Incidence rates of tuberculosis in chronic hepatitis C infected patients with or without interferon based therapy: a population-based cohort study in Taiwan

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Abstract

**Background:** It is debated whether interferon-based therapy (IBT) would affect the incidence of active tuberculosis (TB) among hepatitis C virus (HCV) infected patients. Although some case reports have demonstrated a possible association, the results are currently inconclusive. Therefore, we conducted a nation-wide population study to investigate the incidence of active TB in HCV infected patients receiving IBT in Taiwan.

**Methods:** This 9-year cohort study was based on the Longitudinal Health Insurance Database 2000 (LHID 2000) consisting of 1,000,000 beneficiaries randomly selected from all Taiwan National Health Insurance enrollees in 2000 (>23.7 million). This insurance program covers all citizens in Taiwan. We conducted a retrospective cohort study that identified subjects with HCV infection. IBTs were defined as regimens that included interferon α, peginterferon α2a and peginterferon α2b for at least 2 months. Among them, 621 subjects received IBT, and 2,460 age- and gender-matched subjects were enrolled for analysis. The Cox proportional hazards models were used to estimate the hazard ratio (HR) for active TB, and associated confidence intervals (CIs), comparing IBT cohort and untreated cohort. The endpoint in this study was whether an enrolled subject had a new diagnosis of active TB.

**Results:** During the 9-year enrollment period, the treated and untreated cohorts were followed for a mean (± SD) duration of 6.97 ± 0.02 years and 8.21 ± 0.01 years, respectively. The cumulative incidence rate of active TB during this study period was 0.150 and 0.151 per 100 person-years in the IBT treated and untreated cohorts, respectively. There was no significant difference in the incidence of active TB in either cohort during a 1-year follow-up (Adjusted Hazard Ratio (AHR): 2.81, 95% Confidence Interval (95% CI): 0.61–12.98) or the long-term follow-up (AHR: 1.02, 95% CI: 0.28–3.78). The Cox proportional hazards model demonstrated that IBT was not a risk factor for active TB. The only risk factor for active TB was the occurrence of hepatic encephalopathy.

**Conclusion:** Our results showed that IBT is associated with increased hazard of active TB in HCV infected patients in 1-year follow-up; however, the effect sizes were not statistically significant.

**Keywords:** Interferon, Hepatitis C virus, Tuberculosis

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Background
An estimated 170 million people are chronically infected with Hepatitis C virus (HCV), and 3 to 4 million people are newly infected each year [1]. HCV infection is the major cause of chronic liver disease worldwide and can lead to cirrhosis and hepatocellular carcinoma [1]. Therefore, effective anti-HCV therapies are recommended by national and international guidelines [2]. Pegylated interferons plus ribavirin have been used as the standard treatment of HCV infection for decades [3,4].

Interferons (IFNs) are a group of structurally related cytokines that are important in antiviral activities [5]. There are two types of IFNs, type I and type II. Type I IFNs, such as IFN-α/β, are produced in most cell types in response to microorganism infections and play a crucial role in innate immune activity against viruses [6]. The type II IFN, INF-γ, is the main mediator of the type I immune response and is essential in the control of mycobacterial infection in both animal models and humans [7]. In contrast to INF-γ, the role of INF-α/β in tuberculosis (TB) is controversial. In an in vitro study, IFN-β was shown to improve bacillus Calmette-Guerin (BCG) immunogenicity by increasing human dendritic cell maturation [8]. In an animal model, type I IFN limited the number of target cells that M.tuberculosis infected in the lungs [9]. Early clinical pilot studies demonstrated that aerosolized IFN-α combined with standard therapy for pulmonary TB would lead to better clinical outcomes [10,11]. However, some studies showed that type I IFNs promoted, rather than inhibited, mycobacterial infection. In an in vitro model, type I IFNs impaired the ability of human macrophages to control the growth of M. bovis BCG and M. avium intracellulare complex [12,13]. In an animal model, Manca et al. reported that type I IFNs enhanced the virulence of M. tuberculosis by suppression of the Th1 type immune responses. In addition, the treatment of TB infected mice with IFN-α/β increases lung bacterial loads, resulting in reduced survival [14]. Together, these studies indicate that the role of type I IFNs in mycobacterial infections is still inconclusive.

