The Impact of Age on the Demographic, Clinical, Radiographic Characteristics and Treatment Outcomes of Pulmonary Tuberculosis Patients in Taiwan

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Abstract

Background: The characteristics of pulmonary tuberculosis (TB) in the elderly are different from young patients. This leads to delay in diagnosis and higher mortality from TB in the aged population. The aim of this study was to investigate the impact of age on the demographic, clinical, radiographic characteristics, and treatment outcomes of pulmonary TB patients in Taiwan.

Materials and Methods: We performed a retrospective analysis of the medical charts and chest radiographs of 83 elderly (≥60 years old) and 74 young (< 60 years old) culture-proven pulmonary TB patients from 1 August 2003 to 31 July 2006.

Results: Elderly patients showed lower frequencies of infectious TB contact history, alcoholism, cavity, and positive acid-fast bacilli sputum smears. In contrast, the elderly population had higher frequencies of chronic obstructive lung disease, heart failure, stroke, dyspnea, lower lung field involvement, pleural effusion and mortality. There were no differences between these two groups regarding sex, initial body weight, previous TB disease, hospital admission, diabetes mellitus, end-stage renal disease, neoplasm, liver cirrhosis, upper lung field involvement, cure, and treatment completion. Furthermore, age of 60 and older, lower initial body weight less than 50 kg, coexisting medical diseases, and extensive radiographic disease were factors independently associated with unfavorable outcomes.

Conclusions: Elderly patients with pulmonary TB are more likely to present with negative sputum smears, cavity-negative lesions, lower lung field involvement and pleural effusion on chest radiographs. The prognosis is poor for the elderly pulmonary TB patients with lower body weight, coexisting medical diseases, and extensive radiographic disease.

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Introduction

The incidence of tuberculosis (TB) has been falling in many developed countries; however, there is a trend of an increasing proportion of TB among the elderly [1, 2]. With the decreasing birth rate and increasing life expectancy, the aging of the population is occurring in many parts of the world. Thus, TB in elderly people will become an increasingly important problem [3]. The age of TB patients in Taiwan showed a rising trend from 1957 to 2001. A high index of suspicion and prompt investigation of elderly patients with signs and symptoms characteristic of pulmonary TB may allow earlier diagnosis and treatment [4].

Much of the classical description of TB was derived when TB was a highly prevalent disease in young adults. With age-associated physiological, psychological, and social changes compounded by the high prevalence of chronic degenerative diseases in relatively affluent societies, there are ample reasons to expect that TB in elderly people may exhibit a different course [5]. It has been suggested that the characteristics of TB in elderly people are different from those observed in young adult patients, and that they should be classified as separate diseases [6, 7].

Some reports have described a delay in the diagnosis of TB in elderly patients, mainly due to an atypical presentation of the disease [8] and/or to the lower awareness of the disease among this population [9]. Accordingly, it has also been suggested that when these differences are ignored, the establishment of a diagnosis may be delayed, leading to an increase in morbidity and mortality in the elderly group [10].

Here, we had attempted to compare, in a sizable study sample, the clinical presentation of elderly patients with

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those of young patients. Furthermore, the effect of various factors on treatment outcomes after 1 year from the initiation of anti-TB treatment was assessed. The study sample included inpatients and outpatients in a developed Asian city with an aging population and a high prevalence of TB.

Materials and Methods

Study Setting and Patients

This study was conducted at Kaohsiung Municipal Hsiao-Kang Hospital which is a 500-bed, university-affiliated teaching hospital that serves as a tertiary referral center and a primary-care facility in southern Taiwan. From a retrospective review of medical records, 157 consecutive adult patients with pulmonary TB detected in the period from 1 August 2003 to 31 July 2006 were selected. Cases were identified from the hospital coding system and microbiology department records. Patients included outpatients and inpatients. In this institution, the main criteria for hospital admission of tuberculous patients include sepsis, hemoptysis, respiratory failure, advanced malnutrition, and pleural effusion. However, approximately two-third of hospitalized tuberculous patients are admitted for treatment or diagnosis confirmation even in the absence of the above-mentioned criteria. Patients were excluded because of one of the following reasons: those who were younger than 18 years, or those who were not Taiwanese, and those who were already diagnosed as TB at other hospital. The diagnosis of pulmonary TB was based on at least one sputum culture positive for *Mycobacterium tuberculosis*. This study was reviewed and approved by the human experiment and ethics committee of Kaohsiung Municipal Hsiao-Kang Hospital.

