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Determinants of mortality in elderly patients with tuberculosis: a population-based follow-up study

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SUMMARY

Elderly individuals with tuberculosis (TB) are more likely to have a non-specific clinical presentation of TB and high mortality. However, factors associated with mortality in elderly TB patients have not been extensively studied. This retrospective cohort study aimed to identify factors associated with death among elderly Taiwanese with TB. All elderly patients with TB from 2006 to 2014 in Taipei, Taiwan, were included in a study. Multiple logistic regression was used to identify the factors associated with death in elderly TB patients. The mean age of the 5011 patients was 79·7 years; 74·1% were men; 32·7% had mortality during the study follow-up period. After controlling for potential confounders, age $\geqslant$75 years (reference: 65–74 years), male sex, end-stage renal disease (ESRD), malignancy, acid-fast bacilli-smear positivity, TB-culture positivity, pleural effusion on chest radiograph and notification by an ordinary ward or intensive care unit were associated with a higher risk of all-cause death; while high school, and university or higher education, cavity on chest radiograph and directly observed therapy were associated with a lower risk of all-cause death. This study found that the proportion of death among elderly patients with TB in Taipei, Taiwan, was high. To improve TB treatment outcomes, future control programmes should particularly target individuals with comorbidities (e.g. ESRD and malignancy) and those with a lower socio-economic status (e.g. not educated).

Key words: Elderly, mortality, Taiwan, tuberculosis.

INTRODUCTION

Approximately one-third of the world's population is latently infected with tuberculosis (TB). In 2014, there were an estimated 9·6 million incident cases of TB, and 1·5 million people died from the disease [1].

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In Taiwan, of all notifiable infectious diseases, TB has been the most prevalent for decades [2]. Since 2006, Taiwan's Centers for Disease Control and Prevention (CDC) has adopted a directly observed therapy short-course (DOTS) programme to halve TB incidence and achieve a successful treatment rate of 85% by 2015. Since then, the rate of TB incidence has decreased from 72·5 per 100 000 in 2005 to 48·4 in 2014 [2]. The success rate for TB treatment, however, only slightly improved from 64·1% in 2005 to 70·4% in 2014. Mortality among Taiwanese patients with TB accounted for 81·8% of the cases of unsuccessful TB treatment [2]. Additionally, over 82·1% of TB deaths in Taiwan were among individuals >65 years old [3].

TB in the elderly (>65 years old) has increasingly become a major issue not only because of non-specific clinical presentation of TB but, more importantly, because of a high mortality rate [4, 5]. Since the clinical symptoms of TB and risk factors of mortality in older patients may differ from those in younger patients, TB diseases in this population should be classified as a separate entity [6, 7]. Few studies, however, have determined the factors associated with TB mortality among elderly patients [7].

According to the World Health Organization, death is defined as a patient who dies for any reason during treatment [8]. However, many patients with TB do not die of TB but from other causes such as malignancy or end-stage renal disease (ESRD). A previous review article found that few studies about TB treatment outcomes distinguished TB-specific mortality from other-cause (non-TB-specific) mortality [8]. Developing effective interventions to improve TB outcomes requires better understanding of the factors associated with mortality, particularly for vulnerable populations. We thus attempted to identify prognostic factors associated with mortality among elderly Taiwanese patients with TB infection from 2006 to 2014.

METHODS

Study population and data source

This retrospective cohort study used TB surveillance data collected by the Taipei City Government in Taiwan. The subjects included were elderly Taiwanese individuals (age $\geqslant$65 years) with TB in Taipei from 2006 to 2014. In Taiwan, all suspected TB cases must be reported to Taiwan's CDC within 7 days [2]. After receiving notification, trained case managers use a structured questionnaire to interview patients about their socio-demographic characteristics, clinical findings, underlying diseases, admission history and TB treatments. Patients with TB in Taipei are required by law to be monitored until treatment success, death, or loss to follow-up. For the purpose of monitoring treatment response, case managers followed up all TB cases by phone or in person once every other week. This project was approved by the Institutional Review Board of Taipei City Hospitals (TCHIRB-10505112-E).

Outcome variables

The outcome variable of interest was treatment outcome, which was categorised into two groups: successful treatment and mortality. Mortality was classified as TB-specific or non-TB-specific death, which was determined by the Taiwan Death Certification Registry [9]. TB-specific death in this study was defined as the underlying cause of death being due to TB according to the Taiwan Death Certification Registry (International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes: A010–A018; ICD-10-CM code: A15–A19). Non-TB-specific death was defined as any underlying cause of death other than TB.