The side effects of IFNs include fatigue, influenza-like symptoms, hematological abnormalities, and neuropsychiatric symptoms [15]. Pulmonary manifestations, including sarcoidosis, interstitial pneumonitis and bronchiolitis obliterans organizing pneumonia, are considered rare events [16,17]. Although altered cellular immunodeficiency is associated with a higher incidence of various infections, TB has rarely been reported during HCV treatment [18-22]. This may be because the people receiving interferon-based therapy (IBT) for HCV were mostly located in countries with low TB incidence rates; this creates a difficulty in identifying an association between IBT and active TB. Taiwan is a hyperendemic area of chronic liver diseases and has an HCV seroprevalence ranging from 0.4 to 10.5%, depending on different geographic areas [23]. Because HCV infection can lead to fetal comorbidity, the Bureau of Taiwan National Health Insurance (NHI) has reimbursed IBT since 2003. Taiwan is also an endemic TB area with an intermediate burden of TB. In 2008, 2009 and 2010, the incidence rates of TB in Taiwan were 57.8, 57.2 and 54.5 per 100,000 population, respectively [24]. Therefore, this study used a longitudinal Health Insurance Database 2000 (LHID 2000) that included a nationally representative population, and used an epidemiological approach to evaluate whether IBT is a risk factor for the development of active TB during January 2000 to December 2009.

Methods
Study sample
National Health Insurance (NHI) is a single-payer compulsory program that has been implemented in Taiwan since 1995 and covers all forms of health care for the residents of Taiwan [25]. All citizens who have established a registered domicile for at least 4 months in the Taiwan area should be enrolled in the NHI. There are approximately 23,720,000 individuals in this program. The NHI comprehensively includes a claims database, including ambulatory care, outpatient services, inpatient services and prescription drugs.

We used a database (LHID2000) containing one million randomly selected subjects from the Taiwan National Health Insurance Research Database (NHIRD), which was developed for research purposes. A systematic, random sampling method was used to build this representative database of 1,000,000 NHI enrollees. There were no statistically significant differences in age, sex, or healthcare costs between the sample group and all the enrollees. This data set spans from January 2000 through December 2009 and includes all claims data for these 1,000,000 individuals.

Ethics statement
The identification numbers of all the subjects in the NHRI databases were encrypted to protect the privacy of the individuals. All researchers who used the NHIRD and its data subsets were required to sign a written agreement declaring that they had no intention of attempting to obtain information that could potentially violate the privacy of patients or care providers. This study was approved by the Institutional Ethics Review Board of Kaohsiung Medical University Hospital (Kaohsiung, Taiwan) (IRB No 20130067).

Study design and population-based surveillance methods
This study used a retrospective cohort study design to evaluate the association between IBT and TB events. This study enrolled patients who were 20 or older from this database (LHID2000).

The Taiwan NHIRD did not contain direct laboratory results (such as biochemical data, viral genotype, viral
load, histological characteristics). Therefore, we were unable to identify the HCV infected patients based on laboratory diagnostic criteria. With approval from the NHRI, we were able to use the scrambled patient identification numbers to interlink files, including registry of medical facilities, details of inpatient orders, ambulatory care, and prescriptions.

The definition of HCV infection was based on individuals who had at least two service claims of ambulatory or inpatient care for the treatment of HCV between 2000 and 2008. For only once service claim (The diagnosis coding of NHI in Taiwan is performed according to the International Classification of Disease, 9th Revision, Clinical Modification (ICD-9-CM) diagnostic criteria.) would overestimate the diagnosis of HCV. Therefore, we used at least two service claims of ambulatory or inpatient treatment care to identify this group. (HCV infected patients) [26]. We defined HCV by compatible ICD-9-CM codes of HCV in 070.41, 070.44, 070.51, 070.54, and V02.62.

