Association of Respiratory Tuberculosis with Incident Bone Fracture: Bridging the Tuberculosis Airway Infection and the Osteoporotic Bone

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Abstract

Objective

The relationship between respiratory tuberculosis (RT) and incident fragility fracture and osteoporosis/fragility fracture in the general population is not well determined; therefore, we conducted a nationwide cohort study to investigate this relationship.

Methods

We used the National Health Insurance Research Database of Taiwan to identify 6612 newly diagnosed patients with RT (RT cohort) and 13220 patients without RT (non-RT cohort) from 1999 to 2005. The mean durations of follow-up were (6.73 ± 4.00 years, 8.11 ± 3.24 years) in the (RT cohort, non-RT cohort); respectively. The occurrence of incident fragility fracture and osteoporosis/fragility fracture were followed up until the end of 2011. The adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs) and 98% CIs of incident fragility fracture and osteoporosis/fragility fracture were estimated using the multivariable Cox proportional hazard model after adjusting for age, sex, occupation, drug use, and comorbidities.

Results

A Cox proportional hazards regression analysis was performed and showed the aHRs of [incident fragility fracture; osteoporosis/fragility fracture] were [1.69 (95% CI = 1.26–2.28, 98% CI = 1.18–2.44); 1.42 (95% CI = 1.25–1.61, 98% CI = 1.21–1.65)] between the RT and non-RT cohorts. Regarding the sex, the aHRs of the [incident fragility fracture; osteoporosis/fragility fracture] were [1.57 (98% CI = 1.10–2.33, 98% CI = 1.02–2.41); 1.15 (95% CI = 0.97–1.36, 98% CI = 0.94–1.41)] in the men. The aHRs of the RT cohort without oral steroid use in the [incident fragility fracture; osteoporosis/fragility fracture] were [1.87 (95% CI = 1.20–2.90, 98% CI = 1.09–3.19); 1.41 (95% CI = 1.19–1.67, 98% CI = 1.14–1.74)].
Conclusion
The RT associated with the incident fragility fracture, either in men or absence of oral steroid use.

Introduction
Osteoporosis is the most common type of bone disease [1] and is a major public health problem [2]. Osteoporosis increases the risk of breaking a bone [3]. Approximately 50% of women older than 50 years were predicted to fracture their hip, wrist, or vertebra (bone of the spine) during their lifetime. Studies have reported that one out of 4 osteoporotic hip fractures resulted in long-term nursing home care, and half of these patients are unable to walk without assistance and have a 24% increased risk of death within one year [4,5].

Parathyroid hormone (PTH) stimulates osteoblasts, which increase the production of receptor activator of nuclear factor kappa-B ligand (RANKL) [6]. Hematopoietic cell precursors stimulated by macrophage colony-stimulating factor (M-CSF) facilitate osteoclast production that expresses RANK [6]. Osteoblasts also produce a decoy receptor called osteoprotegerin (OPG) that binds to RANKL and prevents RANKL and RANK interaction [7]. Estradiol increases the production of OPG to diminish bone resorption. Glucocorticoids stimulate RANKL expression and inhibit OPG synthesis by osteoblasts to enhance osteoclast proliferation and differentiation, leading to bone resorption [8].

Patient profiles at a bone health and osteoporosis prevention service center in Ireland revealed that only 13% of patients did not present with comorbidities [9]. Osteoporosis has been reported to be associated with hyperlipidemia, hypertension, diabetes, ischemic heart disease, end-stage renal disease [10], and liver cirrhosis [11]. Infections such as hepatitis C virus (HCV) infection are also risk factors of osteoporosis [11]. Osteoporotic changes [12] in tuberculosis arthritis were observed in previous report [13]. However, the respiratory tuberculosis (RT) intervention associated with bone fracture among patients with or without comorbidities is not found in literature.

Methods and Materials
Study population
The patient selection process used in our study is illustrated in Fig 1. We conducted a retrospective population-based cohort study to investigate the association between RT and risk of incident bone fracture and osteoporosis / fragility fracture. The diagnosis and treatment of the RT is under the strict control of the Centers for Disease Control in Taiwan for avoiding pulmonary tuberculosis (PTB) transmission [14]. The coding of the RT is after the consensus of the chest physician, infection specialist and the well-trained coder. The RT cohort follow up by the public nurse and chest physician or infection specialist. During the study period (1999–2005), we identified newly diagnosed patients with RT (ICD-9-CM 011–012) as the RT cohort, and the initial date of RT diagnosis served as their index date. We randomly selected comparison participants (individuals without RT) from the LHID as the non-RT cohort, and frequency-matched the participants by age and sex at a ratio of 1:2. The index date of the non-RT cohort was randomly assigned a month and day with the same year as the matched cases. We excluded individuals with missing data such as date of birth, sex, and known history of osteoporosis / fragility fracture before the baseline from the study.
Outcome and comorbidities measurement

The primary endpoint of our study was the occurrence of fragility fracture (ICD-9-CM 733.1). The secondary endpoint was osteoporosis /fragility fracture (pathology fractures; ICD-9-CM 733.0, 733.1) [15–17]. All participants were followed up from the index date to the date when the participants stopped claiming insurance and showing signs of incident fragility fracture, osteoporosis / fragility fracture or until December 31, 2011.

Comorbidities were defined as the patient having used medical services for hyperlipidemia (ICD-9-CM 272), hypertension (ICD-9-CM 401–405), diabetes (ICD-9-CM 250), pneumonia (ICD-9-CM 480–488), liver cirrhosis (ICD-9-CM 571), ischemia heart disease (IHD, ICD-9-CM 410–414), end-stage renal disease (ESRD, ICD-9-CM 585), hyperparathyroidism (ICD-9-CM 252.0), celiac disease (ICD-9-CM 579.0), Crohn’s disease (ICD-9-CM 555.0, 555.1, 555.2, and 555.9), alcohol-related illness (ICD-9-CM 291, 303, 305, 571.0, 571.1, 571.2, 571.3, and 790.3), stroke (ICD-9-CM 430–438), chronic obstructive pulmonary disease (COPD; ICD-9-CM 490–496), and lower body weight (ICD-9-CM 783.2) before the end date [18]. We also investigated drug effects and collected the history of oral steroid, bisphosphonates, hormone replacement therapy (HRT), vitamin D supplements, and aromatase inhibitors prescription before the end date. The oral steroid users was defined subjects had ever used the oral...
steroid at least one month [19]. Besides, the bisphosphonates, HRT, vitamin D supplements, and aromatase inhibitors were considered for adjustment, when subjects ever used for one dose before the study end date.