Explanatory variables

Covariates identified in previous studies as risk factors for TB mortality or as major comorbidities linked to TB mortality were assessed in the analyses [10], including demographic factors (age, sex, marital status, education level, nursing home residence, smoking, alcohol use and employment status); clinical findings (chest radiography findings, acid-fast bacilli (AFB) smear status, drug resistance); underlying diseases (malignancy and ESRD); source of notification and mode of treatment. The source of the notification was defined as the department that reported the TB case, including ordinary wards, intensive care units or outpatient services. Treatment mode was categorised as directly observed therapy or self-administered therapy. Directly observed therapy was defined as anti-TB medication ingestion that was directly supervised by a trained observer [11]. Self-administered therapy referred to unsupervised treatment.

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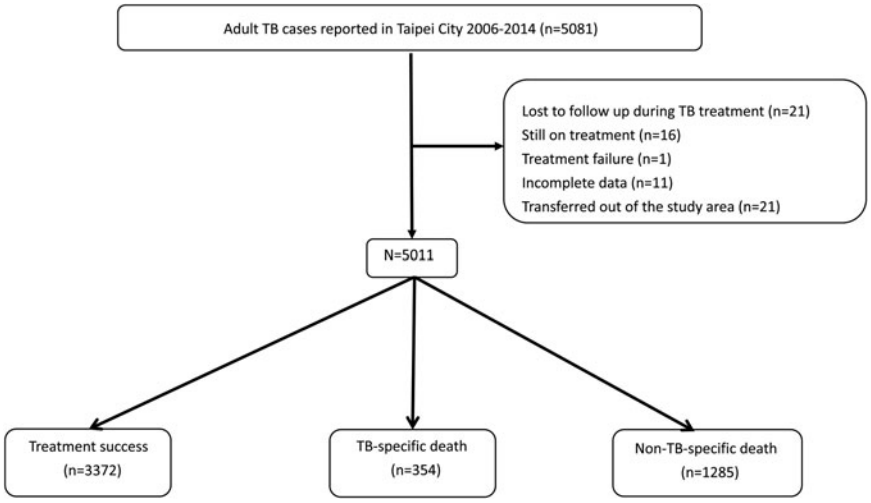

Fig. 1. Study flow diagram. TB, tuberculosis.

Statistical analysis

In univariate analysis, the χ^2 test was used to assess associations of the clinical relevant variables with the outcomes. All variables found to be significant ($P < 0{\cdot}05$) through univariate analysis were considered for inclusion in multivariate analysis. Multiple logistic regression was used to assess the multivariate associations of the factors with all-cause mortality. Furthermore, multinomial logistic regression was used to identify the factors associated with TB-specific and non-TB-specific mortality. Adjusted odds ratios (AOR) with 95% confidence intervals (CI) were reported to show the strength and direction of these associations. All data management and analyses were performed using the SAS 9·4 software package (SAS Institute, Cary, NC).

RESULTS

Characteristics of patients with TB

During the 9-year study period, there were 5081 TB cases (age $\geqslant$65 years) reported to the Taipei TB Control Department. Of these, 21 were lost to follow up, 16 were still on treatment, 1 had treatment failure, 11 had incomplete data and 21 had transferred out of Taipei City (Fig. 1). The remaining 5011 were included in the subsequent analysis. Overall, the mean and median ages of the study subjects were 79·7 years (range 65–113) and 80 years (interquartile range 74–85), respectively; 74·1% were men; 67·3% (3372) were successfully treated; 7·1% (354) died of TB-specific causes and 25·6% (1285) died of non-TB-specific causes during TB treatment.

The TB-specific mortality rates were 3·3%, 5·7% and 12·7% in patients aged 65–74, 75–84 and $\geqslant$85 years, respectively. Additionally, the non-TB-specific mortality rates were 14·0%, 26·0% and 36·2% in patients aged 65–74, 75–84 and $\geqslant$85 years, respectively.

Univariate analyses of factors associated with all-cause mortality

The χ^2 test revealed variables that were significantly associated with all-cause mortality, i.e. age 75–84 or $\geqslant$85 years, unemployment, residence in a long-term care facility, ESRD, malignancy, AFB-smear positivity, TB-culture positivity, pleural effusion on chest radiograph and notification from an ordinary ward or intensive care unit (Table 1). Additionally, variables significantly associated with a lower chance of all-cause mortality were elementary school, high school, and university or higher education, a cavity on chest radiograph and directly observed therapy.

