The impact of cancer development on the risk of mycobacterial diseases among rheumatoid arthritis patients

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SUMMARY

Mycobacterial diseases are prevalent in cancer and rheumatoid arthritis (RA) patients, especially those receiving tumor necrosis factor-α inhibitor (TNFi). However, the impact of cancer development on the risk of mycobacterial diseases among RA patients is unknown. Data from the Taiwan National Health Insurance Research Database were used to conduct a retrospective study to assess the occurrence of mycobacterial diseases in RA patients developing cancer (cancer-positive), those using TNFi (TNFi-exposure), those with cancer and using TNFi (cancer-TNFi-comb), and those without cancer and not using TNFi (cancer-TNFi-free). Cancer and TNFi exposure were time-dependent, and independent risk factors of mycobacterial diseases were assessed by Cox regression. Among 1344 RA patients diagnosed during 2000–2013, 68 (5·1%) developed cancer before their end points. The incidence rates of mycobacterial diseases in the cancer-positive ($n = 56$), TNFi-exposure ($n = 290$), cancer-TNFi-comb ($n = 12$), and cancer-TNFi-free ($n = 986$) subgroups were 6·7, 2·0, 7·6, and 1·3 per 1000 person-years, respectively. As compared with the cancer-TNFi-free group, the risk for mycobacterial diseases increased for the TNFi-exposure group (adjusted HR = 3·6, 95% confidence interval (95% CI) 1·1–11·5, $P = 0·032$) and remained high for cancer-positive (adjusted HR = 14·6, 95% CI 3·3–63·7, $P < 0·001$) after adjustment. This study suggested that cancer development increased the risk of mycobacterial diseases in RA patients, and risk assessment for this subgroup should be considered.

Key words: Cancer, mycobacterial diseases, rheumatoid arthritis, tuberculosis (TB).

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INTRODUCTION

Tuberculosis (TB), an airborne mycobacterial disease, remains a major global infectious disease, causing high mortality and morbidity [1]. Although the incidence rate of TB is declining slowly, the incidence of mycobacterial diseases caused by non-tuberculous mycobacteria (NTM) continues to rise worldwide, associated with poor outcomes in certain populations [2–4]. Both TB and NTM infections may result in public health problems, and they specifically tend to occur in vulnerable patients with immunocompromising conditions.

Cancer patients are relatively immunocompromised, so they are also susceptible to mycobacterial infections [5]. Cancers tend to occur in patients with systemic rheumatic diseases because of immunological defects, inflammatory burden, and exposure to smoking and disease-modifying anti-rheumatic drugs (DMARD) such as methotrexate [6, 7]. Notably, rheumatoid arthritis (RA) patients have a higher risk of developing malignant neoplasm compared with non-RA populations [8, 9]. RA patients also are immunocompromised because of their underlying autoimmune disease and immunosuppressant treatment. Although cancer and RA both carry the risk of mycobacterial infection, information regarding the clinical impact of cancer development on the risk of mycobacterial diseases in RA patients remains scant [10]. To better control mycobacterial diseases in RA patients, it would be valuable to comprehensively understand the potential risk factors of mycobacterial infection in this population.

With respect to mycobacterial infections in RA, patients may receive tumor necrosis factor-α inhibitor (TNFi) therapy for refractory RA disease, and those who receive TNFi have a higher risk of TB than those who do not because of reactivation of latent TB infection (LTBI) [11–13]. Previous studies have focused on the effects of baseline comorbidities and the subsequent use of TNFi on the risk of mycobacterial diseases in RA patients, but they did not take into account potential risk factors that may have occurred during the course of RA, such as cancer development [13, 14]. In addition, although cancer and TNFi exposure during the RA course are not rare, the risk of mycobacterial diseases in RA patients, both with and without cancer, and with or without TNFi therapy, have not been specifically investigated.

We hypothesized that RA patients with cancer and those with TNFi treatment would have greater risk of mycobacterial diseases as compared to RA patients without cancer and TNFi exposure (i.e., cancer-TNFi-free). To test this hypothesis, we conducted a population-based retrospective cohort study and assessed the impact of malignancy on the risk of mycobacterial diseases in RA patients after controlling for the TNFi factor.