Ethics statement
The NHIRD encrypts patient personal information to protect privacy and provides researchers with anonymous identification numbers associated with relevant claims information, including sex, date of birth, medical services received, and prescriptions. Therefore, patient consent is not required to access the NHIRD. This study was approved to fulfill the condition for exemption by the Institutional Review Board (IRB) of China Medical University (CMUH104-REC2-115). The IRB also specifically waived the consent requirement.

Statistical analysis
We presented the mean and standard deviation (SD) for age and percentages for sex, age groups, occupation, comorbidities, and each type of drug used. We used the chi-squared test and Student’s t-test to assess the differences in the distribution between the RT and non-RT cohorts. The incidence–density of fragility fracture, osteoporosis / incident fragility fracture were calculated as the number of patients with incident fragility fracture, osteoporosis / fragility fracture divided by the sum of person–years (per 1000 person–years). We also measured the cumulative incidence curves of incident fragility fracture, osteoporosis / fragility fracture for both cohorts by using the Kaplan–Meier method. We used the log-rank test to assess the different incidence curves. We demonstrated the incidence–density between the RT and non-RT cohorts after stratifying the data on the basis of sex, age, occupation, comorbidities, oral steroid used, follow-up period (<2 and ≥2 years), and oral steroid use. The incidence rate ratio (IRR) of incident fragility fracture, osteoporosis / fragility fractures for these variables between the two cohorts was assessed using the Poisson regression model. The multivariable Cox proportional hazards model was used to estimate hazard ratios (HRs) and 95% and 98% confidence intervals (CIs) for the risk of incident fragility fracture, osteoporosis / fragility fracture between the two cohorts. The Bonferroni adjustment was used in multiple comparisons.

All the statistical analyses were performed using the SAS 9.4 statistical package (SAS Institute Inc., NC, USA). We used the R software (R Foundation for Statistical Computing, Vienna, Austria) to plot the cumulative incidence of both cohorts. A \( p\)-value < 0.05 and \( p\)-value < 0.02 was considered significant in the 2-tailed tests performed this study.

Results
This study included 6612 patients with RT and 13220 normal controls from 1999 to 2005 (Table 1). The frequency-matched cohorts demonstrated a similar age and sex distribution \( p\)-value > 0.05), in which 69.7% were men and 43.5% were ≥65 years old. Except for hypertension, celiac disease and Chron’s disease, the percentage of comorbidities in the RT cohort was greater than that in the non-RT cohort. RT cohort used the oral steroid (51.5%) or bisphosphonates (1.53%) was more common than comparison cohort.

The cumulative incidence of incident fragility fracture (Fig 2A, log-rank \( P < 0.001 \)) were significantly higher for patients in the RT cohort than for participants without RT. During the 44517 and 107232 person-years follow-up, the overall incidence density of fragility fractures was 1.69-fold significantly higher in RT patients than in the non-RT cohort (2.02 vs 1.11 per 1000 person-y), with an adjusted HR = 1.69 (95% CI = 1.26–2.28; 98% CI = 1.18–2.44) (Table 2). Stratified by sex, men with RT had a 57% increased fragility fracture risk compared to the non-RT cohort. The RT cohort was significantly associated with a higher risk of fragility
fracture compared with the non-RT cohort for aged of 65–75 years (adjusted HR = 1.76, 95% CI = 1.12–2.75; 98% CI = 1.02–3.03) and ≥75 years (adjusted HR = 1.94, 95% CI = 1.18–3.19; 98% CI = 1.06–3.56). The adjusted HR of fragility fracture was higher in RT cohort regardless of white collar (adjusted HR = 2.19, 95% CI = 1.21–3.97; 98% CI = 1.06–4.52). The risk of fragility fracture was observed in patients with comorbidities (adjusted HR = 1.90, 95% CI = 1.43–2.52; 98% CI = 1.34–2.68) in the RT cohort than in the non-RT cohort. Stratified by oral steroid, RT patients with oral steroid or without oral steroid had an increased fragility fracture risk.

### Table 1. Comparison of demographics and comorbidity between with and without respiratory tuberculosis cohorts.

|                   | Respiratory tuberculosis |          |          | p-value |
|-------------------|--------------------------|----------|----------|---------|
|                   | No (N = 13220)           | Yes (N = 6612) |          |
|                   | n    | %    | n    | %    |         |
| **Sex**           |      |      |      |      |         |
| Women             | 4008 | 30.3 | 2004 | 30.3 | 0.99    |
| Men               | 9212 | 69.7 | 4608 | 69.7 |         |
| **Age, year**     |      |      |      |      | 0.99    |
| <35               | 2274 | 17.2 | 1137 | 17.2 |         |
| 35–65             | 5196 | 39.3 | 2598 | 39.3 |         |
| ≥65               | 5750 | 43.5 | 2877 | 43.5 |         |
| Mean (SD)¹        | 56.7 | 20.2 | 56.9 | 20.3 | 0.64    |
| **Occupation**    |      |      |      |      | <0.001  |
| White collar      | 5685 | 43.0 | 2468 | 37.3 |         |
| Blue collar       | 4839 | 36.6 | 2641 | 39.9 |         |
| Others            | 2696 | 20.4 | 1503 | 22.7 |         |
| **Comorbidity**   |      |      |      |      |         |
| Hyperlipidemia    | 3439 | 26.0 | 1576 | 23.8 | <0.001  |
| Hypertension      | 6446 | 48.8 | 3283 | 49.7 | 0.24    |
| Diabetes          | 2909 | 22.0 | 1793 | 27.1 | <0.001  |
| Pneumonia         | 4712 | 35.6 | 4019 | 60.8 | <0.001  |
| Live cirrhosis    | 3565 | 27.0 | 2376 | 35.9 | <0.001  |
| IHD               | 3597 | 27.2 | 2038 | 30.8 | <0.001  |
| Stroke            | 3319 | 25.1 | 1806 | 27.3 | <0.001  |
| COPD              | 5793 | 43.8 | 4982 | 75.4 | <0.001  |
| ESRD              | 183  | 1.38 | 170  | 2.57 | <0.001  |
| Alcohol-related illness | 374 | 2.83 | 447  | 6.76 | <0.001  |
| Hyperparathyroidism | 12 | 0.09 | 18   | 0.27 | 0.002   |
| Celiac disease    | 0    | 0.00 | 1    | 0.02 | -       |
| Chron's disease   | 236  | 1.79 | 133  | 2.01 | 0.27    |
| Lower body weight | 323  | 2.44 | 286  | 4.33 | <0.001  |
| **Treatment**     |      |      |      |      |         |
| Oral steroid      | 4340 | 32.8 | 3402 | 51.5 | <0.001  |
| Bisphosphonates   | 76   | 0.57 | 101  | 1.53 | <0.001  |
| HRT               | 1218 | 9.21 | 651  | 9.85 | 0.15    |
| Vitamin D supplements | 21 | 0.16 | 12   | 0.18 | 0.71    |
| Aromatase inhibitors | 13  | 0.10 | 10   | 0.15 | 0.30    |

