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Determinants of mortality before start of and during tuberculosis treatment among elderly patients: a population-based retrospective cohort study

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Abstract

Background: people with weakened immunity because of age or co-morbidities comprised the fastest growing portion of tuberculosis (TB). Higher mortality before or during TB treatment was observed. In spite of the increasing longevity worldwide, surveys focussing specifically on elderly TB are scarce.
Objective: to identify prognostic factors of mortality before and during TB treatment among the elderly.
Methods: we provided a retrospective cohort study of patients aged 65 and above with pulmonary TB in an Asian city with ageing population. A total of 2,546 patients were enrolled, including 743 (29.2%) cases aged 85 or beyond. Study subjects were categorised by treatment outcomes: treatment success, death prior to TB treatment or death during TB treatment.

Demographics and laboratory findings were compared between the three groups.
Results: after controlling for potential confounders, advanced age was the leading determinant of mortality. Adjusted odds ratios (AORs) of death during treatment were 1.79 (aged 75–84) and 3.43 (aged 85 and above) while comparing with patients aged 65–74. AORs of death prior to treatment were 2.95 and 5.66. Other prognostic factors included malignancy, end-stage renal disease receiving dialysis, need of intensive or long-term care, result of sputum acid-fast bacilli examination, findings of pleural effusion on chest X-ray and educational level.
Conclusion: this research manifested significant determinants of mortality in elderly patients prior to or during TB treatment. High awareness, timely intervention and close monitoring of treatment are recommended to older TB patients, especially with the properties mentioned in this study.

Keywords: *tuberculosis, older people, aged, mortality, unfavourable outcomes*

Introduction

Tuberculosis (TB) has long prevailed and caused a great number of deaths of infectious disease worldwide. Each year, over 8 million of new cases were notified and 1 million died from it. Individuals with weakened immunity because of age is one of the fastest growing strata [1, 2]. In last decade, patients aged 65 and older comprised approximately one-third of the TB population in the United States or Europe [3, 4]. In Asian countries, the percentage may exceed 50% [5]. Though the Directly Observed Therapy and Short-course drug therapy (DOTS) has been widely applied with significant benefits, treatment outcomes of elderly patients seemed to be more obstinate to improve than younger ones. According to recent reviews, rates of cure or treatment completed of TB were much lower in subjects aged 65 and above (i.e. documented sputum culture conversions, USA: 74 versus 80% [3]; cure or treatment completed at 1 year, Hong Kong: 72.4 versus 87.4% [6]).

Deaths at diagnosis or during treatment are the major negative outcomes of elderly TB patients [7–9]. In our previous analysis, it compromised 98.2% reasons of unfavourable and 23.2% of total endpoints [5]. Besides, while comparing with elderly patients with hospitalised community-acquired pneumonia, mortality rate of TB was 2- to 3-fold higher than those with TB (i.e. USA, mortality of national survey of TB: 28.2% [3] versus analysis of hospitalised community-acquired pneumonia of Medicare: 10.6% [10]). A number of reports implied that delayed diagnosis of TB may play a role in it. Among older subjects, TB could present with non-specific clinical manifestations. Typical symptoms, such as fever, haemoptysis and acid-fast bacilli (AFB) in sputa, are usually less likely while comparing with younger adults [11, 12]. These factors may postpone the timely intervention and worsen treatment outcomes.

While longevity is swelling worldwide, a more comprehensive knowledge of the epidemiological features of elderly TB population is crucial to improve the efficacy of management policy. However, information specifically focussing on elderly TB population is scarce. Here, we performed a city-wide cohort study of elderly patients to identify determinants of mortality before start of and during TB treatment in this rapidly expanding population. The study sample was taken from a well-formulated surveillance database of TB in an Asian city with high proportion of older patients.

