Research

Tuberculosis-associated mortality in Shanghai, China: a longitudinal study

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Objective To determine excess mortality in a cohort of people with tuberculosis in Shanghai.

Methods Participants were local residents in 4 (of 19) districts in Shanghai, registered in one of four tuberculosis clinics between January 1, 2004 and December 31, 2008. Baseline data were collected at the most recent diagnosis of tuberculosis and mortality was assessed between March and May of 2014. We calculated standardized mortality ratios (SMR) and case-fatality rates for all participants and for subgroups. Univariate and multivariate Cox regression models were used to quantify associations between co-morbidities and mortality from all causes and from tuberculosis.

Findings We registered 4569 subjects in the cohort. Overall, the cohort had an SMR for deaths from all causes of 5.2 (95% confidence interval, CI: 4.8–5.6). Males had a higher SMR than females (6.1 versus 3.0). After adjustment for age and sex, hazard ratios (HR) for deaths from all causes were significantly greater in previously treated people (HR: 1.26; 95% CI: 1.08–1.49) and sputum smear-test positive people (HR: 1.55; 95% CI: 1.35–1.78). The risk of death from tuberculosis was also significantly greater for previously treated people (HR: 1.88; 95% CI: 1.24–2.86) and smear positive people (HR: 3.16; 95% CI: 2.06–4.87).

Conclusion People with tuberculosis in Shanghai have an increased risk of mortality. Earlier diagnosis and more vigilant follow-up may help to reduce mortality in this group.

Introduction

China has approximately 1 million new cases of tuberculosis per year,2–4 resulting in a substantial burden of premature mortality.5 Several factors are known to increase the risk of tuberculosis-associated mortality, including drug resistance, disease severity, irregular or incomplete treatment, human immunodeficiency virus (HIV) infection, smoking and alcoholism.6 Multidrug-resistant (MDR) tuberculosis poses a major threat to tuberculosis control. A national survey done in 2008 found that 5.7% of people newly diagnosed with tuberculosis, and 25.6% of those who had previously been treated, had MDR-tuberculosis.7 In Shanghai, China, people being treated for tuberculosis had a case-fatality rate (CFR) of 5.5% in 2008,8 and in 2010 another national survey reported a CFR of 5.1%.9 The purpose of the present study was to determine the mortality rate and excess mortality in a cohort of people with tuberculosis who were registered in four districts of Shanghai from 2004 to 2008 and to identify groups in this cohort at high risk of death.

Methods

The study sample consisted of local residents from four districts in Shanghai City: Yangpu, Pudong, Putuo and Songjiang, with a total population of 9.23 million in 2014. The districts were chosen based on geographic location and tuberculosis notifications. Our study population consisted of 5001 local participants who were registered in tuberculosis clinics under the national tuberculosis programme between January 1, 2004 and December 31, 2008. We included both newly diagnosed and previously treated participants.

Beginning in the 1990s, the national tuberculosis programme implemented a mandatory reporting system for people with tuberculosis in Shanghai. Each person with suspected tuberculosis who seeks health care in facilities in Shanghai is referred to a specialized tuberculosis hospital or clinic where chest X-rays, sputum smears and cultures are done to confirm the diagnosis. Three sputum specimens are routinely collected from each person. People with bacteriological confirmation or abnormal chest X-ray results are routinely treated at a tuberculosis reference hospital or clinic. All M. tuberculosis isolates were sent to the tuberculosis reference laboratory at the Shanghai Center for Disease Control and Prevention (CDC) or to the Shanghai Pulmonary Hospital for drug susceptibility testing.

The ethics committee of the School of Public Health of Fudan University approved the study. All participants provided written informed consent to allow their information to be stored and used for research. The study was a sub-study conducted within a larger underlying study.

Definitions

An isolate was considered as MDR-tuberculosis if it was resistant to both isoniazid and rifampin. Cause of death was based on information in the death certificate and classified according to the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10).a Deaths

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among people with both HIV and tuberculosis are classified as deaths from HIV in ICD-10. Due to a low percentage of HIV-positive people in the study population (0.28–3.30%), all participants were assumed to be HIV-negative. The case-fatality rate is defined as the risk of death from tuberculosis among people diagnosed with active tuberculosis.

