose sputum microorganisms were isolated, would affect their TB treatment outcome.

We analyzed TB treatment outcome by calculating 180-day post-admission mortality. There were 110 patients died. Mortality rates showed a significant difference according to whether there were microorganisms isolated or not. Fifty-one patients with microorganisms died, a mortality rate of 39.8%, which was significantly higher than that of the patients with no microorganisms. Eleven of patients with microorganism died of infectious diseases. Their mortality rate of 8.6% was significantly higher than that of patients with no microorganisms (1.7%). We could confirm the causative organisms in five of the eleven patients with microorganisms at the time of diagnosis of infectious disease. The causative organisms were not always the same species isolated at admission; in only one case MRSA was isolated at the time of admission and diagnosis of infectious disease. Although the isolation of microorganisms did not always result in critical infectious diseases, the mortalities of the patients with microorganisms were higher than that of the patients with no microorganisms. The pathogenesis of the isolation of microorganisms possibly depends upon the host immune condition. We previously showed that some underlying conditions affected TB treatment outcome [1]. In consideration of the comorbidities of the patients with microorganisms, poor PS, respiratory failure, and aging were associated with poor treatment outcomes and possibly confound with the isolation of organisms.

Twenty-one patients died of infectious diseases. Eighteen of them had pneumonia, four cases had sepsis, and one had pneumonia complicated by sepsis. At least fourteen of them had aspiration pneumonia, which was reported to be frequent in persons 60 years or older [20]. Therefore, this result in our subjects with a median age of 63 years is not unusual. Four patients of them developed MRSA pneumonia; One of them had isolated MRSA at admission, the other three cases had not. Although all of MRSA were RFP-sensitive (microdilution method) at admission, MRSA isolated from MRSA pneumonia were RFP-resistant. RFP was administered to almost all of the patients in the TB ward, since it is a key drug for TB treatment. Such antibiotics selective pressure would make MRSA RFP-resistant. Treating MRSA infection in the TB ward, we have to take this selective pressure.

There are some limitations to this study. This study was a retrospective analysis of smear-positive pulmonary TB patients. Some patients underwent antibiotics therapy before admission. In univariate analysis, antibiotics therapy significantly affected the rate of the isolation of microorganisms, although not selected as an independent factor associated with the isolation in multivariate analysis. Since the differential diagnosis of pulmonary TB and pneumonia is difficult, it is possible that we missed pneumonia caused by microorganisms and thought to be the cases died from TB, especially in extensive pulmonary TB. However, the all-cause mortality was higher in the patients with microorganisms. Patients with organisms were expected to have poor treatment outcome owing to TB itself or comorbidities in spite of TB treatment.

In conclusion, about one of sixths patients carried microorganisms, having poor treatment outcome. There were complicated backgrounds, impaired ADL, aging, and respiratory failure in patients with microorganisms. The patients with microorganisms

did not always develop infectious diseases, but their treatment outcome was poor, with higher mortality, due to underlying conditions of them. Thus, attention should be paid to TB patients with the above factors.

Conflicts of interest

None.

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