Methods

Study population and data source

This is a 7-year retrospective cohort study performed in Taipei City, Taiwan. TB surveillance data collected by Taipei city government were analysed. Study subjects were citizens of Taipei city aged 65 and above with culture-positive pulmonary TB (PTB) between 2006 and 11. A structured registry form, which was used to collect patient information including socio-demographic characteristics, clinical findings, underlying diseases and TB treatments, was applied to each case. Patients were registered to Taipei city government until treatment success, treatment failure, transfer, default or death, as defined in the criteria of TB control of World Health Organization (WHO) [13]. Every study cases were invited to join DOTS, which included a trained supervisor to observe patients taking medications and adherence-promoting incentives equal to USD$2 per day [9].

Patients who were lost, transferred or had treatment failure were not included for final analysis because of limited number [14]. This study was approved by the Institutional Review Board of Taipei City Hospital.

Outcome variables

Study subjects were categorised according to the treatment outcomes: treatment success, death prior to initiation of TB treatment or death during TB treatment. The group of treatment success was defined as patients who were cured, confirmed bacteriologically or completed an appropriate course of TB treatment within study period. Death prior to initiation of treatment was defined as death between the time of getting registered to the TB surveillance system and receiving any one of TB medications that defined by WHO. Death during treatment was defined as death occurred while receiving TB medications, irrespective of cause.

Explanatory variables

Explanatory variables included sociodemographic factors (i.e. age, gender, marital status, education level, nursing home residency, smoking, alcohol use and employment status), laboratory findings (i.e. readings of chest X-ray (CXR), results of AFB smear, drug resistance status), underlying diseases (i.e. malignancy and end-stage renal disease (ESRD) receiving dialysis) and source of notification. The source of notification was defined as the medical department that reported the case to the TB surveillance system, including ordinary wards, intensive care units (ICUs) or outpatient services.

Statistical analysis

Subjects with successful treatment were regarded as the reference group. In bivariate analysis, χ^2 test was used to assess the association of selected factors and treatment outcomes. All variables found to be statistically significant ($P < 0.10$) were considered for inclusion in backward stepwise multinomial regression analysis. This yielded a final model that included factors with a P value of <0.05. Adjusted odds ratios (AORs) were reported to show the strength of associations. Analyses were done with SPSS version 19.0 statistical software (SPSS, Chicago, IL, USA).

Results

There were 2,576 cases aged 65 and above identified from the TB surveillance system of Taipei city government within study period. 70.6% subjects received DOTS. Of the identified cases, 30 were excluded due to treatment discontinuation because of lost to follow-up ($n = 16$), still under treatment ($n = 8$), transferred out of the city ($n = 4$) and treatment failure ($n = 2$). The remaining 2,546 patients were enrolled to final analysis.

Mean age of the study subjects was 79.9 years (range: 65–98). Number of subjects aged 65–74, 75–84, and 85 and above were 642 (25.2%), 1,161 (45.6%) and 743 (29.2%), respectively. 77.3% were male. One thousand eight hundred and seventy-one (73.5%) subjects had an education of elementary school or beyond. Fifty-seven subjects (2.2%) had TB history and were regarded as relapse cases. Analysis of laboratory presentation revealed that 1,418 (55.7%) cases had positive results of AFB smear at the initial assessment, 359 (14.1%) had cavity and 216 (8.5%) had pleural effusion on CXR. One thousand six hundred and eighty-nine cases (66.3%) were successfully treated, 204 cases (8.0%) died before start of TB treatment and 653 cases (25.6%) died during TB treatment. Total mortality was decreased from 32.7% in 2006 to 30.4% in 2011 (P for annual trend = 0.597). Patient's characteristics, laboratory findings, treatment outcomes and the results of bivariate analysis are shown in Table 1. Determinates of mortality found by multiple regression are given in Table 2.

Death prior to initiation of treatment

Of 204 patients who died before the start of treatment, 170 (83.3%) cases had AFB-negative results at the initial assessment. Among the remaining, 31 (15.2%) cases died on the same day when AFB-positive results were documented and 3 (1.5%) were initially diagnosed as non-tuberculosis mycobacteria infections.