Chi-square test; ¹ Student's t-test; White collar: civil services, institution workers, enterprise, business and industrial administration personnel; Blue collar: farmers, fishermen, vendors, and industrial laborers; Others: retired, unemployed, and low-income populations; HRT, Hormone Replacement Therapy; IHD, ischemia heart disease; COPD, chronic obstructive pulmonary disease; ESRD, end-stage renal disease.

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compared to the non-RT cohort. The adjusted HR of fragility fracture was significantly higher in the more than two follow-up year (adjusted HR = 1.67, 95% CI = 1.16–2.40; 98% CI = 1.07–2.59).

The overall incidence of osteoporosis / fragility fracture was 9.61 per 1000 person–years and 7.29 per 1000 person–years in the RT and non-RT cohorts, respectively (Table 3). Fig 2B shows that the cumulative incidence of osteoporosis / fragility fracture was higher in the RT cohort than in the non-RT cohort (log-rank test < 0.001) at the end of the follow-up period. After adjustment for age, sex, drug use and comorbidities, the RT cohort was observed to be at a significantly higher risk of osteoporosis / fragility fracture compared with the non-RT cohort (adjusted HR = 1.42, 95% CI = 1.25–1.61; 98% CI = 1.21–1.65). The risk of osteoporosis was presented 1.36-fold (95% CI = 1.18–1.56; 98% CI = 1.14–1.61) in RT cohort. The RT cohort (except patients aged <65 years) was significantly associated with a higher risk of osteoporosis / fragility fracture compared with the non-RT cohort, particularly at the age of 65–75 years and ≥75 years. The adjusted HR of osteoporosis / fragility fracture was higher in RT cohort regardless of white collar (adjusted HR = 1.57, 95% CI = 1.24–1.99; 98% CI = 1.18–2.10), and others (adjusted HR = 1.72, 95% CI = 1.34–2.22; 98% CI = 1.27–2.34).

The statistically significant increased risk of osteoporosis / fragility fracture was observed in patients with comorbidities (adjusted HR = 1.48, 95% CI = 1.31–1.68; 98% CI = 1.28–1.72) in the RT cohort. The RT cohort without oral steroid use was at a 1.40-fold increased risk of osteoporosis / fragility fracture compared with the non-RT cohort without oral steroid use (adjusted HR = 1.40, 95% CI = 1.17–1.67; 98% CI = 1.13–1.73), and the RT cohort was at a 1.46-fold increased osteoporosis / fragility fracture risk compared with the non-RT cohort with oral steroid use (adjusted HR = 1.46, 95% CI = 1.21–1.76; 98% CI = 1.16–1.83). The adjusted HR of osteoporosis / fragility fracture was significantly higher in the first two follow-up year (adjusted HR = 1.59, 95% CI = 1.28–1.97; 98% CI = 1.08–1.52) and in later on (adjusted HR = 1.33, 95% CI = 1.14–1.57; 98% CI = 1.07–2.59).

The incidence rate of fragility fracture was higher for those with comorbidities of hypertension, diabetes, pneumonia, liver cirrhosis, and IHD in both cohorts (Table 4). The risk of fragility fracture was higher among patients without hypertension (adjusted HR = 2.81, 95%
CI = 1.44–5.51) than patients with hypertension (adjusted HR = 1.52, 95% CI = 0.97–2.36) (P for interaction = 0.02).

Table 5 shows the osteoporosis / fragility fracture risk between the RT and non-RT cohorts stratified by different comorbidities. Our results consistently showed that the RT cohort was significantly associated with an increased risk of osteoporosis / fragility fracture compared with the non-RT cohort in the presence of different comorbidities, such as hyperlipidemia, hypertension, diabetes, pneumonia, live cirrhosis, and IHD. The RT cohort without lower body weight have the higher risk of osteoporosis / fragility fracture (adjusted HR = 1.41, 95% CI = 1.24–1.60; 98% CI = 1.20–1.65), compared with the non-RT cohort also.
Table 3. Incidence and adjusted hazard ratio of osteoporosis / fragility fracture stratified by sex, age, comorbidity, oral steroid used and follow-up time between with and without respiratory tuberculosis cohorts.