Multivariates analyses of factors associated with all-cause mortality

All variables found to be significant ($P < 0{\cdot}05$) through univariate analysis were considered for inclusion in multivariate analysis. After adjusting for sociodemographic factors and comorbidities, risk factors associated with all-cause mortality included age 75–84 years (AOR = 2·18, 95% CI 1·82–2·61), age $\geqslant$85 years (AOR = 4·57, 95% CI 3·78–5·53), residence in a long-term care facility (AOR = 1·57, 95% CI 1·22–2·01),

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Table 1. *Univariate analyses of risk factors for mortality in elderly TB patients, Taipei, Taiwan (2006–2014)*

Factor	Number of patients	All-cause deaths	Univariate analysis
		n (%)	OR (95% CI)
Age (years)			
65–74	1389	241 (17·4)	1
75–84	2168	686 (31·6)	2·21 (1·87–2·60)***
⩾85	1454	712 (49·0)	4·57 (3·85–5·43)***
Sex			
Female	1299	401 (30·9)	1
Male	3712	1238 (33·4)	1·12 (0·98–1·29)
Marital status			
Unmarried	378	134 (35·5)	1
Married	4633	1505 (32·5)	0·88 (0·70–1·09)
Education level			
No education	656	253 (38·6)	1
Elementary school	1425	473 (33·2)	0·79 (0·65–0·96)*
High school	1485	434 (29·2)	0·66 (0·54–0·80)***
University or higher	921	260 (28·2)	0·63 (0·51–0·78)***
Unknown	524	219 (41·8)	1·14 (0·91–1·45)
Smoker			
No	4497	1485 (33·0)	1
Yes	514	154 (30·0)	0·87 (0·71–1·06)
Unemployment			
No	537	144 (26·8)	1
Yes	4474	1495 (33·3)	1·37 (1·12–1·67)**
LTCF residences			
No	4687	1474 (31·5)	1
Yes	324	165 (50·9)	2·26 (1·80–2·84)***
DM			
No	3995	1331 (33·3)	1
Yes	1016	308 (30·3)	0·87 (0·75–1·01)
ESRD			
No	4806	1535 (31·9)	1
Yes	205	104 (50·7)	2·19 (1·66–2·90)***
Malignancy			
No	4538	1392 (30·7)	1
Yes	473	247 (52·2)	2·47 (2·04–2·99)***
TB relapse			
No	4846	1591 (32·8)	1
Yes	165	48 (29·1)	0·84 (0·60–1·18)
Acid-fast bacilli smear			
Negative	3099	955 (30·8)	1
Positive	1912	684 (35·8)	1·25 (1·11–1·41)***
TB culture			
Negative	1261	359 (28·5)	1
Positive	3750	1280 (34·1)	1·30 (1·13–1·50)***
Cavities on CXR			
No	4434	1479 (33·4)	1
Yes	577	160 (27·7)	0·77 (0·63–0·93)**
Pleural effusion on CXR			
No	4282	1348 (31·5)	1
Yes	729	291 (39·9)	1·45 (1·23–1·70)***
Extrapulmonary TB			
No	4638	1523 (32·8)	1
Yes	373	116 (31·1)	0·92 (0·74–1·16)
MDR-TB			
No	4990	1634 (32·8)	1

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Table 1 (*cont.*)

Factor	Number of patients	All-cause deaths *n* (%)	Univariate analysis OR (95% CI)
Yes	21	5 (23·8)	0·64 (0·23–1·76)
Mode of treatment			
SAT	1573	659 (41·9)	1
DOT	3438	980 (28·5)	0·55 (0·49–0·63)***
Source of notification			
Outpatient services	2413	513 (21·3)	1
Ordinary ward	2410	994 (41·2)	2·60 (2·29–2·95)***
Intensive care unit	188	132 (70·2)	8·73 (6·29–2·95)***

OR, odds ratio; CI, confidence interval; LTCF, long-term care facility; DM, diabetes mellitus; ESRD, end-stage renal disease; TB, tuberculosis; CXR, chest radiograph; MDR-TB, multidrug-resistant tuberculosis; SAT, self-administrated treatment; DOT, directly observed treatment.
*<0·05; **<0·01; ***<0·001.