As shown in Table 1, age was the most relevant factor of mortality before the start of TB treatment. It increased from 3.3% (aged 65–74), 8.1% (aged 75–84) to 12.0% (aged 85 and above). Other variables associated with higher risks of mortality were lower education levels, smoking, malignancy, AFB smear negativity and getting notification from ICUs.

Table 2 displays the results of multinomial regression. Advanced age remained to be the most important variable of mortality prior to TB treatment. Patients aged 75–84 had an AOR of 2.64 while comparing with those aged 65–74. Patients aged 85 and above had an AOR of 5.04. Malignancy, negative results of AFB smear and notification from ICUs were related to higher mortality rates as well. In contrast, patients with cavity on CXR or higher level of education had lower risks of death before the initiation of TB treatment.

Death during TB treatment

Among 653 patients who died during TB treatment, 416 (63.7%) and 65 (10.0%) subjects were reported as TB cases by ICUs or ordinary wards. Ninety-six (14.7%) subjects had malignancy; 30 (4.6%) had ESRD and were under dialysis therapy. Seventy-five (11.5%) subjects stayed at nursing homes for long-term care.

According to the results of bivariate analysis, higher mortality during TB treatment was coherent to advanced age, from 16.2% (aged 65–74), 24.3% (aged 75–84) to 35.9% (aged 85 and above). Other noticeable prognostic factors were nursing home residency, unemployment, ESRD receiving dialysis, malignancy, AFB positivity, pleural effusion on CXR and notification from ordinary wards or ICU instead of outpatient healthcare facilities. Patients with education above high school had lower risk of death during treatment. Multinomial regression confirmed the impacts to mortality of advanced age, nursing home residency, malignancy, ESRD receiving dialysis, cavity or pleural effusion on CXR, AFB positivity and source of notification.

Discussion

TB has been identified to be a latent infectious disease that may reactivate by immunosensescence, malnutrition, comorbidities or other conditions related to increasing age. In view of swelling longevity worldwide, a number of countries now face the challenge of elderly TB [12, 15, 16]. The present study was a city-wide, population-based survey with standardised surveillance system. Since patients aged 65 or above accounted for more than a half of total TB population in the city of research [5], this survey offered a representative exploration of determinants of mortality among older TB patients.

In this study, approximately one-third of subjects died before start of or during TB treatment. Though it was much higher than

Table 1. Sociodemographic and clinical findings by treatment outcome among elderly TB patients in Taipei, Taiwan—2006–11