| Variables                  | Respiratory tuberculosis | Compared to non-respiratory tuberculosis |
|----------------------------|--------------------------|------------------------------------------|
|                            | No PY Rate | Event PY Rate | Yes PY Rate | Event PY Rate | IRR (95% CI) | Adjusted HR† (95% CI) | Adjusted HR† (98% CI) |
| Overall                    | 782 107232 7.29 | 428 44517 9.61 | 1.32(1.21, 1.43) | 1.42(1.25, 1.61)*** | 1.42(1.21, 1.65)** |
| Osteoporosis (ICD-9-CM: 7330) | 663 33713 10.5 | 338 7.59 | 1.23(1.12, 1.34) | 1.36(1.18, 1.56)*** | 1.36(1.14, 1.61)** |
| Sex                        |             |               |               |               |               |                           |                           |
| Women                      | 354 33713 10.5 | 189 15002 12.6 | 1.20(1.04, 1.39)* | 1.11(0.92, 1.34) | 1.11(0.89, 1.40) |
| Men                        | 428 73519 5.82 | 239 29515 8.10 | 1.39(1.26, 1.54) | 1.15(0.97, 1.36) | 1.15(0.94, 1.41) |
| P for interaction          |             |               |               |               | 0.34         |                           |                           |
| Age, year                  |             |               |               |               |               |                           |                           |
| <65                        | 210 67869 3.09 | 129 30751 4.19 | 1.36(1.21, 1.52) | 1.03(0.81, 1.30) | 1.03(0.77, 1.37) |
| 65–75                      | 284 23387 12.1 | 169 8699 19.4 | 1.60(1.37, 1.87) | 1.50(1.22, 1.85)*** | 1.50(1.17, 1.93)** |
| ≥75                        | 288 15976 18.0 | 130 5066 25.7 | 1.42(1.21, 1.68) | 1.49(1.19, 1.86)*** | 1.49(1.14, 1.96)** |
| P for interaction          |             |               |               |               | 0.74         |                           |                           |
| Occupation                 |             |               |               |               |               |                           |                           |
| White collar               | 236 48453 4.87 | 121 18665 6.48 | 1.33(1.16, 1.52) | 1.57(1.24, 1.99)*** | 1.57(1.18, 2.10)** |
| Blue collar                | 359 38758 9.26 | 184 16878 10.9 | 1.18(1.03, 1.34)* | 1.16(0.95, 1.40) | 1.16(0.92, 1.46) |
| Others                     | 187 20021 9.34 | 123 8974 13.7 | 1.47(1.24, 1.74) | 1.72(1.34, 2.22)*** | 1.72(1.27, 2.34)** |
| P for interaction          |             |               |               |               | 0.48         |                           |                           |
| Comorbidity                |             |               |               |               |               |                           |                           |
| No                         | 62 24565 2.52 | 5 3705 1.35 | 0.53(0.35, 0.82)** | 1.11(0.44, 2.81) | 1.11(0.36, 3.43) |
| Yes                        | 720 82667 8.71 | 423 40812 10.4 | 1.19(1.09, 1.30) | 1.48(1.31, 1.68)*** | 1.48(1.28, 1.72)** |
| P for interaction          |             |               |               |               | 0.38         |                           |                           |
| Oral steroid               |             |               |               |               |               |                           |                           |
| No                         | 516 73083 7.06 | 200 23253 8.60 | 1.22(1.09, 1.37) | 1.40(1.17, 1.67)*** | 1.40(1.13, 1.73)** |
| Yes                        | 266 34149 7.79 | 228 21264 10.7 | 1.38(1.22, 1.55) | 1.46(1.21, 1.76)*** | 1.46(1.16, 1.83)** |
| P for interaction          |             |               |               |               | 0.73         |                           |                           |
| Follow-up, year            |             |               |               |               |               |                           |                           |
| <2                         | 257 25419 10.1 | 162 11455 14.1 | 1.40(1.28, 1.53) | 1.59(1.28, 1.97)*** | 1.28(1.08, 1.52)** |
| ≥2                         | 525 81813 6.42 | 266 33062 8.05 | 1.25(1.15, 1.37) | 1.33(1.14, 1.57)*** | 1.67(1.07, 2.59)** |

PY: person-year; Rate: incidence rate (per 1,000 person-years); IRR: incidence rate ratio; Adjusted HR†: multiple analysis including age, sex, occupation, drug of oral steroid, bisphosphonates, hormone replacement therapy (HRT), vitamin D supplements, and aromatase inhibitors and each comorbidity (including hyperlipidemia, hypertension, diabetes, pneumonia, liver cirrhosis, ischemia heart disease (IHD), stroke, chronic obstructive pulmonary disease (COPD), end-stage renal disease (ESRD), alcohol-related illness, hyperparathyroidism, celiac disease, Chron’s disease, and lower body weight); *p<0.05, **p<0.02, ***p<0.001

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Table 4. Incidence and adjusted hazard ratio of fragility fracture stratified by different comorbidity in respiratory tuberculosis and non-respiratory tuberculosis groups.

| Variables                  | Respiratory tuberculosis | Compared to without respiratory tuberculosis |
|----------------------------|--------------------------|----------------------------------------------|
|                            | No | Yes     | IRR (95% CI) | Adjusted HR† (95% CI) | Adjusted HR† (98% CI) |
| Hyperlipidemia             |     |         |              |                        |                        |
| No                         | 90 | 78246   | 1.15         | 66                      | 32997                  | 2.00 |
| Yes                        | 29 | 28886   |               | 24                      | 11520                  | 2.08 |
| P for interaction          |    |         |              |                         |                        | 0.52 |
| Hypertension               |     |         |              |                        |                        |
| No                         | 31 | 57441   | 0.54         | 37                      | 24315                  | 1.52 |
| Yes                        | 88 | 49792   | 1.77         | 53                      | 20202                  | 2.62 |
| P for interaction          |    |         |              |                         |                        | 0.02 |
| Diabetes                   |     |         |              |                        |                        |
| No                         | 85 | 84771   | 1.00         | 66                      | 33583                  | 1.97 |
| Yes                        | 34 | 22462   | 1.51         | 24                      | 10934                  | 2.19 |
| P for interaction          |    |         |              |                         |                        | 0.31 |
| Pneumonia                  |     |         |              |                        |                        |
| No                         | 52 | 70796   | 0.73         | 26                      | 19286                  | 1.35 |
| Yes                        | 67 | 36436   | 1.84         | 64                      | 25231                  | 2.54 |
| P for interaction          |    |         |              |                         |                        | 0.22 |
| Liver cirrhosis            |     |         |              |                        |                        |
| No                         | 81 | 78405   | 1.03         | 59                      | 27834                  | 2.12 |
| Yes                        | 38 | 28828   | 1.32         | 31                      | 16683                  | 1.86 |
| P for interaction          |    |         |              |                         |                        | 0.38 |
| IHD                        |     |         |              |                        |                        |
| No                         | 70 | 80293   | 0.87         | 51                      | 32385                  | 1.57 |
| Yes                        | 49 | 26939   | 1.82         | 39                      | 12132                  | 3.21 |
| P for interaction          |    |         |              |                         |                        | 0.71 |
| ESRD                       |     |         |              |                        |                        |
| No                         | 119| 105958  | 1.12         | 89                      | 43658                  | 2.04 |
| Yes                        | 0  | 1274    | 0            | 1                       | 859                    | 1.16 |
| P for interaction          |    |         |              |                         |                        | 0.97 |
| Alcohol-related illness    |     |         |              |                        |                        |
| No                         | 118| 104094  | 1.13         | 83                      | 41430                  | 2.17 |
| Yes                        | 1  | 3138    | 0.32         | 7                       | 3086                   | 2.27 |
| P for interaction          |    |         |              |                         |                        | 0.11 |
| Hyperparathyroidism        |     |         |              |                        |                        |
| No                         | 118| 107120  | 1.1          | 90                      | 44375                  | 2.03 |
| Yes                        | 1  | 112     | 8.95         | 0                       | 142                    | 0   |
| P for interaction          |    |         |              |                         |                        | 0.96 |
| Celiac disease             |     |         |              |                        |                        |
| No                         | 119| 107232  | 1.11         | 90                      | 44505                  | 2.02 |
| Yes                        | 0  | 0       |              | 12                      | 0                      | 0   |
| P for interaction          |    |         |              |                         |                        | 0.06 |
| Chron’s disease            |     |         |              |                        |                        |
| No                         | 115| 105230  | 1.09         | 88                      | 43519                  | 2.02 |
| Yes                        | 4  | 2002    | 2.00         | 2                       | 997                    | 2.01 |
| P for interaction          |    |         |              |                         |                        | 0.38 |