METHODS

Data source and participants

This was a retrospective, population-based cohort study in Taiwan using data from the Longitudinal Health Insurance Database-2005, a subset of the National Health Insurance Research Database (NHIRD), which included the data of 1 million National Health Insurance (NHI) beneficiaries randomly sampled from the NHIRD. Patients who had newly diagnosed RA (International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code 714·0) and had received traditional DMARD such as methotrexate for more than 30 defined daily doses (DDD) between 1 January 2000 and 31 December 2013 were selected from the Longitudinal Health Insurance Database-2005. The diagnostic accuracy of RA was further verified by inclusion in the Registry for Catastrophic Illness Patient Database (RCIPD), a unique subcomponent of the NHIRD [13]. Major illnesses that place a heavy burden on beneficiaries, such as RA and cancer, are included in the catastrophic illness registries, and the diagnosis of illness must be certified by reviewers at the Bureau of National Health Insurance [15]. Therefore, the diagnosis of RA met the 1987 American College of Rheumatology criteria [16, 17].

RA patients who were <20 years old or had an antecedent history of mycobacterial infection or cancer were excluded. Finally, the enrolled RA participants were tracked from the time their RA diagnosis was made to 31 December 2013 or the date of withdrawal from the NHI system, to ascertain the occurrence of outcome. In addition to the RA cohort (n = 1344), a non-RA cohort was also selected through a two-stage approach [18]. For each RA patient, four age-, sex-, and index year-matched non-RA subjects who satisfied the above criteria were randomly sampled from the database. Among these, 1 : 1 propensity score-matched non-RA cases (n = 1344) for RA patients were selected on the basis of the nearest propensity score, predicting RA assignment from

age, sex, income level, and comorbidities. Our research was approved by the Institutional Review Board (IRB) of Taipei Veterans General Hospital (IRB: 2015-04-004AC).

Variables and definition

The outcome of interest was the development of mycobacterial diseases, including TB and NTM disease, during the follow-up period. TB disease was defined by compatible ICD-9-CM codes (010–018 in ICD-9-CM) and validated by the prescription of, at least, two anti-TB medications for more than 60 days. In Taiwan, all diagnosed TB cases must be reported to the Center for Disease Control within a week of diagnosis and should be monitored for anti-TB treatment. Since the culture confirmation of TB would take up to 2 months in general, linking the diagnosis code and anti-TB drugs for more than 60 days to define confirmed TB cases in the NHIRD is reasonable [19]. Similarly, diseases caused by NTM were defined as those compatible ICD-9-CM codes (031·0, 031·2, 031·8, 0·31·9 in ICD-9-CM) in an inpatient setting or at three or more outpatient visits [20].

An incidence of cancer in an RA patient during the follow-up period was defined as a newly diagnosed cancer (ICD-9-CM codes 140–208) that was confirmed by the patient's inclusion in the RCIPD [15]. The TNFi medications that were available in Taiwan before 31 December 2013 were etanercept, adalimumab, and golimumab. Of these, etanercept was the first TNFi to be approved by Taiwan's National Health Insurance Bureau in 2003, followed by adalimumab and golimumab in 2007 and 2012, respectively. The date on which an RA patient started to use any TNFi before the end point was noted. In addition, the dispensed doses and types of steroids used during the follow-up period were recorded. The DDD of a given drug was standardized by using the Anatomical Therapeutic Chemical-DDD system of the World Health Organization (http://www.whocc.no). The DDD of prednisolone was 10 mg; that of dexamethasone, 1·5 mg; that of methylprednisolone, 7·5 mg. Based on the drug dosages and the durations of prescriptions, the cumulative DDD of corticosteroids was estimated as the sum of the dispensed DDDs of dexamethasone, methylprednisolone, and prednisolone from the index date to the end point.

Diabetes mellitus (DM) (ICD-9 code 250) and chronic obstructive pulmonary disease (COPD) (ICD-9 codes 491, 492, and 496), two common risk factors for mycobacterial diseases, were identified from NHIRD if the diagnosis presented in an inpatient or in three or more outpatient records. In addition, according to the average monthly income of the insured person, a patient was grouped into high-income ($\geqslant 40\,000$ New Taiwan Dollars) or low-income status.

Statistical analysis

The results are presented as mean ± S.D. for continuous variables and as proportions (%) for categorical variables. The independent t test was used to compare continuous variables; the χ^2 statistic, to compare frequency measures. Univariate and multivariate Cox regression models were used to assess the impact of putative risk factors for mycobacterial diseases in RA patients. TNFi exposure and the development of cancer were treated as time-varying covariates, and their impacts on the risk of mycobacterial diseases were assessed by Cox proportional hazards regression with time-dependent variables. In all analyses, $\alpha = 0·05$ was set for significance, and 95% confidence intervals (95% CIs) were calculated for the adjusted hazard ratios (HRs). Statistical analysis was performed using SPSS v20·0 (SPSS Inc., Chicago, Illinois, USA).