A total of 12,547 subjects with ICD-9-CM codes of HCV were identified. Furthermore, we excluded patients who were diagnosed as having HCV on only 1 occasion (n = 3,877), who were below 20 years old (n = 77) and who had a history of TB diagnosis codes (ICD-9 code:010–018) before the first HCV coding and at the same time as the first HCV coding (n = 281). Therefore, 8,312 patients with a diagnosis coding of HCV on at least two medical claims were enrolled (Figure 1).

**Definition of study cohorts: cohorts treated and not treated with IBT**

Combination regimens with peginterferon α (either 2a or 2b) and ribavirin have been introduced for treating HCV infection in Taiwan since October 1, 2003. Generally, antiviral therapy was initiated as peginterferon α2a

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**Figure 1** Study flow chart for the enrollment of participants.
more than 90 days during the study period \[28,29\].

mecillin, ciprofloxacin, moxifloxacin, and levofloxacin) for streptomycin, cycloserine, prothionamide, amikacin, kanamycin, ciprofloxacin, moxifloxacin, and levofloxacin for more than two anti-TB medications (i.e., isoniazid). ICD-9-CM codes of TB (010–018) plus the prescription of more than two anti-tuberculosis medications (i.e., isoniazid, rifampin, pyrazinamide, ethambutol, rifater, rifinah, streptomycin, cycloserine, prothionamide, amikacin, kanamycin, ciprofloxacin, moxifloxacin, and levofloxacin) for more than 90 days during the study period \[28,29\].

The definition of active TB

We defined active TB as at least one outpatient visit or one hospital admission during the follow-up period with ICD-9-CM codes of TB (010–018) plus the prescription of more than two anti-tuberculosis medications (i.e., isoniazid, rifampin, pyrazinamide, ethambutol, rifater, rifinah, streptomycin, cycloserine, prothionamide, amikacin, kanamycin, ciprofloxacin, moxifloxacin, and levofloxacin) for more than 90 days during the study period \[28,29\].

It is possible that patients with other diseases (e.g., non-tuberculous mycobacterial infection, lung cancer, or latent TB infection) were misdiagnosed with active TB and put on anti-tuberculosis medications initially. To avoid this misclassification of outcome, we screened the NHIRD records of patients who were classified as active TB cases by this definition. If the ICD-9 codes of TB (010–018) in these patients were replaced by those of nontuberculous mycobacterial infection (031), lung cancer (162), or positive tuberculin skin test (795.5) during subsequent follow-up with discontinuation of anti-tuberculosis medications, the patients would be reclassified as non-TB.

Study endpoints and adjustment for confounding factors

The endpoint in this study was whether an enrolled subject had a new diagnosis of TB. The IBT and non-treated cohorts were both tracked from the date of selection until the end of 2009 or until loss to follow-up (i.e., withdrawing from the health insurance program) to identify new TB events.

Statistical analysis

All the data processing and statistical analyses were performed with SAS 9.3 software (Cary, NC, USA). Chi-square tests were used to compare the distributions of categorical variables between patients who did or did not receive IBT. The time-to-event analysis involved estimating the probability that an event would occur at different points in time. The endpoint of follow-up in the subjects developing active TB was the date of 1) having taken two anti-TB medications for more than 90 days, and 2) having a TB-specific ICD-9 code, and those lost to follow-up were censored on the date of last visit, creating “censored” data. The most common time-to-event statistical methods are Kaplan-Meier analysis and the proportional hazards model. The Kaplan-Meier
The proportional hazards model was applied to analyze the effect of single and multiple covariates in predicting whether TB developed. Both short-term (1 year after index date) and long-term (9 years after index date) follow-up were included for analysis in this study.