Factors	Treatment success* (*n* = 1,689)	Death prior to initiation of treatment (*n* = 204)		Death during TB treatment (*n* = 653)	
	n (%)	*n* (%)	OR (95% CI)	*n* (%)	OR (95% CI)
Age (years)					
65–74	517 (30.6)	21 (10.3)	1	104 (15.9)	1
75–84	785 (46.5)	94 (46.1)	2.95 (1.81–4.79)	282 (43.2)	1.79 (1.39–2.30)
≥85	387 (22.9)	89 (43.6)	5.66 (3.46–9.27)	267 (40.9)	3.43 (2.64–4.46)
Gender					
Female	390 (23.1)	54 (26.5)	1	134 (20.5)	1
Male	1,299 (72.9)	150 (73.5)	0.83 (0.60–1.16)	519 (79.5)	1.16 (0.93–1.45)
Marital status					
Married	131 (7.8)	16 (7.8)	1	53 (8.1)	1
Unmarried	1,550 (91.8)	188 (92.2)	0.99 (0.58–1.71)	600 (91.9)	0.96 (0.69–1.33)
Unknown	8 (0.8)	0	–	0	–
Education level					
Not educated	185 (11.0)	35 (17.2)	1	91 (13.9)	1
Elementary school	456 (27.0)	49 (24.0)	0.57 (0.36–0.91)	188 (28.8)	0.84 (0.62–1.14)
High school	507 (30.0)	47 (23.0)	0.49 (0.31–0.78)	168 (25.7)	0.67 (0.50–0.91)
University and above	330 (19.5)	18 (8.8)	0.29 (0.16–0.52)	108 (16.5)	0.67 (0.48–0.93)
Unknown	211 (12.5)	55 (27.0)	1.38 (0.86–2.20)	98 (15.0)	0.94 (0.67–1.34)
Nursing home resident					
No	1,594 (94.4)	192 (94.1)	1	578 (88.5)	1
Yes	95 (5.6)	12 (5.9)	1.05 (0.57–1.95)	75 (11.5)	2.18 (1.59–2.99)
Smoker					
No	1,482 (87.7)	188 (92.2)	1	568 (87.0)	1
Yes	196 (11.6)	14 (6.9)	0.56 (0.32–0.99)	85 (13.0)	1.13 (0.86–1.49)
Unknown	11 (0.7)	2 (1.0)	1.43 (0.32–6.52)	0	–
Any alcohol use					
No	1,581 (93.6)	196 (96.1)	1	619 (94.8)	1
Yes	93 (5.5)	6 (2.9)	0.52 (0.23–1.20)	29 (4.4)	0.80 (0.52–1.22)
Unknown	15 (0.9)	2 (1.0)	1.08 (0.24–4.74)	5 (0.8)	0.81 (0.31–2.35)
Unemployment					
No	193 (11.4)	20 (9.8)	1	56 (8.6)	1
Yes	1,496 (88.6)	184 (90.2)	1.19 (0.73–1.93)	597 (91.4)	1.38 (1.01–1.88)
ESRD receiving dialysis					
No	1,650 (97.7)	199 (97.5)	1	623 (95.4)	1
Yes	39 (2.3)	5 (2.5)	1.06 (0.41–2.73)	30 (4.6)	2.04 (1.26–3.31)
Malignancy					
No	1,570 (93.0)	176 (86.3)	1	557 (85.3)	1
Yes	119 (7.0)	28 (13.7)	2.10 (1.35–3.26)	96 (14.7)	2.27 (1.71–3.03)
TB history					
New case	1,652 (97.8)	199 (97.5)	1	638 (97.7)	1
Relapse	37 (2.2)	5 (2.5)	1.12 (0.44–2.89)	15 (2.3)	1.05 (0.57–1.93)
Acid-fast bacilli smear					
Negative	949 (56.2)	170 (83.3)	1	299 (45.8)	1
Positive	740 (43.8)	34 (16.7)	0.26 (0.18–0.38)	354 (54.2)	1.52 (1.27–1.82)
Cavity on chest X-ray					
No	1,427 (84.5)	191 (93.6)	1	569 (87.1)	1
Yes	262 (15.5)	13 (6.4)	0.37 (0.21–0.66)	84 (12.9)	0.80 (0.62–1.05)
Pleural effusion on chest X-ray					
No	1,574 (93.2)	183 (89.7)	1	573 (87.7)	1
Yes	115 (6.8)	21 (10.3)	1.57 (0.96–2.56)	80 (12.3)	1.91 (1.41–2.58)
MDR-TB					
No	1,680 (99.5)	204 (100)	–	646 (98.9)	1
Yes	9 (0.5)	0	–	7 (1.1)	2.02 (0.75–5.45)
Source of notification					
Outpatient services	980 (58.0)	120 (58.8)	1	172 (26.3)	1
Ordinary ward	672 (39.8)	69 (33.8)	0.84 (0.61–1.15)	416 (63.7)	3.52 (2.88–4.32)
Intensive care unit	37 (2.2)	15 (7.4)	3.31 (1.77–6.21)	65 (10.0)	10.01 (6.48–15.46)

CI, confidence interval; ESRD, end-stage renal disease; MDR-TB, multidrug-resistant tuberculosis; OR, odds ratio; PTB, pulmonary tuberculosis.
*Reference group.