Mortality was measured as: (i) the standardized mortality ratio (SMR; see Box 1); and (ii) the case-fatality rate at 1, 5 and 10 years from the start of treatment. The case-fatality rate was estimated as the number of deaths divided by the total number of people with active tuberculosis.

### Baseline survey

Inclusion criteria were as follows: registered in a tuberculosis clinic under the national tuberculosis programme between January 1, 2004 and December 31, 2008; having household registration or continuous residence at the study site for at least 6 months in the previous year; and provision of written informed consent by the participants or their relatives. Baseline data were collected at the most recent diagnosis of tuberculosis (between 2002 and 2008) and included name, age, sex, residential address, category of treatment and date of registration from the national tuberculosis programme register. Comorbidities, behavioural risk factors (such as smoking) and other data were extracted from paper copies of medical records.

### Follow-up

From March to May 2014, health workers visited the households of all participants at least once and interviewed participants or their close relatives who lived in the same household. Deaths were reported by household members and mortality data, including date of death, were collected from death certificates. For quality control, 10% of subjects were re-interviewed; trained public health workers checked data by telephone or in direct visits. Participants were followed up for a range of 1886 to 25205 days (5.17 to 10.67 years), starting from registration to the last follow-up in 2014 until the date of death.

### Regression analysis

Univariate and multivariate Cox regression models were used to identify significant co-morbidities during treatment for tuberculosis that were associated with all-cause mortality in SPSS statistical software version 16.0 (SPSS Inc., Chicago, United States of America). Hazard ratios (HR), 95% confidence intervals (CI), and P-values were calculated to assess the significance of associations.

### Results

A total of 5001 participants met our inclusion criteria (Table 1). Of these, 432 were excluded from analysis because they were misdiagnosed, declined to participate in the follow-up, relocated to a district without a tuberculosis registry or failed to provide a new address. Of 4569 participants with successful follow-up (91.4%), 3396 were men (74.3%) and 1173 were women (25.7%; Table 1). Among the participants, 3601 (78.8%) survived the entire follow-up period from the start of treatment and 968 (21.2%) died. Men were more likely than women to have lung cavitation (29.4% versus 20.3%; P < 0.001), two or more comorbidities (3.0% versus 1.5%, P = 0.008) and be smear-positive (48.0% versus 39.1%, P < 0.001), but were less likely to have received previous treatment (10.9% versus 35.5%, P < 0.001).

The overall SMR was 5.2 (95% CI: 4.8–5.6); the SMR increased with age and sex. The adjusted HRs for deaths from all causes and from tuberculosis, which was also high for those aged 80 years and older (69.02%). The 5 year case-fatality rate was 7.48%, 17.20%, and 21.23%, respectively (Table 2). Participants with comorbidities also had high SMRs, especially those with chronic obstructive pulmonary disease (COPD) (22.6) and cancer (30.1).

The 1, 5 and 10 year case-fatality rates were 7.48%, 17.20%, and 21.23%, respectively (Table 2). Participants with disseminated pulmonary disease had the highest 1 year case-fatality rate (40.00%), whereas those with cancer had the highest 5 year case-fatality rate (61.11%). The 5 year case-fatality rate was also high for participants older than 79 years (58.89%), with COPD (45.45%), chronic bronchitis (44.83%) or MDR-tuberculosis (39.02%). At the 10 year follow up, the case-fatality rate was highest for participants with cancer (69.44%) or COPD (63.64%) and was also high for those aged 80 years and older (69.02%).

Table 3 shows the hazard ratios (HR) for deaths from all causes and from tuberculosis, with and without adjustment for age and sex. The adjusted HRs for deaths from all causes were 1.50 (95% CI: 0.91–2.48) for participants with MDR-tuberculosis, 1.55 (95% CI: 1.35–1.78) for smear-positive participants, and 1.26 (95% CI: 1.08–1.49) for previously treated participants. The adjusted HRs for deaths from tuberculosis were 1.77 (95% CI: 0.62–5.06) in participants with MDR-tuberculosis, 3.16 (95% CI: 2.06–4.87) for smear-positive participants and 1.88 (95% CI: 1.24–2.86) for previously treated participants. We also calculated the adjusted HRs for participants with diabetes (0.97; 95% CI: 0.80–1.17), COPD (1.47; 95% CI: 0.86–2.50), hypertension (1.43; 95% CI: 0.84–2.46), chronic bronchitis (1.42; 95% CI: 1.05–1.94) and cancer (1.93; 95% CI: 1.29–2.90).