RESULTS

Study enrollment and characteristics of RA population

In total, 2084 RA patients who had received traditional DMARD for more than 30 DDD were identified during the period from 1 January 2000 to 31 December 2013. Of these, 1391 patients had RA catastrophic illness certificates, and a total of 1344 eligible, and confirmed, RA patients were included in the study (Fig. 1). The overall mean age of the study patients was 54·2 ± 13·2 years, and 79% of the enrolled patients were female.

Among the enrolled RA patients, 986 (73·4%) were cancer-free and never received TNFi therapy (cancer-TNFi-free), 290 (21·6%) were cancer-free but received TNFi (TNFi-exposure), 56 (4·1%) were cancer patients without TNFi treatment (cancer-positive), and the remaining 12 (0·9%) had cancer in combination with TNFi (cancer-TNFi-comb) during the follow-up periods. Overall, 68 (5·1%) RA patients developed cancer during a follow-up of 10 056 person-years, corresponding to an incidence rate of
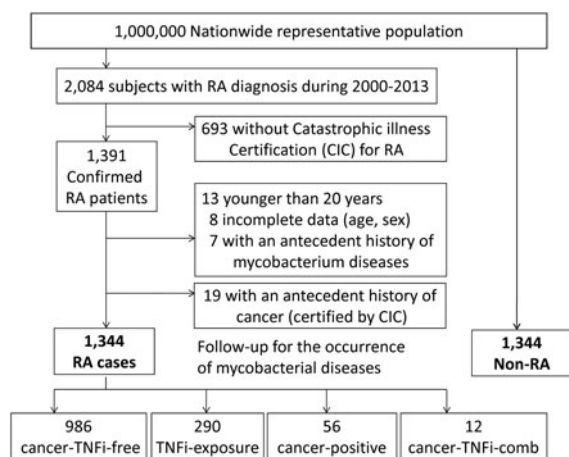
Fig. 1. Flow chart of the study. Cancer-TNFi-comb, patients with emergent cancer and TNFi therapy; RA, rheumatoid arthritis; TNFi, tumor necrosis factor-α inhibitor.

6·8 per 1000 person-years. The most commonly diagnosed three cancer types were breast ($n = 14$, 21%), colon/rectal ($n = 10$, 15%), and lung cancer ($n = 7$, 10%), whereas hematologic malignancies accounted for only five cases.

Characteristics and rates of mycobacterial diseases among RA subgroups

The characteristics of RA patients classified by TNFi use and cancer development are shown in Table 1. As compared with the cancer-TNFi-free subgroup, patients in the TNFi-exposure subgroup were relatively younger, had a higher ratio of methotrexate use, and received higher doses of corticosteroid, while those in the cancer-positive subgroup were older and contracted more mycobacterial diseases during the follow-up period. Overall, mycobacterial diseases occurred in 18 (1·3%) RA patients during a mean follow-up period of $7·4 ± 3·8$ years, yielding an incidence rate of 1·8 per 1000 person-years. These included nine patients (1%) from the cancer-TNFi-free subgroup, five (2%) from the TNFi-exposure subgroup, three (5%) from the cancer-positive subgroup, and one (8%) from the cancer-TNFi-comb subgroup, yielding the corresponding incidence rates of 1·3, 2·0, 6·7, and 7·6 per 1000 person-years, respectively, of mycobacterial diseases in the four subgroups.

Independent risk factors for mycobacterial diseases in RA population

Figure 2 presents the mean follow-up years, period of exposure to TNFi, and period of exposure to cancer in

the cancer-TNFi-free, TNFi-exposure, and cancer-positive subgroups. In order to clearly model the risk factors that develop over time in these subgroups, the cancer-TNFi-comb subgroup was excluded due to their mixed time points of TNFi start and cancer occurrence. Then the time-dependent exposure of TNFi and cancer were incorporated into the analysis by multivariate Cox regression. As shown in Table 2, the independent risk factors for mycobacterial diseases in RA patients were age $\geqslant 60$ years (adjusted HR 4·9, 95% CI 1·5–15·8, $P = 0·008$), male sex (adjusted HR = 5·1, 95% CI 1·9–13·9, $P = 0·001$), COPD (adjusted HR = 3·9, 95% CI 1·0–15·1, $P = 0·049$), TNFi-exposure (adjusted HR = 3·6, 95% CI 1·1–11·5, $P = 0·032$), and cancer-positive (adjusted HR = 14·6, 95% CI 3·3–63·7, $P < 0·001$) as compared with cancer-TNFi-free after adjustment for confounding factors. In addition, the risk of mycobacterial diseases was fourfold higher in the cancer-positive subgroup than in the TNFi-exposure subgroup, with a statistical trend toward significance (adjusted HR = 4·1, 95% CI 0·8–20·2, $P = 0·086$).