## Results

### Baseline characteristics of the study population

Among the 699 HCV patients who received IBT, 621 patients (88.84%) were treated for a minimum of 2 months and were therefore eligible as the IBT-treated cohort (n = 621). The control cohort comprised 2,460 untreated patients who were selected from those not receiving IBT (Figure 1). Table 1 shows the baseline characteristics of the two cohorts. Most patients in both cohorts were aged between 50 to 69 years. To compare with the untreated cohort, patients in IBT-treated cohort had more malignancy and non-alcoholic liver cirrhosis. ($P = 0.035$ and $<0.001$, respectively) Patients in the untreated cohort had more ESRD and hepatic encephalopathy ($P = 0.003$ and 0.043, respectively).

### Incidences of TB among the two cohorts

During the 9-year enrollment period, the treated and untreated cohorts were followed up for a mean ($\pm$ SD) duration of 6.97 ± 0.02 years and 8.21 ± 0.01 years, respectively. Among the treated cohort, which included those who had ever received IBT for a minimum of 8 weeks, the mean ($\pm$ SD) duration of the antiviral regimen was 20.29 ± 4.50 weeks. During a 1-year follow-up, 3 patients developed TB in IBT treated cohort and 5 patients developed TB in untreated cohort. During the long-term follow-up, 3 patients developed TB in IBT- treated cohort and 12 patients developed TB in untreated cohort. The cumulative incidences of TB during this study period were 0.150 and 0.151 per 100 person-years in the IBT treated and untreated cohorts in long-term follow-up, respectively. There was no significant difference in the incidence of active TB in either cohort during a 1-year follow-up (Adjusted Hazard Ratio (AHR): 2.81, 95% Confidence Interval (95% CI): 0.61–12.98) or the long-term follow-up (AHR: 1.02, 95% CI: 0.28 – 3.78) (Table 2). Further analysis by the log-rank test revealed no significant difference of the incidence of TB in both cohorts during 1-year and long-term follow-up periods ($P = 0.261$ and 0.987, respectively) Figure 2 showed the crude cumulative incidence of tuberculosis among both cohorts in 1-year follow-up.

### Multivariate-adjusted association of antiviral therapy with active TB

The Cox proportional hazards model demonstrated that IBT was not associated with active TB (Tables 3 and 4). The only factor associated with the development of active TB was the occurrence of hepatic encephalopathy. (Hazard Ratio (HR):54.90 and 95% CI: 2.82–1069.53 in

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### Table 1 Characteristics of the enrolled patients

| Variable                        | Interferon-based therapy | $P$ value |
|---------------------------------|--------------------------|-----------|
|                                 | Yes (n = 621)            | No (n = 2460) |
| Sex, n (%)                      |                          |           |
| Male                            | 351 (56.5)               | 1380 (56.1) | 0.849 |
| Female                          | 270 (43.5)               | 1080 (43.9) |
| Age, n (%)                      |                          |           |
| 20 – 29                         | 22 (3.5)                 | 84 (3.4)  | 0.999 |
| 30 – 39                         | 54 (8.7)                 | 217 (8.8) |           |
| 40 – 49                         | 123 (19.8)               | 485 (19.7) |           |
| 50 – 59                         | 231 (37.2)               | 906 (36.8) |           |
| 60 – 69                         | 154 (24.8)               | 620 (25.2) |           |
| ≧70                             | 37 (6.0)                 | 148 (6.0)  |           |
| Comorbid disease, n (%)         |                          |           |
| Human immunodeficiency virus infection | 2 (0.3)     | 12 (0.5)   | 0.583 |
| Chronic obstructive pulmonary disease | 41 (6.6)   | 128 (5.2)  | 0.171 |
| Connective tissue disease       | 182 (29.3)               | 702 (28.5) | 0.704 |
| Silicosis                       | 1 (0.2)                  | 1 (0.04)   | 0.615 |
| Diabetes mellitus               | 126 (20.3)               | 449 (18.3) | 0.244 |
| End stage renal disease         | 7 (1.1)                  | 83 (3.4)   | *0.003 |
| Malignancy                      | 38 (6.1)                 | 102 (4.1)  | *0.035 |
| Liver disease, n (%)            |                          |           |
| Non-alcoholic liver cirrhosis   | 99 (15.9)                | 214 (8.7)  | *<0.001 |
| Alcoholic liver cirrhosis       | 7 (1.1)                  | 27 (1.1)   | 0.949 |
| Other alcoholic liver disease   | 11 (1.8)                 | 28 (1.1)   | 0.207 |
| Liver disease severity, n (%)   |                          |           |
| Ascites                         | 4 (0.6)                  | 19 (0.8)   | 0.740 |
| Esophageal varices              | 4 (0.6)                  | 20 (0.8)   | 0.668 |
| Hepatic encephalopathy          | 0 (0)                    | 16 (0.7)   | *0.043 |