Sputum samples were obtained by spontaneous morning expectoration. All sputum smears were concentrated and stained with Ziehl–Neelsen stains to screen for TB by trained microbiology technicians. Each sputum sample was prepared in a Löwenstein–Jensen culture medium and Middlebrook 7H11 selective agar and maintained for at least 8 weeks to detect the presence of growing organisms. All patients had a medical chart, microbiology results, and chest radiograph (CXR). The initial CXR taken when patients first visited hospital were independently reviewed by two external chest physicians, both of whom were unaware of the patient's clinical data. Differences were then resolved by consensus.

Study Design and Data Collection

Elderly patients were defined as patients aged 60 and older. Patients aged 18–59 were defined as young patients. There were approximately equal numbers of patients for comparison. Demographic information that we collated include age, sex, initial body weight taken when patients first visited hospital and whether or not hospital admission. We recorded risk factors for TB infection including previous TB disease, infectious TB contact history, alcoholism, illegal drug use, long term glucosteroid use, immunosuppressive drug use and coexisting medical diseases such as diabetes mellitus, end-stage renal disease, neoplasm, chronic obstructive lung disease, liver cirrhosis, heart failure, stroke, human immunodeficiency virus (HIV) infection, silicosis, and gastrectomy history. Initial presenting symptoms before patients first visited hospital included the presence of cough, expectoration, hemoptysis, weight loss, fever, night sweats, anorexia, fatigue and dyspnea. Patients were considered to have positive cough, expectoration, fever, night sweats, anorexia, fatigue and dyspnea if these symptoms were present for 2 weeks or more; less than this was coded as negative for the analysis. Weight loss was defined as positive if it was greater than 10% of the body weight within the last 6 months. Fever was defined as a body axillary temperature above 37.5 °C. Hemoptysis was recorded as positive if it occurred even once.

The results of the CXR were categorized as the involved field and the pattern. The involved field was categorized as right upper field, right lower field, left upper field and left lower field. An upper field lesion was defined as the presence of any lesion above the third posterior rib. The radiographic presentation was categorized as normal, nodule, consolidation, infiltration, cavity, atelectasis, or pleural effusion. The chart reviewer was unaware of the age of the patient. Culture results and the initial smear interpretation of each sputum sample were verified.

Treatment outcomes after 1 year from the initiation of anti-TB treatment were extracted from the records. They were analyzed and defined according to the World Health Organization recommendations [11]. ''Cure'' is defined as a patient who was sputum smear-negative in the last month of treatment and on at least one previous occasion. ''Treatment completed'' is defined as a patient who had completed treatment but who did not meet the criteria to be classified as a cure or a failure. ''Treatment failure'' is defined as a patient who was sputum smear-positive at 5 months or later during treatment. ''Died'' is defined as a patient who dies for any reason during the course of treatment. ''Default'' is defined as a patient whose treatment was interrupted for 2 consecutive months or more. ''Transfer out'' is defined as a patient who has been transferred to another recording and reporting unit and for whom the outcome is not known. A favorable outcome was defined as including cure and treatment completed. Any other outcome was classified as unfavorable.

Statistical Analysis

Univariate comparisons between elderly patients and young patients were performed using the χ^2 test or a Fisher's exact test for categorical variables and the Student's t-test for continuous variables where appropriate. All tests of significance were two sided; $p < 0.05$ was considered statistically significant.

To identify variables that might affect treatment outcomes, comparison of the groups with favorable and unfavorable outcomes was made using univariate analysis and multiple logistic regression analysis. An attempt was made to include all key factors from demographic characteristics, bacteriology results, coexisting medical diseases, initial presenting symptoms, and initial presenting CXR findings, but, to simplify the statistical analysis, preference is given to summary variables and dichotomized variables with likely effect on outcome. Nine variables were thus selected: aged 60 and older, male, lower initial body weight less than 50 kg, hospital admission, coexisting medical diseases, dyspnea, extensive radiographic disease that is defined as radiographic extent greater than that of one lung, presence of cavity, and positive initial sputum smear. After the initial univariate analysis, the variables were put into the regression model to identify those independently associated with unfavorable outcome. A forward stepwise approach was used in the regression analysis, with the probability of F to enter being 0.05 or less and the probability of F to remove being 0.10 or greater. All analyses were performed using a statistical software program (version 12.0, SPSS, Chicago, IL, USA).