Table 2. Multinomial regression: demographic and clinical variables associated with death before and during TB treatment among elderly TB patients in Taipei, Taiwan (2006–11)[a]

Death prior to initiation of treatment			Death during TB treatment		
Factors	AOR	95% CI	Factors	AOR	95% CI
Age (years)			Age (years)		
65–74	1		65–74	1	
75–84	2.64	1.60–4.35	75–84	1.87	1.43–2.44
≥85	5.04	3.02–8.41	≥85	3.4	2.56–4.53
Education level			Education level		
Not educated	1		Not educated	1	
Elementary school	0.58	0.36–0.95	Elementary school	0.91	0.65–1.26
High school	0.46	0.28–0.75	High school	0.71	0.51–0.98
University and above	0.25	0.13–0.46	University and above	0.75	0.52–1.08
Unknown	1.36	0.83–2.22	Unknown	0.97	0.67–1.41
–	–	–	Nursing home resident	1.59	1.12–2.25
Malignancy	2.72	1.70–4.35	Malignancy	2.75	2.01–3.75
–	–	–	ESRD receiving dialysis	1.92	1.13–3.24
–	–	–	Cavity on chest X-ray	0.72	0.53–0.96
–	–	–	Pleural effusion on CXR	1.76	1.27–2.44
AFB positivity	0.29	0.20–0.44	AFB positivity	1.57	1.27–1.92
Source of notification			Source of notification		
Outpatient services	1		Outpatient services	1	
Ordinary ward	0.91	0.65–1.27	Ordinary ward	2.89	2.33–3.59
Intensive care unit	2.97	1.53–5.77	Intensive care unit	8.22	5.23–12.94

AOR, adjusted odds ratio; CI, confidence interval; ESRD, end-stage renal disease; PTB, pulmonary tuberculosis.
[a]Reference is successfully treated individuals.

elderly patients hospitalised because of community-acquired pneumonia (i.e. 10.6% from the study of Kaplan *et al.* [10]), the mortality was close to the result of Pratt *et al.* [3] who analysed the data from National Tuberculosis Surveillance System of United States within 1993 and 2008. In their investigation, subjects older than 65 years comprised 24.4% of adult TB. Twenty-one per cent died during therapy. 7.2% were dead at diagnosis, and the ratio was augmented significantly according to advanced age. Salvado *et al.* [17] observed the similar phenomenon, and the mortality was increased with age. While comparing TB patients aged 65–79 with those aged >80, overall mortality was significantly higher in the latter group (20.7 versus 51.9%). Our survey confirmed these findings; in addition, ORs were reported by stratifying elderly patients by 10 years of age and factors relating to higher mortality were provided. This information may be advantageous in comprehending the population dynamics of elderly TB.

Some experts suggested that high mortality of TB in the elderly may be related to waning immunity and more co-morbidities [13]. According to results of multinomial regression, disease states such as malignancy or staying in ICUs were related to increasing risks of death prior to treatment. In addition to malignancy and the need of intensive care, ESRD receiving dialysis and the requirement of long-term medical service in nursing homes were associated to elevated mortality during TB treatment. This may be owing to the fact that these patients were suffered from complex diseases. Opportune diagnosis and profitable treatment were special challenges to healthcare providers among this population. According to the review of Hagan G. *et al.* [18], management of TB in ICUs was a great challenge in regards to the difficulty of accurate interpretation of laboratory results, prompt assessment of drug effectiveness and adverse effects. Additionally, these patients were more easily to have respiratory failure, organ dysfunction or drug toxicity.