Specifically, the risk of TB was significantly higher for cancer-positive (adjusted HR = 15·6, 95% CI 3·6–68·5, $P < 0·001$) and marginally elevated for TNFi-exposure (adjusted HR = 3·3, 95% CI 0·9–11·8, $P = 0·066$) as compared with cancer-TNFi-free. However, the risk of NTM diseases in the subgroups was impractical to assess because there were only two NTM cases in the RA cohort.

The risk of mycobacterial diseases in non-RA population and competitor subgroups

Among 1344 propensity score-matched non-RA patients, 28 (2·1%) developed cancer before the end points, and eight (0·6%) had emergent mycobacterial diseases (all were TB cases, one with cancer and the other seven without). The incidence rate of mycobacterial diseases in the non-RA cohort was 1·1 per 1000 person-years. In a multivariate analysis, both age and time-dependent cancer significantly increased the risk of mycobacterial diseases in the non-RA cohort (adjusted HR = 1·1, 95% CI 1·0–1·2, $P = 0·017$ and HR = 22·0, 95% CI 1·5–334·0, $P = 0·026$) after adjustment for sex, high income, DM, COPD, and corticosteroid dosage.

In an analysis comparing the risk of mycobacterial diseases between subgroups stratified by cancer and RA, RA patients with cancer had a 10-fold increased risk of mycobacterial diseases as compared

Table 1. *Characteristics and mycobacterial diseases in whole population of RA patients (n = 1344) and subgroups stratified by TNFi use and cancer development during the follow-up periods*

Variable	Whole population (n = 1344)	Cancer-TNFi-free (n = 986)	TNFi-exposure (n = 290)	Cancer-positive (n = 56)	Cancer-TNFi-comb (n = 12)
Age, years	54 ± 13	54 ± 13	52 ± 12*	63 ± 13*,#	56 ± 11
Age ⩾60	466 (35)	350 (35)	77 (27)*	35 (62) *,#	4 (33)
Male sex	288 (21)	215 (22)	57 (20)	12 (21)	4 (33)
High income	745 (55)	563 (57)	153 (53)	23 (41)*	6 (50)
Diabetes mellitus	100 (7)	76 (8)	16 (6)	7 (13)	1 (8)
Chronic obstructive pulmonary disease	31 (2)	24 (2)	5 (2)	2 (4)	0
Methotrexate use	833 (62)	586 (59)	204 (70)*	33 (59)	10 (83)
Average annual cumulative DDD of corticosteroids	118 ± 251	115 ± 282	132 ± 135*	106 ± 107	96 ± 102
Corticosteroid use > 0·5 DDD/day	296 (22)	190 (19)	90 (31)*	14 (25)	2 (17)
Interval from RA diagnosis to TNFi use	–	–	4·4 ± 3·3	–	5·6 ± 3·3
Interval from RA diagnosis to cancer	–	–	–	5·0 ± 3·1	7·3 ± 4·3
Follow-up period before end point, years	7·4 ± 3·8	7·1 ± 3·9	8·4 ± 3·5*	7·9 ± 3·5	11·0 ± 3·2*,#,@
Mycobacterium disease	18 (1)	9 (1)	5 (2)	3 (5)*	1 (8)
Tuberculosis disease	16 (1)	8 (1)	4 (1)	3 (5)*	1 (8)
Non-tuberculous mycobacteria infection	2	1	1	0	0

RA, rheumatoid arthritis; TNFi, tumor necrosis factor-α inhibitor; DDD, defined daily dose.

Continuous data expressed as mean ± S.D. and categorical data as number (%).