Results

Demographic Characteristics and Bacteriology Results

Of the 157 culture-proven pulmonary TB patients, 83 patients aged 60 and older (52.9%) and 74 patients aged 18–59 (47.1%) participated in this study. The elderly group had a median age of 74 years of age and the young group had a median age of 46 years of age. The baseline demographic characteristics and bacteriology results of elderly and young patients with pulmonary TB are shown in table 1. The male sex predominated in both groups, making up approximately 75%. There were no statistically significant differences between the two groups with respect to male predominance, initial body weight, previous TB disease, and hospital admission. The elderly people were less likely to have infectious TB contact history. No patient had the following risk factors for TB infection, including illegal drug use, long term glucosteroid use, immunosuppressive drug use, HIV infection, silicosis, and gastrectomy history. Besides, there was a lower frequency of sputum acid-fast bacilli positivity in the elderly.

Coexisting Medical Diseases

The coexisting medical diseases of the patients are summarized in table 2. Chronic obstructive lung disease, heart failure and stroke were more common in elderly patients. The elderly people were less likely to have alcoholism. There were no statistically significant differences between these two groups regarding diabetes mellitus, end-stage renal disease, neoplasm and liver cirrhosis.

Initial Presenting Symptoms

The patients' clinical symptoms at initial presentation are shown in table 3. Dyspnea was more common among elderly patients. There were no statistically significant differences between these two groups in the presence of cough, expectoration, hemoptysis, weight loss, fever, night sweat, anorexia and fatigue.

Initial Presenting CXR Findings

The initial presenting CXR findings are given in table 4. Among elderly patients, it was more common to find the lower lung field affected irrespective of whether TB was in the right or left side. However, the difference of cases where TB affected the upper field was not significant statistically between these two groups. Elderly patients had more pleural effusion but fewer cavity findings. In addition, the proportion of patients with normal, nodule, consolidation, infiltration and atelectasis pattern revealed by the CXR was not significantly different between these two groups.

Table 1
Comparison of demographic characteristics and bacteriology results of elderly and young patients with pulmonary tuberculosis (TB)[a].

	Age ≥ 60 year (n = 83)	Age < 60 year (n = 74)	OR (95% CI)	p-Value
Median age (years)	74	46		
Male sex	62 (74.7)	56 (75.7)	1.054 (0.510–2.178)	0.888
Initial body weight (SD) (kg)	53.53 (12.21)	56.54 (12.29)		0.138
Previous TB disease	14 (16.9)	9 (12.2)	1.465 (0.594–3.616)	0.405
Infectious TB contact history	1 (1.2)	7 (9.5)	0.117 (0.014–0.972)	0.027
Hospital admission	36 (43.4)	31 (41.9)	1.062 (0.564–2.002)	0.851
Positive acid-fast bacilli sputum smear	49 (59.0)	56 (75.7)	0.463 (0.233–0.922)	0.027

[a]Data are presented as No. (%) unless otherwise indicated

Table 2
Coexisting medical diseases in elderly and young patients with pulmonary TB[a].

	Age ≥ 60 year (n = 83)	Age < 60 year (n = 74)	OR (95% CI)	p-Value
Chronic obstructive lung disease	18 (21.7)	4 (5.4)	4.846 (1.558–15.074)	0.003
Diabetes mellitus	27 (32.5)	22 (29.7)	1.140 (0.579–2.244)	0.705
End-stage renal disease	2 (2.4)	1 (1.4)	1.802 (0.160–20.295)	1.000
Heart failure	6 (7.2)	0 (0.0)	1.078 (1.015–1.145)	0.030
Stroke	11 (13.3)	0 (0.0)	1.153 (1.060–1.254)	0.001
Neoplasm	7 (8.4)	3 (4.1)	2.180 (0.543–8.757)	0.336
Liver cirrhosis	2 (2.4)	5 (6.8)	0.341 (0.064–1.812)	0.256
Alcoholism	3 (3.6)	11 (14.9)	0.215 (0.057–0.803)	0.014

[a]Data are presented as No. (%) unless otherwise indicated

Table 3
Initial presenting symptoms in elderly and young patients with pulmonary TB[a].