### Box 1. Estimating tuberculosis mortality

In 2002, the World Health Organization (WHO) defined any death of a tuberculosis patient during treatment as attributable to tuberculosis, irrespective of the final cause of death. As a result, several recent studies used all-cause mortality as a surrogate marker of mortality attributable to tuberculosis. Since 2013, WHO Global Tuberculosis Reports have defined mortality from tuberculosis as any death caused by tuberculosis in HIV-negative individuals. When reported as a rate, tuberculosis mortality has typically been expressed as a person-time mortality rate or more commonly as a case-fatality rate (the risk of death from tuberculosis among individuals with active tuberculosis) within a specific time period. However, the case-fatality rates reported for tuberculosis, which range from 12% to 44%, cannot be compared among studies because they were determined as cumulative mortality using different follow-up durations. In addition, the tuberculosis mortality rate is affected by the baseline mortality rate of the study population.

A better, though indirect, measure of tuberculosis mortality is the standardized mortality ratio (SMR). The SMR is defined as the observed mortality in people with tuberculosis relative to the expected mortality based on the age-specific mortality rates in a standard population. We used the national population of China in 2013 as our standard population.
The cumulative survival curves (Fig. 1) show that the highest risk of death was in the first year, especially during the 2-month intensive treatment phase. After the treatment period, survival improved, especially when considering deaths from tuberculosis only.

**Discussion**

The risk of death in the study population was five times that in the general population of China (SMR 5.2). This is lower than previously reported for people with tuberculosis in India (6.1), the Netherlands (8.3), and Ethiopia (10.0), at least in part because there is less co-infection with HIV in China. Men had higher mortality rates than women, which may be because of sex differences in clinical characteristics (smear results, cavitation, prevalence of comorbidities and MDR-tuberculosis), a higher likeli-

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### Table 1. Mortality in tuberculosis patients, Shanghai, China, 2004–2014