Table 2. *Multivariates analyses of risk factors for all-cause mortality in elderly TB patients, Taipei, Taiwan (2006–2014)*

Factors	AOR (95% CI)
Age (years)	
65–74	1
75–84	2·18 (1·82–2·61)***
⩾85	4·57 (3·78–5·53)***
Education level	
No education	1
Elementary school	0·91 (0·74–1·13)
High school	0·72 (0·58–0·89)**
University or higher	0·64 (0·51–0·81)***
Unknown	1·02 (0·79–1·32)
LTCF residences	1·57 (1·22–2·01)***
Unemployment	0·95 (0·76–1·19)
ESRD	2·63 (1·92–3·60)***
Malignancy	3·01 (2·43–3·74)***
AFB-smear positivity	1·59 (1·37–1·85)***
TB-culture positivity	1·53 (1·29–1·81)***
Cavity on CXR	0·76 (0·61–0·95)*
Pleural effusion	1·40 (1·16–1·69)***
DOT	0·34 (0·29–0·39)***
Source of notification	
Outpatient services	1
Ordinary ward	2·50 (2·17–2·88)***
Intensive care unit	6·71 (4·72–9·54)***

TB, tuberculosis; AOR, adjusted odds ratio; CI, confidence interval; LTCF, long-term care facility; ESRD, end-stage renal disease; AFB, acid-fast bacilli; CXR, chest radiograph; DOT, directly observed treatment.
*<0·05; **<0·01; ***<0·001.

ESRD (AOR = 2·63, 95% CI 1·92–3·60), malignancy (AOR = 3·01, 95% CI 2·43–3·74), AFB-smear positivity (AOR = 1·59, 95% CI 1·37–1·85), TB-culture positivity (AOR = 1·53, 95% CI 1·29–1·81), pleural effusion on chest radiograph (AOR = 1·40, 95% CI 1·16–1·69) and notification from an ordinary ward (AOR = 2·50, 95% CI 2·17–2·88) or intensive care unit (AOR = 6·71, 95% CI 4·72–9·54) (Table 2). Additionally, protective factors for all-cause mortality included a high school education (AOR = 0·72, 95% CI 0·58–0·89), a university or higher education (AOR = 0·64, 95% CI 0·51–0·81), a cavity on chest radiograph (AOR = 0·76, 95% CI 0·61–0·95) and directly observed therapy (AOR = 0·34, 95% CI 0·29–0·39).

Factors associated with TB-specific and non-TB-specific mortality

Multinomial regression showed that, after controlling for other variables, risk factors associated with TB-specific and non-TB-specific mortality included age ⩾75 years, residence in a long-term care facility, ESRD, AFB-smear positivity, TB-culture positivity and notification from an ordinary ward or intensive care unit (Table 3). Protective factors for TB-specific and non-TB-specific mortality included directly observed therapy. Additionally, malignancy and pleural effusion on chest radiographs were significantly associated with a higher risk of non-TB-specific mortality; while high school, university or higher education and a cavity on chest radiograph were significantly associated with a lower risk of non-TB-specific mortality.

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Table 3. *Multinomial regression: demographic and clinical variables associated with TB-specific and non-TB-specific death among elderly TB patients in Taipei, Taiwan (2006–2014)*[a]

Factors	TB-specific death AOR (95% CI)	Non-TB-specific death AOR (95% CI)
Age (years)		
65–74	1	1
75–84	2·01 (1·41–2·87)***	2·22 (1·83–2·69)***
⩾85	5·94 (4·18–8·44)***	4·22 (3·43–5·18)***
Education level		
No education	1	1
Elementary school	0·89 (0·62–1·28)	0·92 (0·73–1·16)
High school	0·70 (0·49–1·01)	0·72 (0·57–0·91)**
University or higher	0·76 (0·51–1·13)	0·61 (0·47–0·79)***
Unknown	0·73 (0·46–1·16)	1·11 (0·84–1·46)
LTCF residences	1·84 (1·25–2·70)**	1·50 (1·15–1·96)**
Unemployment	0·93 (0·62–1·39)	0·95 (0·75–1·22)
ESRD	2·34 (1·37–4·00)**	2·70 (1·95–3·74)***
Malignancy	1·21 (0·77–1·90)	3·53 (2·83–4·40)***
AFB-smear positivity	2·49 (1·91–3·23)***	1·40 (1·19–1·65)***
TB-culture positivity	1·74 (1·27–2·38)***	1·49 (1·24–1·78)***
Cavity on CXR	1·07 (0·76–1·51)	0·68 (0·53–0·86)**
Pleural effusion	1·30 (0·92–1·83)	1·43 (1·17–1·74)***
DOT	0·31 (0·24–0·41)***	0·34 (0·29–0·40)***
Source of notification		
Outpatient services	1	1
Ordinary ward	2·96 (2·27–3·87)***	2·39 (2·06–2·79)***
Intensive care unit	8·66 (5·23–14·33)***	6·25 (4·32–9·04)***

TB, tuberculosis; AOR, adjusted odds ratio; CI, confidence interval; LTCF, long-term care facility; ESRD, end-stage renal disease; AFB, acid-fast bacilli; CXR, chest radiograph; DOT, directly observed treatment.
[a] Reference is successfully treated individuals.
<0·01; *<0·001.