*Indicates a significant difference ($P < 0.05$) between cancer-TNFi-free and compared groups; [#] $P < 0.05$ between TNFi-exposure and compared groups; [@] $P < 0.05$ between cancer-positive and compared groups.
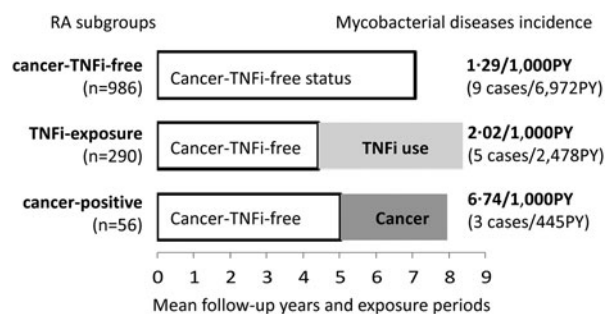
Fig. 2. Mean follow-up years, exposure periods, and incidence of mycobacterial diseases among RA subgroups classified by TNFi and emergent cancer. TNFi, tumor necrosis factor-α inhibitor; PY, person-years.

with non-RA controls without cancer (adjusted HR = 10·2, 95% CI 2·6–38·6, P = 0·001) after adjustment. As shown in Table 3, in the older population (≥60 years), the risk of mycobacterial diseases was significantly higher for the RA subgroups with cancer as compared with the two reference subgroups, namely non-RA without cancer and RA without cancer. In the younger population, the risk remained higher for the RA subgroup with cancer as compared with the other two reference subgroups.

DISCUSSION

This is the first population-based cohort study to evaluate the impact of ensuing cancer on the risk of mycobacterial diseases among RA patients. Notably, we simultaneously accounted for the influence of two important time-dependent variables: TNFi use and cancer development. As expected, TNFi-exposure significantly increased the risk of mycobacterial diseases as compared with cancer-TNFi-free. Our novel finding is that an emergent cancer (cancer-positive) in RA patients was associated with exponentially higher risk of mycobacterial diseases as compared with cancer-TNFi-free status (adjusted HR = 14·6, 95% CI 3·3–63·7, P < 0·001). In addition, incident cancer in RA patients carried a fourfold elevated risk of mycobacterial diseases as compared with TNFi therapy alone, with a statistical trend toward significance.

Mycobacterial diseases are serious public health issues worldwide. In Taiwan, a TB endemic area, the TB incidence in the general population was high in 2011, with a rate of 55 cases/100 000 people. In addition, the NTM incidence was estimated to increase, and a hospital-based study in northern Taiwan

Table 2. *Univariate and multivariate Cox regression analysis of factors associated with mycobacterial diseases (n = 1332; 12 patients with both cancer and TNFi use, cancer-TNFi-comb was excluded for analysis)*

Variable	Mycobacterial diseases (n = 17)	No mycobacterial diseases (n = 1315)	Crude HR (95% CI)	P value	Adjusted HR (95% CI)	P value
Age ≥60	13 (76)	449 (34)	6·4 (2·10–19·67)	0·001	4·9 (1·51–15·77)	0·008
Male sex	10 (59)	274 (21)	6·1 (2·33–16·20)	<0·001	5·1 (1·90–13·94)	0·001
High income	7 (41)	732 (56)	0·8 (0·29–2·02)	0·590	1·1 (0·38–2·92)	0·914
Diabetes mellitus	4 (24)	95 (7)	4·7 (1·53–14·52)	0·007	3·0 (0·92–9·92)	0·069
Chronic obstructive pulmonary disease	3 (18)	28 (2)	7·8 (2·34–27·10)	0·001	3·9 (1·01–15·06)	0·049
Methotrexate use	13 (76)	810 (62)	1·6 (0·52–5·07)	0·400	2·1 (0·60–7·45)	0·244
Corticosteroid use >0·5 DDD/day	7 (41)	287 (22)	2·8 (0·98–6·79)	0·056	1·8 (0·66–5·07)	0·242
Cancer-TNFi-free	9 (53)	977 (74)	1·00 (reference)		1·00 (reference)	
TNFi-exposure[a]	5 (29)	285 (22)	3·7 (1·20–11·60)	0·023	3·6 (1·12–11·46)	0·032
Cancer-positive[a]	3 (18)	53 (4)	15·5 (4·04–59·41)	<0·001	14·5 (3·32–63·72)	<0·001

TNFi, tumor necrosis factor-α inhibitor; DDD, defined daily dose; HR, hazard ratio; CI, confidence interval.

Categorical data expressed as number (%).

[a] Time-dependent variables.