(Continued)
The RT cohort without oral steroid use was at a 1.87-fold increased risk of fragility fractures (adjusted HR = 1.87, 95% CI = 1.20–2.90; 98% CI = 1.09–3.19) compared with the non-RT cohort (Table 6). The RT cohort using oral steroid demonstrated a statistically significant increased risk of fragility fractures in men (adjusted HR = 1.89, 95% CI = 1.19–3.00; 98% CI = 1.07–3.32). Similar results were observed for osteoporosis / fragility fracture.

Discussion

A published meta-analysis including 167 studies evaluated the risk factors for a low bone marrow density (BMD)-related fracture in men and women, and reported age (>70 years), low body weight [body mass index (BMI) <20 to 25 kg/m²], weight loss (>10%), physical inactivity, prolonged corticosteroid use, and previous osteoporotic fracture as high risk factors [20]. An additional 102 studies assessed 15 other proposed risk factors but provided insufficient evidence in support of a male population [20]. This study suggested that the incidence of fragility fracture (adjusted HR = 1.69), osteoporosis / fragility fracture (adjusted HR = 1.42) in the RT cohort is higher than in the non-RT cohort, irrespective of age, sex, steroids use and comorbidities.

Respiratory tuberculosis is one of the diseases characterized granuloma formation which was controlled by cellular immune reactions, interferon-gamma (INF-gamma) which mediate inflammatory reactions increased in the tuberculosis [21]. Expression levels of IFN-gamma have a positive correlation to bone fracture [22]. The cytokine IFN-gamma stimulates neopterin release. High levels of neopterin were associated with increased hip fracture risk [23]. These previous finding imply that the RT associated with the bone fracture, even without comorbidities or steroid use. Holloway et al. study in 3 to 5% of active cases of tuberculosis [24] with bone fracture (e.g. compression fracture) in accordance with our study [25]. However, these hypothesis warrant further research.

Vitamin D deficiency and a low calcium intake were risk factors for osteoporosis observed in men. A study conducted by Ho-Pham et al suggested that vitamin D deficiency was also reported to be a risk factor for tuberculosis in men but not in women [26]. The dual effect of vitamin D deficiency on RT and osteoporosis may confound the association between RT and bone fracture. These factors support the higher risk of the fragility fracture (adjusted HR = 1.57, P for interaction = 0.06) observed in a male population than in female belonging to

| Table 4. (Continued) |
|-----------------------|
| **Respiratory tuberculosis** | **Compared to without respiratory tuberculosis** |
| Variables | No | Yes | Event PY Rate | Event PY Rate | IRR (95% CI) | Adjusted HR† (95% CI) | Adjusted HR† (98% CI) |
| Lower body weight | | | | | | | |
| No | 115 | 104556 | 1.10 85 | 42491 | 2.00 | 1.85(1.69, 2.03)*** | 1.83(1.35, 2.48)*** | 1.83(1.26, 2.65)*** |
| Yes | 4 | 2676 | 1.49 | 5 | 2026 | 2.47 | 1.62(0.99, 2.66) | 1.70(0.33, 8.70) | 1.70(0.23, 12.4) |
| P for interaction | | | | | | | 0.97 |

PY: person-year; Rate: incidence rate (per 1,000 person-years); IRR: incidence rate ratio; Adjusted HR†: multiple analysis including age, sex, occupation, drug of oral steroid, bisphosphonates, hormone replacement therapy (HRT), vitamin D supplements, and aromatase inhibitors and each comorbidity [including hyperlipidemia, hypertension, diabetes, pneumonia, live cirrhosis, ischemia heart disease (IHD), stroke, chronic obstructive pulmonary disease (COPD), end-stage renal disease (ESRD), alcohol-related illness, hyperparathyroidism, celiac disease, Chron’s disease, and lower body weight]; **p<0.02, ***p<0.001

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Table 5. Incidence and adjusted hazard ratio of osteoporosis / fragility fracture stratified by different comorbidity in respiratory tuberculosis and non-respiratory tuberculosis groups.