*means $P < 0.05$.
Discussion

In this population-based cohort study, IBT was not associated with active TB in HCV patients after adjustment for possible confounding factors, such as HIV infection, silicosis, COPD, connective tissue disease and malignancy. During the 1-year and long-term follow-up periods, the crude cumulative TB incidences in both cohorts were not significantly different. The incidence of TB in the IBT treated cohort was 0.150 per 100 person-years during this study period, which was lower than the reported incidence rates of HIV-HCV co-infected patients receiving IBT (0.7 cases per 100 person-years) in Spain and HCV patients (1.4 cases per 100 person-years) in Pakistan [32,33].

The role of IFNs in exacerbating TB infection remains controversial. Few case reports have described the association between IBT and active TB [18-22]. TB events in clinical trials of HCV patients treated with IBT were rarely reported. Only one study in Taiwan [34] reported 308 treatment-naive HCV-1–infected patients receiving IBT resulted in one case with TB reactivation at week 32 of IBT.

Three HCV infected patients with active TB were identified in the IBT-treated cohort in this study. These TB cases were confirmed within 38 weeks of IBT initiation. IBT was not an independent risk factor for the development of active TB in our study; the only risk factor reported was advanced liver disease. Because of the multiple levels of immune dysfunction, cirrhotic patients are predisposed to infectious diseases, including bacterial and TB infection [35]. In Taiwan, liver cirrhosis and chronic liver disease were significant risk factors associated with death in a TB infected population [36]. Our results demonstrate that the association of hepatic encephalopathy and TB may indicate a vulnerability to TB for cases with compromised liver function. Further prospective study is necessary to clarify the role of IBT in active TB cases during the hepatitis treatment course.

The HCV shares risk factors and routes of transmission with some infectious diseases. Compared to people without HCV infection, HCV carriers were significantly associated with many infectious diseases, including TB [37]. It is presumed that HCV itself is a risk factor for TB infection regardless of whether the HCV was treated with IBT. Although IBT is not associated with increasing hazard of active TB in HCV infected patients in our study, it seemed to be higher among IBT group with one-year follow-up. It is reasonable to be careful the occurrence of active TB while using IBT to treat HCV infected patients in one-year period. Further study to evaluate this issue by enrolling greater sample size is necessary.

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**Table 3 Results of the multivariate-adjusted cox proportional hazards model for active tuberculosis cases in 1-year follow-up**

|                         | Adjusted hazard ratio | 95% confidence interval | P value |
|-------------------------|-----------------------|-------------------------|---------|
| Male                    | 2.75                  | 0.55–13.79              | 0.218   |
| Age                     | 1.07                  | 0.99–1.15               | 0.103   |
| Comorbidity             |                       |                         |         |
| Human immunodeficiency virus infection | -                     | -                       |         |
| Chronic obstructive pulmonary disease | -                     | -                       |         |
| Connective tissue disease | 0.33                 | 0.04–2.78              | 0.309   |
| Silicosis               | -                     | -                       |         |
| Diabetes mellitus       | 2.81                  | 0.62–12.75             | 0.180   |
| End stage renal disease | -                     | -                       |         |
| Malignancy              | 1.78                  | 0.20–15.69             | 0.602   |
| Liver disease           |                       |                         |         |
| Non-alcoholic liver cirrhosis | 0.97                | 0.11–8.46              | 0.976   |
| Alcoholic liver cirrhosis | -                     | -                       |         |
| Other alcoholic liver disease | -                   | -                       |         |
| Liver disease severity  |                       |                         |         |
| Ascites                 | -                     | -                       |         |
| Esophageal varices      | -                     | -                       |         |
| Hepatic encephalopathy  | 54.90                 | 2.82–1069.53           | *0.008  |
| Interferon-based therapy| 2.81                  | 0.61–12.98             | 0.185   |