	Age ≥ 60 year (n = 83)	Age < 60 year (n = 74)	OR (95% CI)	p-Value
Cough	74 (89.2)	68 (91.9)	0.725 (0.245–2.145)	0.561
Expectoration	54 (65.1)	58 (78.4)	0.514 (0.252–1.049)	0.065
Hemoptysis	9 (10.8)	15 (20.3)	0.478 (0.196–1.170)	0.101
Weight loss	26 (31.3)	26 (35.1)	0.842 (0.433–1.638)	0.613
Fever	26 (31.3)	17 (23.0)	1.529 (0.750–3.120)	0.241
Night sweats	7 (8.4)	4 (5.4)	1.612 (0.452–5.743)	0.458
Anorexia	21 (25.3)	13 (17.6)	1.589 (0.731–3.456)	0.240
Fatigue	9 (10.8)	3 (4.1)	2.878 (0.749–11.065)	0.110
Dyspnea	26 (31.3)	13 (17.6)	2.140 (1.004–4.565)	0.046

[a]Data are presented as No. (%) unless otherwise indicated

Table 4
The initial presenting chest radiograph findings in elderly and young patients with pulmonary TB[a].

	Age ≥ 60 year (n = 83)	Age < 60 year (n = 74)	OR (95% CI)	p-Value
Right upper field	58 (69.9)	51 (68.9)	1.046 (0.530–2.065)	0.896
Right lower field	52 (62.7)	34 (45.9)	1.973 (1.043–3.734)	0.036
Left upper field	52 (62.7)	47 (63.5)	0.964 (0.503–1.845)	0.911
Left lower field	51 (61.4)	30 (40.5)	2.338 (1.231–4.437)	0.009
Normal	3 (3.6)	6 (8.1)	0.425 (0.102–1.764)	0.308
Nodule	39 (47.0)	34 (45.9)	1.043 (0.556–1.955)	0.896
Consolidation	66 (79.5)	56 (75.7)	1.248 (0.588–2.648)	0.564
Infiltration	73 (88.0)	63 (85.1)	1.275 (0.508–3.199)	0.605
Cavity	19 (22.9)	37 (50.0)	0.297 (0.150–0.589)	<0.001
Atelectasis	12 (14.5)	5 (6.8)	2.332 (0.781–6.969)	0.121
Pleural effusion	19 (22.9)	7 (9.5)	2.842 (1.119–7.215)	0.024

[a]Data are presented as No. (%) unless otherwise indicated

Treatment Outcomes

Treatment outcomes after 1 year from the initiation of anti-TB treatment are depicted in table 5. Mortality for elderly patients was 26.5% in sharp contrast to 4.1% for young patients ($p < 0.001$). Only 65.1% of elderly patients had favorable outcomes (cure or treatment completion) in comparison with 86.5% of young patients. Univariate analysis shows that age of 60 and older ($p = 0.002$), lower initial body weight ($p = 0.002$), coexisting medical diseases ($p = 0.016$), dyspnea ($p = 0.023$), and extensive radiographic disease ($p = 0.014$) were all associated with unfavorable outcomes. On multiple logistic regression

Table 5
Treatment outcomes after 1 year from the initiation of anti-TB treatment in elderly and young patients with pulmonary TB[a].

	Age ≥ 60 year (n = 83)	Age < 60 year (n = 74)	OR (95% CI)	p-Value
Cure	21 (25.3)	24 (32.4)	0.706 (0.352–1.413)	0.324
Treatment completed	33 (39.8)	40 (54.1)	0.561 (0.298–1.058)	0.073
Treatment failure	0 (0)	0 (0)		
Died	22 (26.5)	3 (4.1)	8.536 (2.436–29.907)	0.000
Default	2 (2.4)	4 (5.4)	0.432 (0.077–2.431)	0.422
Transfer out	4 (4.8)	1 (1.4)	3.696 (0.404–33.838)	0.371
Still on treatment	1 (1.2)	2 (2.7)	0.439 (0.039–4.943)	0.602

[a]Data are presented as No. (%) unless otherwise indicated

Table 6
Independent predictive factors of unfavorable outcomes for pulmonary TB.

	Parameter estimate (β)	SE of β	OR (95% CI)	p-Value
Older age (≥ 60 year)	1.060	0.468	2.888 (1.154–7.224)	0.023
Lower initial body weight (< 50 kg)	1.452	0.457	4.272 (1.745–10.458)	0.001
Coexisting medical disease	1.315	0.511	3.726 (1.368–10.148)	0.010
Extensive radiographic disease	0.856	0.435	2.355 (1.004–5.523)	0.049

analysis, only age of 60 and older, lower initial body weight, coexisting medical diseases, and extensive radiographic disease remained as independent and significant risk factors (table 6). All independent risk factors have odds ratios more than two.