DISCUSSION

In this large cohort study of 5011 TB cases, the overall proportion of death was 32·7% in 2006–2014. After controlling for potential confounders, age ⩾75 years, ESRD, malignancy, AFB-smear positivity, TB-culture positivity, pleural effusion on chest radiograph and notification by ordinary ward or intensive care units were associated with a higher risk of all-cause death; while high education, a cavity on chest radiograph and directly observed therapy were associated with a lower risk of all-cause death.

This study found that the mortality was extremely high in elderly patients with TB, which was higher than 3·9% in Taiwanese elderly population without TB [12]. As compared with patients aged 65–74 years, patients aged 75 years and older had an even higher risk of TB-specific and non-TB-specific mortality. Higher mortality among older TB patients may be due to waning immunity and increased comorbidities. Additionally, elderly patients with TB are more likely to experience a delay in TB diagnosis and treatment [13], which might cause the high mortality in this population. Since elderly individuals are at an increased risk of TB infection [1], clinicians need to be aware of TB in this population.

We identified individual socio-economic status variables that were risk factors for mortality. Specifically, individuals with at least a high school education were associated with a lower risk of death. Prior studies have reported that people with higher socio-economic status are more likely to receive superior treatment and additional diagnostic procedures [14]. Moreover, patients with low educational levels had a poor understanding of TB, which resulted in a delay in diagnosis [15], interruption of treatment [16] and a higher rate of mortality [17]. To improve TB treatment outcomes in elderly individuals, future control programmes should particularly target patients with a lower educational level.

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This study found that a cavity on chest radiograph was associated with a lower risk of mortality. The protective effect of cavitary diseases on TB mortality in this study may reflect the fact that cavitary diseases raise the suspicion for TB in clinicians' minds and reduce diagnostic delay [18]. Since elderly patients with TB are more likely to have a non-specific clinical presentation at TB onset (e.g. no cavity lesions on chest radiograph) [4, 19], elderly patients suspected to have TB should be evaluated carefully to ensure early initiation of treatment.

This study showed that patients receiving directly observed therapy had a lower risk of mortality than those on self-administered therapy. In the Taipei DOTS programme, each directly observed treatment (DOT) observer monitors 5–10 patients with TB. DOT observers are trained to interview patients with TB about their TB symptoms and complications of treatment under the supervision of public health nurses. When patients with TB on DOT have, for example, worsened dyspnoea or blurred vision, public health nurses contact the doctors to arrange a hospital visit. Public health nurses daily check the regimen and dosage of TB drugs of each DOT patient according to TB treatment guidelines daily [20], and remind prescribing doctors, if needed, to ensure the patients are provided with appropriate TB drugs. DOT has been recommended for TB patients to improve treatment adherence [21]. Our study suggests that DOT programme should be applied to all elderly patients with TB to further reduce mortality.

Consistent with previous reports, long-term care facility residences [23], malignancy [24], ESRD [24], AFB-smear positivity [25], TB-culture positivity [24], pleural effusion on chest radiograph [24] and notification from an ordinary ward or intensive care unit [25] were associated with a higher risk of mortality.

The strengths of this study included that this was a city-wide population-based study with a large number of patients enrolled in the cohort, and treatment outcomes were tracked and recorded using standardised systems. However, several limitations should be considered when interpreting the findings of this study. First, this was a secondary-data study. Important information about TB patients, e.g. intravenous drug use, was not available in the surveillance data. Second, the cause of death among TB patients relied on ICD-9-CM codes in the Taiwan Death Certification Registry, and the outcome of cause of death may have been misclassified. This non-differential misclassification of outcome would bias the results towards a null association. Finally, the external validity of our findings may be a concern because almost all our enrollees were Taiwanese. The generalisability of our results to other non-Asian ethnic groups requires further verification.

CONCLUSIONS

According to the above analysis, this study found that the proportion of death among elderly patients with TB in Taipei, Taiwan, was high. Age $\geqslant$75 years, ESRD and malignancy were associated with a higher risk of all-cause mortality; while high education, a cavity on chest radiograph and directly observed therapy were associated with a lower risk of all-cause death. To improve TB treatment outcomes, future control programmes should particularly target individuals with comorbidities (e.g. ESRDs and malignancy) and those with a lower socio-economic status (e.g. not educated). Additionally, a directly observed therapy programme should be applied to all elderly patients with TB to further reduce mortality.

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DECLARATION OF INTEREST

None.

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