*means P < 0.05.
Several limitations of this study warrant discussion. First, although we did not demonstrate an association between IBT and active TB in this study, this lack of association maybe related to the different TB prevalences in the different age populations in our country. In the IBT treated cohort, 69.2% (430/621) of patients were less than 60 years old. However, the TB incidence rate generally increases in older population, especially in those over 65 years old [24]. IBT in HCV infected patients in the elderly population needs further investigation. Second, the Taiwan NHIRD did not contain direct laboratory results. Therefore, we were unable to determine how viral genotype, viral load and CD4 numbers might influence the outcomes. Because of the limitation of this database, there was no standard procedure for diagnosis of TB infection (acid-fast stain, culturing and histopathology). Instead, we defined TB infection according to ICD-9-CM codes of TB with taking anti-TB medication for more than 3 months. It is likely that some patients with TB infections did not submit claims for medication, or died before 3 months of treatment, which may underestimate the total number of MTB infected patients. Third, some patients were treated with corticosteroids, which are known to increase the risk of TB [38]. Although we adjusted for patients with connective tissue diseases and COPD, a proportion of the patients exposed to corticosteroids would be underestimated. Finally, this study lacked information on several important risk factors, such as smoking, nutritional status, intravenous drug abuse, and occupational exposure, which are also not available in the NHIRD.

Conclusion

Our results showed that IBT is associated with increased hazard of active TB in HCV infected patients in 1-year follow-up; however, the effect sizes were not statistically significant.

Abbreviations

TB: tuberculosis; IFN: interferon; IBT: interferon-based therapy, COPD, chronic obstructive pulmonary disease; HCV: Hepatitis C virus; IBT: interferon-based therapy; IFNs: Interferons; LHID: longitudinal Health Insurance Database; NHI: National Health Insurance; TB: tuberculosis.

Competing interests

The authors declared that they have no competing interests.

Authors’ contributions

Shang-Yi Lin and Tun-Chieh Chen contributed equally to the drafting of the manuscript. Po-Liang Lu, Chun-Yu Lin, Wei-Ru Lin and Yi-Hsin Yang conducted the analysis, interpreted the data, and performed the statistical analyses. Yen-Hsu Chen critically revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

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References

1. National Institutes of Health National institutes of health consensus development conference statement: management of hepatitis C. 2002 June 10–12, 2002. Hepatology 2002; 36(Suppl 1):13–20.

2. Strader DB, Wright T, Thomas DL, Seeff LB. Diagnosis, management, and treatment of hepatitis C. Hepatology 2004, 39:1147–1171.
3. European Association for the Study of the Liver: EASL clinical practice guidelines: management of hepatitis C virus infection. J Hepatol 2011, 55:245–264.

4. Ghany MG, Strader DB, Thomas DL, Seeff LB: Diagnosis, management, and treatment of hepatitis C: an update. Hepatology 2009, 49:1335–1374.

5. Isaacs A, Lindenmann J: Virus interference. I. The interferon. Proc N Soc Lond B Biol Sci 1957, 147:258–267.

6. Gorny'N, Navajas JM, Lee J, David M, Rae: Immunomodulatory functions of type I interferons. Nat Rev Immunol 2012, 12:125–135.

7. Kuo H, Kelly SG, Doms RW: Dynamic roles of type I and type II IFNs in virus interference. I. The interferon. J Leukoc Biol 2009, 85:462–468.