Delayed diagnosis is a resistant problem of TB population, especially among older subjects. Misinterpretation of initial symptoms and laboratory findings is one of the indicators [10]. Some researches revealed that non-specific presentation at TB onset, such as negative results of AFB smear, no cavity or lesions on CXR, was more prevalent in older than younger patients [4, 15] In our study, the overall positive rate of AFB smear examinations was 44.3% which was slightly higher than studies in Hong Kong [6], USA [3] and Spain [17]. However, it was much lower than the rate of adult patients based on our previous analysis [5]. According to the results of multinomial regression, patients with AFB positivity prior to initiation of TB treatment had lower risk of death. This finding is coherent to some reports that presented the significant association between AFB negativity and higher mortality before start of treatment [16]. Possible reasons included that older patients may have difficulties in coughing up a suitable sputum sample for AFB examining because of poor physical properties. The inaccurate interpretation of laboratory findings could result in delayed diagnosis, which led to higher mortality [19–21]. Though AFB smear is the standard screening method of TB, it may also

be one of the important barriers of timely intervention. In contrast, we found that the presence of cavity on CXR was related to lower mortality while patients received TB treatment. It implied that radiological findings may be beneficial for favourable outcomes. Lin *et al.* [22] had manifested that cavity on CXR was a sign of value for TB diagnosis among elderly, which hastened clinicians to make diagnosis. In the other part of view, it is worthwhile to apply new diagnostic methods (e.g. Gene X-pert or fluorescence microscopy) [23, 24] as well as to improve the sensitivity of *Mycobacterium tuberculosis* detection in sputum samples by improving the quality of sputum collection [25] to reduce delays in intervention of elderly TB.

Socioeconomic status (SES) was important prognostic factor of mortality among older TB patients as well. Education is one of the representative factors [26]. Hoa *et al.* [27] notified that patients with lower educational levels had poor understanding of TB. It resulted in diagnosis delay and unfavourable outcomes. Besides, education was found to have a remarkable latent effect on mortality into late life [28]. Prior researches mentioned that people with lower education of SES variables were related to poor long-term outcomes of a number of chronic diseases, even with standard treatment protocol (e.g. acute myocardial infarction or diabetes) [29, 30]. It may be partially explained by limited access to appropriate care, less diagnostic procedure and failure to identify symptoms correctly among population with disadvantaged SES. These previous findings intensified our results concerning the impacts of education in elderly TB population. Therefore, to improve the efficacy of TB management in the older population, the control programmes and education are recommended to target to those with lower educational levels.

Certain limitations should be considered when interpreting our findings. First, this was a research based on secondary data. Individualised information that was not recorded in the registry form, such as specific disease states at its severity (e.g. diabetes, HIV and lung diseases) or social history (e.g. contact history and drug abuse), was not available to discuss. Second, cause of death was not routinely documented in the surveillance system. It was not practicable to distinguish whether TB was the major cause of death. Third, because of limited number of subjects with multiple drug-resistant TB (MDRTB), we cannot establish the association between MDRTB and mortality.

Conclusion

In conclusion, this study found that TB patients aged 65 and above had high mortality. Advanced age, malignancy and notification from ICUs were associated with elevated risks of death before or during TB treatment. In addition, patients with ESRD under dialysis and staying in nursing homes had higher mortality during TB treatment. Cavity of CXR was significantly associated with lower mortality during treatment, and AFB negativity increased the risk of death before start of treatment. High awareness, timely intervention and close monitoring of treatment of TB are recommended to older patients with the properties mentioned in this study to improve the favourable outcomes of TB management and control policy.

Key points

- The most evident determinant of elderly mortality prior to or during TB treatment is advanced age (AORs 1.87–5.04).
- Other remarkable factors are specific co-morbidities (e.g. malignancy), pleural effusion on CXR and lower educational level.
- Nearly half of TB elderly had negative results of acid-fast smear. It was related to higher mortality prior to TB treatment.
- Clinicians should keep high awareness and apply multiple diagnostic procedures to the elderly TB suspects.

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Conflicts of interest

None declared.

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