| Group                        | No. | Person-years follow-up | Observed deaths | Mortality rate per 1 000 person-years | Expected deaths | SMR (95% CI) |
|------------------------------|-----|------------------------|-----------------|--------------------------------------|-----------------|--------------|
| All                          | 4569| 29 744                 | 968             | 32.5                                 | 282.7           | 5.2 (4.8–5.6) |
| **Age group, years**         |     |                        |                 |                                      |                 |              |
| 0–19                         | 46  | 301                    | 0               | 0.0                                  | 0.6             | 0.0 (0.0–2.0) |
| 20–39                        | 1007| 7471                   | 15              | 2.0                                  | 5.0             | 0.3 (0.2–0.5) |
| 40–59                        | 1771| 12 500                 | 175             | 14.0                                 | 58.6            | 2.3 (1.9–2.65) |
| 60–79                        | 1212| 7280                   | 411             | 56.5                                 | 285.8           | 9.1 (8.2–10.0) |
| ≥ 80                         | 525 | 2101                   | 363             | 172.8                                | 401.4           | 27.9 (25.1–30.9) |
| **Unknown**                  | 8   | 46                     | 4               | 87.9                                 | 0.5             | 14.2 (3.9–36.3) |
| **Sex**                      |     |                        |                 |                                      |                 |              |
| Male                         | 3396| 21 628                 | 819             | 37.9                                 | 236.9           | 6.1 (5.7–6.5) |
| Female                       | 1173| 8116                   | 149             | 18.4                                 | 62.9            | 3.0 (2.5–3.5) |
| **Diagnosis**                |     |                        |                 |                                      |                 |              |
| Secondary pulmonary          | 4108| 26 698                 | 882             | 33.0                                 | 254.7           | 5.3 (5.0–5.7) |
| Primary pulmonary            | 50  | 332                    | 3               | 9.0                                  | 3.1             | 1.5 (0.3–4.3) |
| Disseminated pulmonary       | 15  | 70                     | 8               | 114.8                                | 0.9             | 18.5 (8.0–36.5) |
| Extra-pulmonary              | 367 | 2475                   | 71              | 28.7                                 | 22.8            | 4.6 (3.6–5.8) |
| Other                        | 29  | 169                    | 4               | 23.6                                 | 1.8             | 3.8 (1.0–9.8) |
| **Treatment management**     |     |                        |                 |                                      |                 |              |
| Directly-observed            | 1152| 7702                   | 227             | 29.5                                 | 71.4            | 4.8 (4.2–5.4) |
| Self-administered            | 30  | 261                    | 4               | 15.3                                 | 1.9             | 2.5 (0.7–6.3) |
| Hospitalized                 | 1907| 11 922                 | 504             | 42.3                                 | 118.2           | 6.8 (6.2–7.4) |
| Family-observed              | 1250| 8491                   | 197             | 23.2                                 | 77.5            | 3.7 (3.2–4.3) |
| Unknown                      | 230 | 1368                   | 36              | 26.3                                 | 14.3            | 4.2 (3.0–5.9) |
| **Previously treated**       |     |                        |                 |                                      |                 |              |
| Yes                          | 785 | 4953                   | 202             | 40.8                                 | 48.7            | 6.6 (5.7–7.6) |
| No                           | 3784| 24 791                 | 706             | 28.5                                 | 234.6           | 4.6 (4.3–4.9) |
| **MDR-tuberculosis**        |     |                        |                 |                                      |                 |              |
| Yes                          | 41  | 199                    | 17              | 85.5                                 | 2.5             | 13.8 (8.0–22.1) |
| No                           | 1449| 9671                   | 354             | 36.6                                 | 89.8            | 5.9 (5.3–6.6) |
| Unknown                      | 3079| 19 874                 | 597             | 30.0                                 | 190.9           | 4.8 (4.5–5.2) |
| **Sputum smear test**        |     |                        |                 |                                      |                 |              |
| Yes                          | 2341| 12 602                 | 334             | 26.5                                 | 145.1           | 4.3 (3.8–4.8) |
| No                           | 2089| 16 189                 | 616             | 38.0                                 | 129.5           | 6.1 (5.7–6.6) |
| Unknown                      | 139 | 952                    | 18              | 18.9                                 | 8.6             | 3.0 (1.8–4.8) |
| **Cavitation**               |     |                        |                 |                                      |                 |              |
| Yes                          | 1235| 7892                   | 257             | 32.6                                 | 203.2           | 5.3 (4.6–5.9) |
| No                           | 3277| 21 526                 | 691             | 32.1                                 | 76.6            | 5.2 (4.8–5.6) |
| Unknown                      | 57  | 326                    | 20              | 61.4                                 | 3.5             | 9.9 (6.0–15.3) |
| **Comorbidity**              |     |                        |                 |                                      |                 |              |
| Diabetes                     | 473 | 2864                   | 129             | 45.0                                 | 29.3            | 7.3 (6.1–8.6) |
| COPD                         | 22  | 100                    | 14              | 140.0                                | 1.4             | 22.6 (12.3–37.9) |
| Hypertension                 | 67  | 385                    | 28              | 72.8                                 | 4.2             | 11.7 (7.8–17.0) |
| Chronic bronchitis           | 87  | 418                    | 46              | 110.0                                | 5.4             | 17.7 (13.0–23.7) |
| Cancer                       | 36  | 134                    | 25              | 186.8                                | 2.2             | 30.1 (19.5–44.5) |

CI: confidence interval; COPD: chronic-obstructive pulmonary disease; MDR: multidrug-resistant; SMR: standardized mortality ratio.

* Calculated by multiplying the number of people with tuberculosis and age specific mortality rates of general population.

* Observed divided by expected mortality.