Table 3. *The comparative risks of mycobacterial diseases in subgroups of RA and non-RA patients*

Subgroups	Mycobacterial diseases	Adjusted[a] HR (95% CI)	*P* value	Adjusted[b] HR (95% CI)	*P* value
Total (*n* = 2688)					
Non-RA without cancer, *n* = 1316	7 (1)	1·0 (reference)		–	
RA without cancer, *n* = 1279	12 (1)	1·2 (0·45–2·98)	0·757	1·0 (reference)	
Non-RA with cancer, *n* = 28	1 (4)	4·2 (0·47–37·38)	0·199	–	
RA with cancer, *n* = 65	6 (9)	10·2 (2·64–38·59)	0·001	8·1 (2·42–27·43)	0·001
Older (⩾60 years), *n* = 938					
Non-RA without cancer, *n* = 444	4 (1)	1·0 (reference)		–	
RA without cancer, *n* = 427	8 (2)	1·2 (0·35–4·18)	0·760	1·0 (reference)	
Non-RA with cancer, *n* = 28	1 (4)	5·2 (0·51–52·36)	0·165	–	
RA with cancer, *n* = 39	5 (13)	8·0 (1·52–41·77)	0·014	8·3 (1·86–36·92)	0·006
Younger (<60 years), *n* = 1750					
Non-RA without cancer, *n* = 872	3 (<1)	1·0 (reference)		–	
RA without cancer, *n* = 852	4 (<1)	1·02 (0·22–4·78)	0·980	1·0 (reference)	
Non-RA with cancer, *n* = 0	0	–		–	
RA with cancer, *n* = 26	1 (4)	13·4 (1·24–144·50)	0·033	33·8 (1·15–995·17)	0·041

RA, rheumatoid arthritis; HR indicates hazard ratio; CI, confidence interval.
Categorical data expressed as number (%).
The status of cancer exposure was treated as a time-dependent variable in all models.
[a] Adjusted by age, sex, high income, diabetes mellitus, chronic obstructive pulmonary disease, and corticosteroid dosage.
[b] Adjusted by factors mentioned above, methotrexate, and TNFi, tumor necrosis factor-α inhibitor treatment.

reported an NTM infection rate of 15·3 cases/100 000 patients in 2011, although determining an exact rate in the general population will warrant further investigation [3]. More importantly, mycobacterial diseases are increasingly prevalent in patients with autoimmune diseases and malignancy [5, 10]. Although malignant neoplasm is not uncommon in RA patients and cancer patients have various risk factors for mycobacterial diseases in different settings, little is known about the impact of cancer on the risk of mycobacterial diseases in RA patients [8, 9]. This interconnection is of paramount importance for RA patients because they suffer from an increased risk of mycobacterial diseases as a result of underlying autoimmune disease, complications of the currently available TNFi medications, and other potential risk factors [11]. Our study focused on newly diagnosed cancers in RA patients and found a cancer incidence rate of 6·8 per 1000 person-years, which is consistent with a recent report [15]. Our data also showed that cancer-positive patients were older in age upon RA diagnosis than cancer-TNFi-free and TNFi-treated patients; they also had a higher ratio of mycobacterial diseases than their cancer-TNFi-free counterparts. After accounting for the time-dependent exposure of RA patients to TNFi and cancer, cancer-positive cases carried a 14-fold increased risk of mycobacterial diseases as compared with cancer-TNFi-free. To our knowledge,

this is the first study to identify emergent cancer as an independent risk factor for mycobacterial diseases in RA patients after controlling for the TNFi factor.

In previous reports [4, 10, 13, 14], the significant baseline risk factors for mycobacterial diseases in RA populations include advanced age, male sex, TB history, and the presence of DM, COPD, and chronic kidney disease. Our findings are consistent with previous reports in that old age, male sex, and COPD are significantly associated with an increased risk of mycobacterial diseases. Recent studies have investigated the impact of RA-related therapies, such as steroid and TNFi, on the risk of mycobacterial diseases with adjustment for the indicators mentioned above [13, 14]. However, the influence of TNFi on this risk has not been adjusted by the presence of subsequent cancer development in RA patients. In the present study, after excluding cancer-TNFi-comb patients and treating cancer and TNFi exposure in a time-dependent manner, we found that TNFi therapy carried a threefold higher risk of mycobacterial diseases than did cancer-TNFi-free status.

After adjustment for important factors, both emergent cancer and TNFi therapy during RA course were significantly associated with increased risks of mycobacterial diseases. In addition, we noted a fourfold increased risk of mycobacterial diseases in the emergent cancer-positive RA patients as compared with

the TNFi therapy cases, although the association was not statistically significant. Since RA patients applying for TNFi undergo a preliminary screening for LTBI as a risk management protocol, TNFi receiving RA patients might receive concurrent prophylactic therapy against mycobacteria and thus have a lower risk of developing mycobacterial infections as compared with cancer-positive RA patients. Nevertheless, cancer patients without such mitigations carried a significantly increased risk of mycobacterial diseases in this study. We therefore recommend that RA patients developing cancer should be assessed and monitored for mycobacterial diseases, as recommended for RA patients receiving TNFi therapy [21, 22]. However, further investigations are required to better understand the mechanism of cancer-associated mycobacterial diseases in RA patients and to develop effective strategies for management of mycobacterial diseases.