| Variables                      | Respiratory tuberculosis | Compared to without respiratory tuberculosis |
|--------------------------------|--------------------------|-----------------------------------------------|
|                               | No                       | Yes                                           |
|                                | Event PY Rate            | Event PY Rate IRR (95% CI) Adjusted HR (95% CI) Adjusted HR (98% CI) |
| Hyperlipidemia                 |                          |                                               |
| No                             | 533 78246 6.81 295 33997 8.94 1.31(1.19, 1.45)*** 1.42(1.21, 1.66)*** 1.42(1.17, 1.72)*** |
| Yes                            | 249 28986 8.59 133 11520 11.5 1.34(1.15, 1.57)*** 1.43(1.14, 1.79)*** 1.43(1.09, 1.88)*** |
| P for interaction              |                          | 0.72                                          |
| Hypertension                   |                          |                                               |
| No                             | 259 57441 4.51 168 24315 6.91 1.53(1.36, 1.73) 1.50(1.21, 1.87)*** 1.50(1.15, 1.96)*** |
| Yes                            | 523 49792 10.5 260 20202 12.9 1.23(1.10, 1.37)*** 1.34(1.15, 1.58)*** 1.34(1.11, 1.63)*** |
| P for interaction              |                          | 0.048                                         |
| Diabetes                       |                          |                                               |
| No                             | 584 84771 6.89 297 33583 8.84 1.28(1.17, 1.41)*** 1.39(1.20, 1.63)*** 1.39(1.16, 1.68)*** |
| Yes                            | 198 22462 8.82 131 10934 12 1.36(1.16, 1.59)*** 1.42(1.12, 1.80)*** 1.42(1.07, 1.89)*** |
| P for interaction              |                          | 0.71                                          |
| Pneumonia                      |                          |                                               |
| No                             | 452 70796 6.38 159 19286 8.24 1.29(1.14, 1.46)*** 1.52(1.26, 1.84)*** 1.52(1.20, 1.92)*** |
| Yes                            | 330 36436 9.06 269 25231 10.7 1.18(1.05, 1.32)** 1.33(1.12, 1.58)** 1.33(1.08, 1.64)** |
| P for interaction              |                          | 0.19                                          |
| Liver cirrhosis                |                          |                                               |
| No                             | 541 78405 6.9 261 27834 9.38 1.36(1.23, 1.50)*** 1.43(1.22, 1.68)*** 1.43(1.18, 1.74)*** |
| Yes                            | 241 28828 8.36 167 16683 10 1.20(1.04, 1.38)* 1.37(1.11, 1.69)** 1.37(1.06, 1.77)** |
| P for interaction              |                          | 0.87                                          |
| IHD                            |                          |                                               |
| No                             | 465 80293 5.79 251 32385 7.75 1.34(1.21, 1.48)*** 1.51(1.27, 1.79)*** 1.51(1.23, 1.86)*** |
| Yes                            | 317 26939 11.8 177 12132 14.6 1.24(1.08, 1.43)** 1.30(1.07, 1.58)** 1.30(1.02, 1.64)** |
| P for interaction              |                          | 0.26                                          |
| ESRD                           |                          |                                               |
| No                             | 777 105958 7.33 419 43658 9.6 1.31(1.20, 1.42)*** 1.40(1.23, 1.60)*** 1.40(1.20, 1.64)*** |
| Yes                            | 5 1274 3.92 9 859 10.5 2.67(1.46, 4.88)** 2.24(0.56, 8.98) 2.24(0.41, 12.2) |
| P for interaction              |                          | 0.13                                          |
| Alcohol-related illness        |                          |                                               |
| No                             | 769 104094 7.39 410 41430 9.9 1.34(1.23, 1.46)*** 1.40(1.23, 1.59)*** 1.40(1.19, 1.64)*** |
| Yes                            | 13 3138 4.14 18 3086 5.83 1.41(0.96, 2.07) 2.61(1.14, 5.95)* 2.61(0.96, 7.12) |
| P for interaction              |                          | 0.35                                          |
| Hyperparathyroidism            |                          |                                               |
| No                             | 780 107120 7.28 427 44375 9.62 1.32(1.22, 1.43)*** 1.42(1.25, 1.61)*** 1.42(1.21, 1.66)*** |
| Yes                            | 2 112 17.9 1 142 7.06 0.39(0.07, 2.35) - - |
| P for interaction              |                          | 0.29                                          |
| Celiac disease                 |                          |                                               |
| No                             | 782 107232 7.29 428 44505 9.62 1.32(1.22, 1.43)*** 1.42(1.25, 1.61)*** 1.42(1.21, 1.65)*** |
| Yes                            | 0 0 - 0 11.7 0 - - |
| P for interaction              |                          | -                                             |
| Chron’s disease                |                          |                                               |
| No                             | 766 105230 7.28 420 43519 9.65 1.33(1.22, 1.44)*** 1.42(1.25, 1.62)*** 1.42(1.22, 1.67)*** |
| Yes                            | 16 2002 7.99 8 997 8.02 1.00(0.56, 1.80) 0.85(0.31, 2.33) 0.85(0.25, 2.90) |
| P for interaction              |                          | 0.41                                          |

(Continued)
the RT cohort. Dehydroepiandrosterone (DHEA) and testosterone levels were profoundly reduced in the RT cohort along with a modest increase in cortisol and estradiol levels [27]. The low DHEA increased the RANAL activity owing to the decrease of the ratio of OPG / RANKL mRNA in osteoblasts [28], the high cortisol inhibit the OPG activity, thus resulting in the osteoporosis [8]. Wang NB et al, they found the osteoporosis with low BMD in the PTB patients also [29]. BMD changes were more marked in patients with RT than in those of the same age group with other chronic lung diseases agree this finding also [30]. The osteoporosis contribute to the bone fracture. Therefore, the adjusted HR of the RT cohort for fragility fracture was higher than that of the non-RT cohort, particularly in men (for men, adjusted HR = 1.57, \( p < 0.001 \); for women, adjusted HR = 0.98; \( p > 0.05 \)).

Vitamin D deficiency was common in both underweight and normal-weight patients, but an association between vitamin D deficiency and reduced femur neck T scores was indicated only in the underweight patients with RT [31]. The median 25(OH)D level increased after tuberculosis treatment. In Taiwan, patients with RT receive antituberculosis (anti-TB) treatment [16] or anti-TB with a short-term low dose steroid may increase the BMI of patients with RT and malnutrition [32]. The BMD of Taiwanese women shows a positive relationship to body weight and BMI in the femoral neck fracture group [33]. Similarly, patients with inhaled steroid use [34] may have the less incidence of the osteoporosis [35]. Therefore, RT cohort with steroid use and anti-TB drug may have an increased BMI [35], 25(OH)D level [31], and BMD [35]; these may explain the RT cohort with the lower body weight reveal no significant risk of the incident fragility fracture (aHR = 1.70, \( p > 0.05 \)) or osteoporosis / fragility fracture (aHR = 2.03, \( p > 0.05 \)). These hypotheses warrant research.