* Calculated assuming a Poisson distribution.
Table 2. Cumulative case-fatality rates in tuberculosis patients, Shanghai, China, 2004–2014

| Subgroup                  | No. | 1 year | 5 years | 10 years |
|---------------------------|-----|--------|---------|----------|
| All                       | 4569| 7.48   | 17.20   | 21.23    |
| Age group, years          |     |        |         |          |
| 0–19                      | 46  | 0.00   | 0.00    | 0.00     |
| 20–39                     | 1007| 0.40   | 1.09    | 1.39     |
| 40–59                     | 1771| 3.12   | 8.56    | 9.59     |
| 60–79                     | 1212| 10.96  | 25.75   | 33.89    |
| ≥ 80                      | 525 | 28.49  | 58.89   | 69.02    |
| Unknown                   | 8   | 12.50  | 50.00   | 50.00    |
| Sex                       |     |        |         |          |
| Male                      | 3396| 8.73   | 19.73   | 23.96    |
| Female                    | 1173| 3.93   | 10.00   | 12.48    |
| Diagnosis                 |     |        |         |          |
| Secondary pulmonary       | 4108| 7.45   | 17.60   | 21.28    |
| Primary pulmonary         | 50  | 4.00   | 6.00    | 6.00     |
| Disseminated pulmonary    | 15  | 40.00  | 46.67   | 53.33    |
| Extra-pulmonary           | 367 | 6.81   | 12.81   | 19.35    |
| Other                     | 29  | 6.90   | 13.79   | 13.79    |
| Clinical management       |     |        |         |          |
| Directly-observed         | 1152| 5.47   | 15.36   | 19.44    |
| Self-administered         | 30  | 0.00   | 6.67    | 13.33    |
| Hospitalized              | 1907| 11.12  | 21.97   | 26.17    |
| Family-observed           | 1250| 4.32   | 12.24   | 15.44    |
| Unknown                   | 230 | 5.22   | 14.35   | 15.65    |
| Previously treated        |     |        |         |          |
| Yes                       | 785 | 8.54   | 20.25   | 25.48    |
| No                        | 3784| 7.24   | 16.52   | 19.98    |
| MDR-tuberculosis          |     |        |         |          |
| Yes                       | 41  | 12.20  | 39.02   | 41.46    |
| No                        | 1449| 6.69   | 18.91   | 24.15    |
| Unknown                   | 3079| 7.76   | 16.04   | 19.13    |
| Sputum smear test         |     |        |         |          |
| Yes                       | 2341| 9.95   | 21.87   | 26.01    |
| No                        | 2089| 4.93   | 12.40   | 15.75    |
| Unknown                   | 139 | 3.60   | 9.35    | 12.95    |
| Cavitation                |     |        |         |          |
| Yes                       | 1235| 20.16  | 44.78   | 55.47    |
| No                        | 3277| 2.59   | 6.53    | 7.66     |
| Unknown                   | 57  | 12.28  | 29.82   | 35.09    |
| Comorbidity               |     |        |         |          |
| Diabetes                  | 473 | 9.51   | 21.99   | 26.85    |
| COPD                      | 22  | 18.18  | 45.45   | 63.64    |
| Hypertension              | 67  | 8.96   | 29.85   | 41.79    |
| Chronic bronchitis        | 87  | 25.29  | 44.83   | 52.87    |
| Cancer                    | 36  | 36.11  | 61.11   | 69.44    |

COPD: chronic-obstructive pulmonary disease; MDR: multidrug-resistant.

hood of noncompliance with treatment, or the presence of additional risk factors such as smoking.\textsuperscript{31,32} Participants with disseminated pulmonary disease, smear-positive disease or MDR-tuberculosis had higher SMRs than those without these characteristics. This is as expected, given that all of these characteristics are related to disease severity. Among our participants, 25% were undergoing directly observed treatment, short-course (DOTS) facilitated by health-care workers. Contrary to the general expectation that DOTS will substantially increase the effectiveness of treatment for tuberculosis,\textsuperscript{23,24} we found that participants receiving DOTS facilitated by health-care workers had a higher cumulative case-fatality rate than those under self-administered and family-observed management. This may be because people who were willing to remain under DOTS were in poorer health than those under self-administered and family-observed management. Consistent with our findings for Shanghai, studies in Ethiopia,\textsuperscript{25} India\textsuperscript{26} and the United Republic of Tanzania\textsuperscript{27} also reported good treatment outcomes following self-administered tuberculosis treatment. However, contrary results have been obtained in other settings. For example, a study of health-community workers found that DOTS was more beneficial than family-observed management,\textsuperscript{28} and a randomized trial in Nepal indicated that family-observed management produced similar outcomes as health-community worker facilitated DOTS.\textsuperscript{29} Hospitalized people with tuberculosis in China typically have severe disease, which is consistent with this group having the highest cumulative case-fatality rate in our cohort.\textsuperscript{30}

Mortality was highest in the first year, and then declined substantially with time in almost all of the analysed subgroups. During the 10 year follow-up, about one third of the deaths occurred in the first year, and 80% of the deaths occurred within five years of diagnosis. Tuberculosis-related mortality continued to occur even after the completion of treatment. This emphasizes that the definition of tuberculosis mortality should not be restricted to the treatment period alone, because this may lead to an underestimation of tuberculosis-related mortality.