Some plausible mechanisms could be posited to explain the association of emergent cancer and future risk of mycobacterial diseases in RA populations. First, RA patients with cancer may suffer from a double-hit immunosuppression because both RA and cancer entail an underlying immune deficiency as well as immunosuppressant treatment. This makes RA patients more susceptible to mycobacterial diseases, be it for reactivation of LTBI or for contracting new mycobacterial infections [4]. Second, RA patients may have high levels of certain types of cancer that make them susceptible to mycobacterial diseases. Recent reports revealed that RA patients have an increased risk of developing hematologic neoplasm and lung cancer and that patients with such cancers are susceptible to mycobacterial diseases [5, 8, 17, 21, 23–26]. However, due to the limited sample size, it was not feasible for us to evaluate this possibility, for only five and seven of the RA patients in this study developed hematologic neoplasm and lung cancer, respectively. Finally, because age was associated with both cancer and mycobacterial diseases in our results, the relationship between the two conditions may have been confounded by the age factor. However, in our subgroup analysis, this positive association remained significant both in older and in younger RA patients. Hence, mechanisms other than age factors may influence the risk of mycobacterial diseases in RA patients with cancer.

This study has several limitations. First, we examined RA patients living in Taiwan, a TB-endemic area, and identified only a small number of TB cases. It is uncertain whether our findings can be generalized to patients living in low TB-burden areas. Second, we did not have detailed information on the LTBI status of each RA patient in this retrospective study. Hence, the impacts of LTBI on the comparative risks of mycobacterioses between different exposure groups could not be investigated. In addition, we did not assess prophylactic therapy for LTBI in RA patients although prophylaxis does influence the risk of TB in RA patients [13]. This is because the TB risk management plan for patients scheduled to receive TNFi was not announced by the Taiwan Food and Drug Administration until August 2011 [27], which only covered a 2-year period of this 14-year study. Third, as RA patients with both incident cancer and TNFi therapy were excluded from the multivariate Cox regression (Table 2), this study provides limited information on the risk of mycobacterial diseases in this subgroup. However, since they had mixed time points in cancer development and exposure to TNFi, it was reasonable to exclude them so that the comparative risk ascribed to emergent cancer and TNFi therapy could be clear and evident. Fourth, we did not assess the effect of chemotherapy on the risk of mycobacterial diseases in cancer patients because the regimens were diverse. In addition, we had no data about certain important confounding factors, such as inflammatory indicators and personal habits, which were not available in the NHIRD. Whether the increased risk of mycobacterial diseases is associated with cancer treatment and inflammatory status warrants further investigation.

CONCLUSION

This population-based study revealed that both emergent cancer and TNFi therapy during RA course were significantly associated with increased risks of mycobacterial diseases as compared with cancer-TNFi-free status. Hence, clinicians should consider this risk, not only in RA patients receiving TNFi therapy but also in those with ensuing cancer. Further prospective study is required to investigate the mechanism underlying mycobacterial diseases in RA patients with cancer.

ACKNOWLEDGMENTS

DECLARATION OF INTEREST

The authors do not have any conflicts of interest.