The Nanjundaiah et al. report, Lewis rats by injection of heat-killed \( M.\ tuberculosis \) H37Ra (Mtb). The antigen-presenting cells (APCs) took up the microbial antigens. APCs process antigens and then present these Mtb to antigen-specific T cells. These antigen-primed T cells then migrate into the joints, and release proinflammatory cytokines (osteopontin, tumor necrosis factor-\( \alpha \), interleukin) locally leading to arthritic inflammation. These cytokines also stimulate the production of RANKL/MCSF, which activates osteoclasts producing cathepsin K (Cat K) and matrix metalloproteases (MMPs) resulting in bone damage such as osteoporosis [36]. Similarly, sinomenine could attenuate osteoclast formation and Mtb-induced bone loss by

| Table 5. (Continued) | Respiratory tuberculosis | Compared to without respiratory tuberculosis |
|-----------------------|--------------------------|---------------------------------------------|
| Variables             | No Event | Rate | Event | Rate | IRR (95% CI) | Adjusted HR (95% CI) | Adjusted HR (95% CI) |
| Lower body weight     | Event PY | Rate | Event PY | Rate |            |                |                     |
| No                    | 768 | 104556 | 7.35 | 413 | 42491 | 9.72 | 1.32(1.22, 1.44)*** | 1.41(1.24, 1.60)*** | 1.41(1.20, 1.65)*** |
| Yes                   | 14  | 2676  | 5.23 | 15  | 2026  | 7.4  | 1.42(0.91, 2.19)   | 2.03(0.86, 4.82)   | 2.03(0.71, 5.82)   |
| P for interaction     |   |       |   |     |   | 0.74 |                     |                     |                     |

PY: person-year; Rate: incidence rate (per 1,000 person-years); IRR: incidence rate ratio; Adjusted HR: multiple analysis including age, sex, occupation, drug of oral steroid, bisphosphonates, hormone replacement therapy (HRT), vitamin D supplements, and aromatase inhibitors and each comorbidity [including hyperlipidemia, hypertension, diabetes, pneumonia, liver cirrhosis, ischemia heart disease (IHD), stroke, chronic obstructive pulmonary disease (COPD), end-stage renal disease (ESRD), alcohol-related illness, hyperparathyroidism, celiac disease, Chron’s disease, and lower body weight];

*\( p < 0.05 \), **\( p < 0.02 \), ***\( p < 0.001 \)

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mediating RANKL signaling pathways in Li et al study support the RT presenting as systemic inflammation and contribute to the osteoporosis in our study [37].

Women who lived in institutions and had osteoporosis, RT, and cardiac diseases (hypertension) were at risk of a contralateral hip fracture after the initial hip fracture [38]. Activity restriction led to an increased bone resorption in hospitalized women, which possibly affected the risk of osteopenia and osteoporosis [39]. In our study, the patients with the hypertension

| Event | PY   | Rate  | Adjusted HR† (95% CI) | Adjusted HR† (98% CI) |
|-------|------|-------|-----------------------|-----------------------|
| **Fragility fractures** | | | | |
| **Overall** | | | | |
| Without respiratory tuberculosis | 119 | 107232 | 1.11 | 1.00 | 1.00 |
| With respiratory tuberculosis | | | | | |
| Without oral steroid | 34 | 23253 | 1.46 | 1.87(1.20, 2.90)** | 1.87(1.09, 3.19)** |
| With oral steroid | 56 | 21264 | 2.63 | 1.58(1.08, 2.31)* | 1.58(0.99, 2.51) |
| **Men** | | | | | |
| Without respiratory tuberculosis | 73 | 73519 | 0.99 | 1.00 | 1.00 |
| With respiratory tuberculosis | | | | | |
| Without oral steroid | 25 | 14837 | 1.68 | 2.26(1.32, 3.85)** | 2.26(1.18, 4.33)** |
| With oral steroid | 40 | 14678 | 2.73 | 1.89(1.19, 3.00)** | 1.89(1.07, 3.32)** |
| **Women** | | | | | |
| Without respiratory tuberculosis | 46 | 33713 | 1.36 | 1.00 | 1.00 |
| With respiratory tuberculosis | | | | | |
| Without oral steroid | 9 | 8416 | 1.07 | 1.25(0.56, 2.77) | 1.25(0.47, 3.29) |
| With oral steroid | 16 | 6586 | 2.43 | 1.09(0.55, 2.15) | 1.09(0.47, 2.49) |
| **Osteoporosis /fragility fractures** | | | | | |
| **Overall** | | | | | |
| Without respiratory tuberculosis | 782 | 107232 | 7.29 | 1.00 | 1.00 |
| With respiratory tuberculosis | | | | | |
| Without oral steroid | 200 | 23253 | 8.60 | 1.41(1.19, 1.67)** | 1.41(1.14, 1.74)** |
| With oral steroid | 228 | 21264 | 10.7 | 1.42(1.19, 1.70)** | 1.42(1.14, 1.77)** |
| **Men** | | | | | |
| Without respiratory tuberculosis | 428 | 73519 | 5.82 | 1.00 | 1.00 |
| With respiratory tuberculosis | | | | | |
| Without oral steroid | 107 | 14837 | 7.21 | 1.56(1.23, 1.98)** | 1.56(1.17, 2.09)** |
| With oral steroid | 132 | 14678 | 8.99 | 1.43(1.13, 1.81)** | 1.43(1.08, 1.90)** |
| **Women** | | | | | |
| Without respiratory tuberculosis | 354 | 33713 | 10.5 | 1.00 | 1.00 |
| With respiratory tuberculosis | | | | | |
| Without oral steroid | 93 | 8416 | 11.1 | 1.25(0.98, 1.61) | 1.25(0.92, 1.70) |
| With oral steroid | 96 | 6586 | 14.6 | 1.42(1.07, 1.89)* | 1.42(1.00, 2.01) |