Discussion

Some of the observed differences between young and elderly patients may be related to a decrease in the immunologic status associated with aging. It is well known that elderly people have an impaired T-lymphocyte function, including the proliferative response [12]. In our study there also was a lower prevalence of positive acid-fast bacilli sputum smears in the elderly patients. This may be because it is more difficult to obtain adequate sputum from elderly patients. This could be attributed to their inability to produce sputum (due to weakness or to lack of cooperation) or to the 'lower' quality of the delivered sputum, i.e. more saliva secretion than pulmonary secretion. Recently, *Patel* et al. [13] reported the usefulness of fiberoptic bronchoscopy in the diagnosis of TB. Fiberoptic bronchoscopy may be helpful in some elderly patients who are suspected of having TB, but who cannot expectorate adequate sputum. Besides, few studies revealed that smear positivity was increased substantially by provision of simple interventions such as sputum-submission instructions [14, 15]. Perhaps sputum-submission instructions on how to expectorate sputum may aid diagnosis in elderly patients.

The impact of age on the radiographic presentation of pulmonary TB is important because misinterpretation of the images might delay appropriate diagnostic tests and the start of treatment, thus risking the dissemination of *Mycobacterium tuberculosis* to others. Most cases of pulmonary TB in elderly patients are reactivation diseases; 10–20% of cases result from primary infection or reinfection. Although reactivation TB classically involves the upper lobes of the lung, several works have reported atypical radiographic images of tuberculous lesions in elderly patients, suggesting that pulmonary lesions occur more often in lower lung fields [16–19]. Our findings are consistent with the above studies. Thus, clinicians must exercise caution when interpreting radiographic evidence of TB in elderly patients because of the possibility that infection may take hold in an atypical location in the lung fields.

It has been suggested that the higher frequency of lower lung disease in the elderly is due to immunologic abnormalities [20] or to a higher frequency of primary TB [21, 22]. We suggest an alternative explanation, based on the concept that the multiplication of *M. tuberculosis* is favored by a high oxygen tension [23]. Aging leads to increased alveolar ventilation and reduced perfusion [24–27], resulting in increased ventilation/perfusion mismatch and increased alveolar oxygen partial pressure. These changes should affect the lower lobes more than the upper lobes because the latter have a higher ventilation/perfusion ratio and higher alveolar oxygen partial pressure. Therefore, age-induced changes should favor multiplication of *M. tuberculosis* in lower lung zones.

With respect to radiographic images, and in close relationship with the poorer immunologic status, lung cavitation was less frequently seen in elderly patients [16, 19]. This lower frequency of cavitation has also been documented in other immunocompromised patients, such as HIV-positive subjects with associated TB [28]. One recent study revealed that cavitation was a predictor of smear positivity in patients with pulmonary TB [29]. Our data also confirmed a lower level of positive acid-fast bacilli sputum smears compatible with a lower prevalence of cavitation in the elderly pulmonary TB patients. Besides, our study also showed that the frequency of pleural effusion in pulmonary TB patients increased in the elderly. The observation suggests that a significant proportion of elderly patients may have newly acquired rather than reactivated TB, as tuberculous pleural effusion usually develops 3–7 months after exposure.

In the present study, all young pulmonary TB patients survived except 3 (4.1%), whereas 22 (26.5%) of the elderly patients died ($p < 0.001$). Some have even reported mortality rates as high as 20% to 40% in elderly TB patients [30]. Our results confirm that mortality of pulmonary TB patients is significantly higher in the elderly than in the young. Of the factors that have been found to exert an independent influence on outcome, lower initial body weight, coexisting medical diseases, and extensive radiographic disease were all more common in elderly patients. Although some deaths, especially those associated with coexisting medical diseases, might not be averted, careful clinical interpretation of the radiographic images may help to improve the outcomes of many elderly pulmonary TB patients.

In conclusion, this study identified some differences in elderly pulmonary TB patients in comparison to young

ones: a lower prevalence of infectious TB contact, alcoholism, and cavity as well as a lower level of positive acid-fast bacilli sputum smears. In contrast, the elderly population had a higher prevalence of dyspnea, lower lung zone involvement and pleural effusion. As expected, elderly tuberculous patients had more prevalence of some morbid concomitant conditions, such as cardiovascular disorders and chronic obstructive lung disease. In addition, age of 60 and older, lower initial body weight less than 50 kg, coexisting medical diseases, and extensive radiographic disease were factors independently associated with unfavorable outcomes. Pulmonary TB should be included in the differential diagnosis when elderly patients present with those unusual findings, thus avoiding postponing the diagnosis and the silent spread of TB into the community.

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