Previous studies have identified several co-morbidities that are risk factors for all-cause mortality during tuberculosis treatment, including renal failure, respiratory disease, cardiovascular disease, cancer, COPD and diabetes.\textsuperscript{31–33} Our analysis identified several such comorbidities. In univariate analyses, people with tuberculosis with diabetes, COPD, chronic bronchitis, hypertension and cancer also had increased mortality. However, after adjusting for age and sex, only chronic bronchitis and cancer were significantly associated with death from all causes. The impact of chronic bronchitis on all-cause mortality is consistent.
with our previous report. It is possible that damage from chronic bronchitis may exacerbate some of the symptoms of tuberculosis, as both conditions are associated with chronic airflow obstruction and other respiratory symptoms.

Our study has several limitations. First, we did not ascertain the HIV status of participants because HIV testing is not compulsory for people with tuberculosis in China. However, previous screening studies reported that the HIV prevalence among people with tuberculosis in China was low. Second, we determined the cause of death using the death certificate database. In Shanghai, a death registration system was established based on ICD-10 for defining the causes of death. Thus, there may have been misclassification of tuberculosis deaths, although misclassification bias would have been reduced by our policy of confirming cause of death during follow-up. Participants who self-administered treatment were possibly marked as being under DOTS in the tuberculosis management system, which may have introduced a bias. Loss to follow-up during or after treatment may have led to an overestimation of mortality rates, since recording of deaths from the death registration database is nearly complete. Finally, although geographic characteristics and tuberculosis prevalence were considered in selecting the study districts, the selected districts may not have provided a representative sample of the population of Shanghai.

### Conclusion

In this cohort of people with tuberculosis in Shanghai, mortality was higher during treatment, suggesting the importance of improving clinical management and treatment for tuberculosis. Interventions during treatment (i.e. monitoring and managing the side-effects of anti-tuberculosis medication) may reduce the rate of tuberculosis deaths while follow-up can lead to reduced deaths from other causes. Timely detection and management of comorbidities among people with tuberculosis is nec-