PY, person-year; Rate, incidence rate (per 1,000 person-years); Adjusted HR†: multiple analysis including occupation, drug of oral steroid, bisphosphonates, hormone replacement therapy (HRT), vitamin D supplements, and aromatase inhibitors and each comorbidity [such as hyperlipidemia, hypertension, diabetes, pneumonia, liver cirrhosis, ischemia heart disease (IHD), stroke, chronic obstructive pulmonary disease (COPD), end-stage renal disease (ESRD), alcohol-related illness, hyperparathyroidism, celiac disease, crohn disease, and lower body weight];

*p<0.05,

**p<0.02,

***p<0.001
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(aHR = 1.34, \(p\) value < 0.05) and IHD (aHR = 1.30, \(p\) value < 0.05) were association with the osteoporosis / fragility fracture in RT cohort. Meanwhile, women in the RT cohort with the oral steroid use are at an increased risk of osteoporosis / fragility fracture (aHR = 1.42, 95% CI; \(p\) value < 0.05) than the non-RT cohort. These finding in line with previous study. Yet, this result need the random control trial for confirmation.

Previous studies have reported that metabolic-syndrome-relate d diseases such as hyperlipidemia, hypertension, diabetes, ischemic heart diseases, ESRD [10], and liver cirrhosis [11] were more common in patients with osteoporotic fracture. This study also demonstrated that metabolic diseases increased the risk of bone fracture, osteoporosis / fragility fracture. Meanwhile, alcohol-related illness were associated with the bone fractures, osteoporosis / fragility fracture in RT cohort also. Previous studies have rarely reported pneumonia as a risk factor of osteoporosis. In this study, we observed that both acute pneumonia (viral and bacterial) and chronic respiratory infectious diseases (RT) increased the risk of fragility fracture (aHR = 1.69), osteoporosis / fragility fracture (aHR = 1.42).

Respiratory infections were frequently observed in elderly patients with malnutrition. The combined effect of malnutrition, respiratory infection, and physical inactivity contributes to osteoporosis / incident fragility fracture [40]. In our study, we found that a higher incidence of bone fracture, osteoporosis / fragility fracture among the frequently hospitalized patients with RT even without low body weight, or without steroid use; compared with patients without RT. This study increases physicians awareness of incident bone fracture associated with RT.

**Limitations**

Several limitations must be considered when interpreting these findings. The NHIRD does not provide detailed lifestyle information such as smoking, BMI, and physical activity, which were potential confounding factors in this study. However, anti-TB treatment and lifestyle modification of patients with RT may implicate these factors in accelerated bone fracture or osteoporosis / fragility fracture observed in RT. Additionally, information on osteoporosis severity scales such as disease activity, functional impairment, and physical damage may lead to under-diagnosis of this metabolic syndrome. Insufficient drug data such as oral antidiabetic drugs to adjust for the outcomes of interest could be another limitation. The evidence derived from this retrospective cohort study is generally of lower methodological evidence than that from randomized controlled trials because a retrospective cohort study is subject to many biases due to lack of the necessary adjustments for possible confounding factors (such as lack of the important data like serum levels OPG, RANKL, osteoclast activity markers and bone formation markers; and individual data of the histological or densitometric changes in bone). The Nanjundaiah and Li et al. study were experimental study in animals. Therefore, further investigation with a prospective and randomized controlled study design to reveal the cause-effect between RT and bone fracture or osteoporosis / fragility fracture would be worthwhile. In addition, lack of BMD data to do the optimal diagnosis of osteoporosis in the NHIRD is the study limitation. However, NHIRD covers a highly representative sample of Taiwan’s general population because the reimbursement policy is universal and operated by a single-buyer, the government in Taiwan. All insurance claims should be scrutinized by medical reimbursement specialists and peer review according to the standard diagnosed criteria in the study. If these doctors or hospitals make wrong diagnoses or coding, they will be punished with a lot of penalties. Therefore, the diagnoses of osteoporosis based on ICD-9 codes in this study were highly reliable. In addition, fracture reported here is based on ICD codes, not X-ray report. We can’t distinguish between atraumatic and traumatic fractures. Meanwhile, Underlying causes of pathological fractures include osteoporosis, metastatic bone tumor, osteomyelitis, Paget’s
disease, disuse atrophy, hyperparathyroidism, and nutritional or congenital disorders [Coding for Fractures: For The Record Vol. 20 No. 24 P. 28 (Great Valley Publishing Co., Inc)]. After we did analyses, we didn’t find the coding of the [ICD-9-CM -198.5, Secondary malignant neoplasm of bone and bone marrow; ICD-9-CM—170.9, Malignant neoplasm of bone and articular cartilage, site unspecified; ICD-9-CM-731.0, Osteitis deformans without mention of bone tumor] in the RT cohort. The impact of these confounding factors on the fragility fractures needs further investigation. Finally, when performing several tests, increasing the family-wise error rate (FWER, the probability of rejecting at least one null hypothesis erroneously). In statistics, FWER is the probability of making one or more false discoveries, or type errors when performing multiple hypotheses tests. The Bonferroni adjustment will always provide strong control of the family-wise error rate [41]. If the number of comparisons in the test becomes large, the test may become too conservative and no longer allows us to find anything significant [42].

Strength
The nationwide population-based longitudinal cohort study used to investigate the risk factors of incident bone fracture, osteoporosis / fragility fracture in an Asian population with RT was the strength of this study. We investigated drug effects such as oral steroid of the impact on the osteoporosis. We have replaced the smoking history data with the comorbidity which were associated with smoking such as IHD, stroke and COPD for adjustment. Meanwhile the lifestyle such as drinking (alcohol-related disease) and patients received anti-osteoporosis drugs were included for analysis also. Furthermore, the study included participants from the general population representative of a true population, thereby improving the generalizability of our results. Even the BMD unavailable in this study; the policy of diagnosis of the osteoporosis is well established in Taiwan [43]. The coding the osteoporosis under the “guideline for the prevention and treatment of osteoporosis in Taiwan” at most healthcare system [44]. This multidisciplinary system may avoid the diagnosis bias.

Conclusion
The Respiratory tuberculosis associated with the incident fragility fracture, either in men or absence of oral steroid use

Supporting Information
S1 STROBE Checklist.
(DOC)

Author Contributions
Conceptualization: JFY WHH.
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Formal analysis: JFY YCW CCL CLL WHH.
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