8. Desyvertes L, Wolf K, Emst JD: Dynamic roles of type I and type II IFNs in early infection with Mycobacterium tuberculosis. J Immunol 2012, 188:605–6215.

9. Giosue S, Casarini M, Allemanna L, Galluccio G, Mattia P, Pedicelli G, Rebek L, Bisetti A: Increased interferon-alpha expression in patients with pulmonary tuberculosis. Am J Respir Crit Care Med 1998, 158:1156–1162.

10. Giosue S, Casarini M, Ameglio F, Zangrilli P, Palla M, Altieri AM, Bisetti A: Interferon-alpha expression in patients with multidrug-resistant pulmonary tuberculosis. Eur Cytokine Netw 2000, 11:99–104.

11. Bouchonnet F, Boechat N, Bonay M, Hance AJ: BCG immunogenicity by acting on DC maturation. J Leukoc Biol 2009, 85:462–468.

12. Cooper AM, Dalton DK, Stewart TA, Griffin JP, Russell DG, Orme IM: Virus interference. I. The interferon. Proc Natl Acad Sci U S A 2001, 98:7552–7577.

13. Fried MW: Side effects of therapy of hepatitis C and their management. Am J Gastroenterol 2003, 98:1503–1527.

14. Kumar KS, Russo MW, Borzutzky AC, Brown M, Espósito SA, Lobritto SJ: Inclusion in PubMed, CAS, Scopus and Google Scholar. www.biomedcentral.com/submit

15. Bacterial infection-related morbidity and mortality in cirrhosis. Am J Gastroenterol 2007, 102:1510–1517.

16. Lin HH, Ezzati M, Chang HY, Murray M: Association between tobacco smoking and active tuberculosis in Taiwan: prospective cohort study. Am J Respir Crit Care Med 2009, 180:475–480.

17. Lobue P, Meneses D: Treatment of latent tuberculosis infection: an update. Respir Cell 2010, 18:603–622.

18. Davis RM, Novotny TE: The epidemiology of cigarette smoking and its impact on chronic obstructive pulmonary disease. Am Rev Respir Dis 1989, 140:582–584.

19. Pérez-Ellas MJ, García-San Miguel L, González García J, Montes Ramírez ML, Muriel A, Machín-Lázaro JM, Martínez-Baltanás A, Zamora F, Moreno A, Martín-Dávila P, Quereda C, Gómez-Mampaso E, Moreno S: Tuberculosis complicating hepatitis C treatment in HIV-infected patients. Clin Infect Dis 2009, 48:e82–e85.

20. Hayat AS, Shulkin N, Masood N: Study for frequency and aetiology of lymphadenopathy during combination therapy for chronic hepatitis C (pegylated interferon alpha plus ribavirin) at a tertiary care hospital in Hyderabad. J Pak Med Assoc 2011, 61:898–901.

21. Lu CH, Liu C, Lin CL, Liang CC, Hsu SJ, Yang SS, Hsu CS, Tseng TC, Wang CC, Lai MY, Chen JS, Chen PI, Chen DS, Kao JH: Pegylated interferon-a-2a plus ribavirin for treatment-naïve Asian patients with hepatitis C virus genotype 1 infection: a multicenter, randomized controlled trial. Clin Infect Dis 2008, 47:1260–1269.

22. Christou L, Pappas G, Falagas ME: Bacterial-infection-related morbidity and mortality in cirrhosis. Am J Gastroenterol 2007, 102:1510–1517.

23. Lo HY, Suo J, Zhang HJ, Yang SL, Chou P: Risk Factors associated with death in a 12-month cohort tuberculosis patients: 12-month follow-up after registration. Asia Pac J Public Health 2011 Dec 23. [Epub ahead of print]

24. Centers for Disease Control and Prevention: Estimation of hepatitis C virus infection and other infectious diseases: a case for targeted screening? Am J Gastroenterol 2003, 98:167–174.

25. Cheng SH, Chen CC, Chang WL: Hospital response to a global budget program under universal health insurance in Taiwan. Health Policy 2009, 92:158–164.