REFERENCES

1. **World Health Organization.** Global Tuberculosis Report. 2014 (http://apps.who.int/iris/bitstream/10665/137094/1/9789241564809_eng.pdf).
2. **Brode SK, et al.** The epidemiologic relationship between tuberculosis and non-tuberculous mycobacterial disease: a systematic review. *The International Journal of Tuberculosis and Lung Disease* 2014; **18**: 1370–1377.
3. **Chien JY, et al.** Pulmonary infection and colonization with nontuberculous mycobacteria, Taiwan, 2000–2012. *Emerging Infectious Diseases* 2014; **20**: 1382–1385.
4. **Brode SK, et al.** Risk of mycobacterial infections associated with rheumatoid arthritis in Ontario, Canada. *Chest* 2014; **146**: 563–572.
5. **Seo GH, et al.** Cancer-specific incidence rates of tuberculosis: a 5-year nationwide population-based study in a country with an intermediate tuberculosis burden. *Medicine (Baltimore)* 2016; **95**: e4919.
6. **Turesson C, et al.** Malignancy as a comorbidity in rheumatic diseases. *Rheumatology (Oxford)* 2013; **52**: 5–14.
7. **Solomon DH, et al.** Comparative cancer risk associated with methotrexate, other non-biologic and biologic disease-modifying anti-rheumatic drugs. *Seminars in Arthritis and Rheumatism* 2014; **43**: 489–497.
8. **Simon TA, et al.** Incidence of malignancy in adult patients with rheumatoid arthritis: a meta-analysis. *Arthritis Research & Therapy* 2015; **17**: 212.
9. **Raheel S, et al.** Risk of malignant neoplasm in patients with incident rheumatoid arthritis 1980–2007 in relation to a comparator cohort: a population-based study. *International Journal of Rheumatology* 2016; **2016**: 4609486.
10. **Liao TL, et al.** Risk for mycobacterial disease among patients with rheumatoid arthritis, Taiwan, 2001–2011. *Emerging Infectious Diseases* 2015; **21**: 1387–1395.
11. **Ke WM, et al.** Risk of tuberculosis in rheumatoid arthritis patients on tumour necrosis factor-alpha inhibitor treatment in Taiwan. *The International Journal of Tuberculosis and Lung Disease* 2013; **17**: 1590–1595.
12. **Cantini F, et al.** Guidance for the management of patients with latent tuberculosis infection requiring biologic therapy in rheumatology and dermatology clinical practice. *Autoimmunity Reviews* 2015; **14**: 503–509.
13. **Liao TL, et al.** Different risk of tuberculosis and efficacy of isoniazid prophylaxis in rheumatoid arthritis patients with biologic therapy: a nationwide retrospective cohort study in Taiwan. *PLoS ONE* 2016; **11**: e0153217.
14. **Liao TL, et al.** Risk factors and outcomes of nontuberculous mycobacterial disease among rheumatoid arthritis patients: a case-control study in a TB endemic area. *Scientific Reports* 2016; **6**: 29443.
15. **Wu CY, et al.** The risk of cancer in patients with rheumatoid arthritis taking tumor necrosis factor antagonists: a nationwide cohort study. *Arthritis Research & Therapy* 2014; **16**: 449.
16. **Arnett FC, et al.** The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis & Rheumatology* 1988; **31**: 315–324.
17. **Lin YC, et al.** The age-risk relationship of hematologic malignancies in patients with rheumatoid arthritis: a nationwide retrospective cohort study. *Clinical Rheumatology* 2015; **34**: 1195–1202.
18. **Wang YC, et al.** Increased risk of rheumatoid arthritis in patients with migraine: a population-based, propensity score-matched cohort study. *Rheumatology International* 2017; **37**: 273–279.
19. **Hung CL, et al.** Associated factors for tuberculosis recurrence in Taiwan: a nationwide nested case-control study from 1998 to 2010. *PLoS ONE* 2015; **10**: e0124822.
20. **Yeh JJ, et al.** Nontuberculosis *Mycobacterium* disease is a risk factor for chronic obstructive pulmonary disease: a nationwide cohort study. *Lung* 2014; **192**: 403–411.
21. **Kamboj M, et al.** The risk of tuberculosis in patients with cancer. *Clinical Infectious Diseases* 2006; **42**: 1592–1595.
22. **Wallis RS.** Tumour necrosis factor antagonists: structure, function, and tuberculosis risks. *The Lancet Infectious Diseases* 2008; **8**: 601–611.
23. **Smitten AL, et al.** A meta-analysis of the incidence of malignancy in adult patients with rheumatoid arthritis. *Arthritis Research & Therapy* 2008; **10**: R45.
24. **Askling J, et al.** Risks of solid cancers in patients with rheumatoid arthritis and after treatment with tumour necrosis factor antagonists. *Annals of the Rheumatic Diseases* 2005; **64**: 1421–1426.
25. **Wu CY, et al.** Aerodigestive tract, lung and haematological cancers are risk factors for tuberculosis: an 8-year population-based study. *The International Journal of Tuberculosis and Lung Disease* 2011; **15**: 125–130.
26. **Lai CC, et al.** Nontuberculous mycobacterial infections in cancer patients in a medical center in Taiwan, 2005–2008. *Diagnostic Microbiology and Infectious Disease* 2012; **72**: 161–165.
27. **Chan MJ, et al.** Compliance with risk management plan recommendations on laboratory monitoring of antitumor necrosis factor-α therapy in clinical practice. *Journal of the Formosan Medical Association* 2016; **115**: 83–93.