#### Table 3. Crude and adjusted hazard ratios for mortality in tuberculosis patients, Shanghai, China, 2004–2014

| Subgroup                  | HR (mortality from tuberculosis) | HR (mortality from all causes) |
|---------------------------|----------------------------------|-------------------------------|
|                           | Crude               | Adjusted (95% CI) | Crude               | Adjusted (95% CI) |
| **Diagnosis**             |                    |                  |                    |                  |
| Secondary pulmonary       | 1.00               | 1.00             | 1.00               | 1.00             |
| Primary pulmonary         | 0.66               | 1.42 (0.19–10.39) | 0.28               | 0.68 (0.22–2.13) |
| Disseminated pulmonary    | 2.31               | 1.86 (0.26–13.51) | 3.38               | 2.10 (1.04–4.24) |
| Extra-pulmonary           | 0.72               | 0.68 (0.33–1.40)  | 0.84               | 0.81 (0.63–1.05)  |
| Other                     | 1.58               | 1.46 (0.20–10.63) | 0.69               | 0.85 (0.32–2.29)  |
| **Clinical management**   |                    |                  |                    |                  |
| Directly-observed         | 1.00               | 1.00             | 1.00               | 1.00             |
| Self-administered         | –                  | –                | 0.57               | 1.22 (0.45–3.34)  |
| Hospital                  | 1.80               | 2.09 (1.18–3.73)  | 1.43               | 1.39 (1.14–1.69)  |
| Family-observed           | 0.64               | 0.97 (0.47–1.98)  | 0.79               | 0.99 (0.79–1.25)  |
| Unknown                   | 1.70               | 1.76 (0.64–4.87)  | 0.87               | 0.88 (0.57–1.35)  |
| **Previously treated**    |                    |                  |                    |                  |
| Yes                       | 1.67               | 1.88 (1.24–2.86)  | 1.31               | 1.26 (1.08–1.49)  |
| No                        | 1.00               | 1.00             | 1.00               | 1.00             |
| **MDR-tuberculosis**      |                    |                  |                    |                  |
| Yes                       | 2.79               | 1.77 (0.62–5.06)  | 2.12               | 1.50 (0.91–2.48)  |
| No                        | 1.00               | 1.00             | 1.00               | 1.00             |
| Unknown                   | 0.65               | 0.72 (0.48–1.08)  | 0.81               | 0.95 (0.82–1.11)  |
| **Sputum smear test**     |                    |                  |                    |                  |
| Yes                       | 4.33               | 3.16 (2.06–4.87)  | 2.31               | 1.55 (1.35–1.78)  |
| No                        | 1.00               | 1.00             | 1.00               | 1.00             |
| Unknown                   | 1.21               | 1.34 (0.32–5.67)  | 0.93               | 0.97 (0.60–1.56)  |
| **Cavitation**            |                    |                  |                    |                  |
| Yes                       | 1.28               | 1.32 (0.91–1.93)  | 0.99               | 1.04 (0.90–1.20)  |
| No                        | 1.00               | 1.00             | 1.00               | 1.00             |
| Unknown                   | 2.74               | 2.69 (0.97–7.45)  | 1.84               | 1.59 (1.02–2.49)  |
| **Comorbidity**           |                    |                  |                    |                  |
| Diabetes                  | 1.09               | 0.85 (0.49–1.46)  | 1.40               | 0.97 (0.80–1.17)  |
| COPD                      | 1.58               | 0.88 (0.12–6.37)  | 4.05               | 1.47 (0.86–2.50)  |
| Hypertension              | 0.50               | 0.28 (0.04–2.03)  | 5.29               | 1.43 (0.84–2.46)  |
| Chronic bronchitis        | 3.00               | 2.03 (0.91–4.54)  | 3.33               | 1.42 (1.05–1.94)  |
| Cancer                    | 1.96               | 1.26 (0.31–5.16)  | 5.10               | 1.93 (1.29–2.90)  |

CI: confidence interval; COPD: chronic obstructive pulmonary disease; HR: hazard ratios; MDR: multidrug resistant.

* Based on Cox regression models, adjusted for age and sex.
Weibing Wang et al.

Research
Tuberculosis in China

necessary to prevent deaths during treatment for tuberculosis, as reported by other studies. People with tuberculosis and major comorbidities such as chronic bronchitis and lung cancer need careful management. When appropriate, follow-up and assessment coordinated by tuberculosis departments may improve the management of these conditions. Post-treatment mortality could be used as additional evidence of case fatality (obtained through routine reports) to better characterize overall mortality in people with tuberculosis.

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ملخص

الوفاة الناتجة عن مرض السل في شانغهاي بالصين: دراسة طولية

الغرض تحديد الزيادة في حالات الوفاة في مجموعة من المصابين بالسلا في شانغهاي.

الطريقة كان المشاركين من السكان المحليين في شانغهاي، وقد تم تسجيلهم في واحدة من أربع عيادات لعلاج السل في الفترة بين 1 كانون الثاني/يناير 2004 و31 كانون الأول/ديسمبر 2008. وقد تم جمع البيانات الأساسية على مستوى أحدث الحالات التي تم تشخيصها كحالات الإصابة بالسل، كما تم تقدير الوفيات في الفترة بين 1 مارس/آذار و1 أيار/مايو 2014. وحسبا لنتائج الدراسة، لم يتم في هذه الدراسة إحصاءات عن حالات الوفاة الناتجة عن السلا في شانغهاي.

النتائج تم تسجيل 4569 حالة من المصابين بالسلا في شانغهاي. وجدنا نسب الوفيات القياسية الناتجة عن جميع الأسباب في هذه المجموعة بلغت 5.2 (95% CI: 4.8 – 5.6). وعندما تم استخدام نماذج انحدار كوكس ذات المتغيرات المتعددة، وجدنا أن الخطر الارتيابي للوفاة الناتجة عن السلا (HR: 1.55; 95% CI: 1.35 – 1.78) في الرجال أكثر ارتفاعًا بشكل ملحوظ مقارنةً مع النساء. ووجدنا أن حالات السلال التي بدأت مع ظهور سلالات جديدة كانت تتراوح نسبة أرجحية مقدارها 1.26 (95% CI: 1.14 – 1.40) بالنسبة للوفيات الناتجة عن السلا.

الاستنتاج يتيح لمختصي السلا في شانغهاي زيادة حذر خطر الوفاة للنفاذ. وقد يساعد التشخيص المبكر للمرض والمرتبطة بالعديد من المبايعة للطبية.}&
Objective Determining the submortality in a cohort of patients with tuberculosis in Shanghai.

Methods The participants were inhabitants of 4 districts (19) of Shanghai, enrolled in one of four tuberculosis clinics between 1 January 2004 and 31 December 2008. The data were collected at the time of the last diagnosis and treatment of tuberculosis. The standardized mortality ratio (SMR) and the mortality rate were calculated for all participants and subgroups. Models of univariable and multivariable Cox regression were used to quantify the associations between comorbidities and mortality, all-cause mortality, and mortality due to all causes.

Results In a cohort of 4569 subjects, the SMR for all-cause mortality was 5.2 (95% CI: 4.8–5.6). Men had a higher SMR than women (6.1 vs. 3.0). Adjusting for age and sex, the SMR for previous treatment was 1.26 (95% CI: 1.08–1.49) and for sputum smear positivity was 1.55 (95% CI: 1.35–1.78). The risk of death due to tuberculosis was also significantly higher for individuals with previous treatment (OR: 1.88; 95% CI: 1.24–2.86) and for those with positive sputum smears (OR: 1.55; 95% CI: 1.35–1.78). The risk of death from all causes was significantly higher for men (6.1) than for women (3.0). After adjusting for age and sex, the relative risk was 1.26 (95% CI: 1.08–1.49) and 1.24–2.86 for previous treatment and positive sputum smears, respectively.

Conclusion Among patients with tuberculosis in Shanghai, the risk of death is higher for men and for those with previous treatment and positive sputum smears. Earlier diagnosis and more vigilant follow-up may help to reduce the mortality in this group.

Resumen
La mortalidad por tuberculosis en Shanghai, China: un estudio longitudinal

Objetivo Determinar el exceso de mortalidad en una cohorte de personas con tuberculosis en Shanghái.

Métodos Los participantes eran residentes de 4 de 19 distritos de Shanghai, registrados en uno de los cuatro consultorios antituberculosos entre el 1 de enero de 2004 y el 31 de diciembre de 2008. Se recogieron datos de referencia de los diagnósticos de tuberculosis más recientes y se evaluó la mortalidad entre marzo y mayo de 2014. Se calcularon las tasas de mortalidad estandarizadas (SMR) y la tasa de mortalidad de todos los participantes y por subgrupos. Se utilizaron modelos de regresión de Cox univariantes y multivariantes para cuantificar las asociaciones entre la comorbilidad y la mortalidad de todas las causas de tuberculosis.

Resultados Se registraron 4,569 sujetos en la cohorte. En general, la cohorte tenía una SMR para muertes de todas las causas de 5,2 (intervalo de confianza del 95%, IC: 4,8–5,6). Los hombres tenían una SMR mayor que las mujeres (6,1 frente a 3,0). Tras ajustarlos de acuerdo a edad y sexo, el riesgo de mortalidad de las muertes de todas las causas era significativamente mayor en personas tratadas con anterioridad (HR: 1,26 (IC del 95%: 1,08–1,49) y personas con pruebas de esputo positivas (HR: 1,55 (IC del 95%: 1,35–1,78). El riesgo de muerte por tuberculosis también era significativamente mayor en personas tratadas con anterioridad (HR: 1,88 (IC del 95%: 1,24–2,86) y personas con pruebas de esputo positivas (HR: 3,16 (IC del 95%: 2,06–4,87).

Conclusión Las personas con tuberculosis en Shanghái tienen un mayor riesgo de mortalidad. Unos diagnósticos más tempranos y un seguimiento más atento podrían ayudar a reducir la mortalidad de este grupo.
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