Increased risk of osteoporosis in patients with nonalcoholic fatty liver disease
A population-based retrospective cohort study

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Abstract
The study aims to investigate the association between nonalcoholic fatty liver disease (NAFLD) and osteoporosis. We employed a retrospective cohort study design using the National Health Insurance Research Database in Taiwan. Our study included 2 cohorts: 4318 patients with NAFLD and 17,272 patients without NAFLD for comparison. They were matched by sex and age on the date of enrollment between January 1, 2000 and December 31, 2003. The study population in both groups was observed from the enrollment date until December 31, 2013. The incidence and the risk ratios of subsequent osteoporosis were calculated separately in both cohorts. A Cox proportional hazards model was used to assess the potential confounding variables of NAFLD on the pathogenesis of osteoporosis.

The eligible study participants comprised 4318 patients in the NAFLD and 17,272 in control cohorts. The median follow-up duration was 10.7 and 10.83 years in the NAFLD and control groups, respectively. The risk of new-onset osteoporosis was higher in patients with NAFLD than in the comparison cohort. In addition, the difference of the incidence of new-onset osteoporosis remained significant among the 2 cohorts in the follow-up durations of within 1 year and more than 10 years. Patients with NAFLD were 1.35 times more likely to develop subsequent osteoporosis compared with those without NAFLD (95% confidence interval = 1.20–1.53).

Our finding indicates that NAFLD might increase the risk of developing new-onset osteoporosis. For earlier detection and intervention, screening for osteoporosis in patients with the NAFLD, especially those with lower income and co-morbid with diabetes mellitus and chronic obstructive pulmonary disease, may be recommended.

Abbreviations: ALT = alanine aminotransferase, AST = aspartate aminotransferase, BMD = bone mineral density, BNHI = Bureau of National Health Insurance, COPD = chronic obstructive pulmonary disease, CRP = C-reactive protein, HR = hazard ratios, ICD-9-CM = International Classification of Diseases Ninth Revision Clinical Modification, IL = interleukin, LHID 2000 = Longitudinal Health Insurance Database 2000, MOHW = Ministry of Health and Welfare, NAFLD = nonalcoholic fatty liver disease, NHI = National Health Insurance, NHIRD = National Health Insurance Research Database, NHRI = National Health Research Institutes, RR = risk ratio, TNF = tumor necrosis factor.

Keywords: epidemiology, nonalcoholic fatty liver disease, osteoporosis, risk factors

1. Introduction

Nonalcoholic fatty liver disease (NAFLD) refers to the accumulation of fat in the liver that is not caused by excessive alcohol use. In developed countries where the prevalence of obesity is high, NAFLD is a common liver disease; however, NAFLD develops and progresses in an insidious pattern and lacks obvious signs and symptoms for earlier detection.[1] Moreover, laboratory data among the patients with NAFLD may reveal either a normal or mild increase in the serum alanine aminotransferase (ALT) and the aspartate aminotransferase (AST) levels. Some patients are complicated by liver inflammation with varying degrees of hepatic fibrosis and diagnosed with nonalcoholic steatohepatitis. In a published study, in Taiwan, the prevalence of NAFLD was 11.5%.[2] In addition, NAFLD has been proven to be associated with systematic diseases including cardiovascular diseases, diabetes mellitus, and thyroid gland abnormalities.[3]

As for osteoporosis, a skeletal condition caused by systemic low bone mass and microarchitectural damage, resulting in higher probability of fractures. Numerous epidemiologic studies have proven that osteoporosis is prevalent both in western and eastern nations.[4,5] However, similar to the clinical manifestations observed in patients with NAFLD, patients with osteoporosis often show no remarkable clinical signs and
symptoms until fractures occur. Therefore, the diagnosis of osteoporosis is easily under-recognized, and the prevalence of the disease is often underestimated.

Osteoporosis is linked to many physical disorder or health-related behaviors such as estrogen deficiency, endocrine disorder, hypertension, and smoking. Interestingly, patients with NAFLD present comorbid clinical profiles similar to osteoporosis. For example, NAFLD is associated with hypertension, dyslipidemia, insulin resistance, and diabetes. Studies have shown that bone mineral density (BMD) probably be affected in some condition and disorder including obesity, depression, nephropathy, and heart failure. Duarte et al found that elevated inflammation may play a major role in NAFLD. Patients with NAFLD were considered to have tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) overexpression; impairment in Kupffer cell phagocytosis may also play an important role in NAFLD. Although the exact role of IL-6 in the pathogenesis of NAFLD is still waiting to be determined, elevation of IL-6 levels was also observed in patients with NAFLD. An increased production of TNF-α produced by hepatocytes and nonparenchymal cells in patients with NAFLD was noted in several studies.

Osteopontin, a T-helper 1 cytokine, exacerbates inflammation in several chronic inflammatory diseases including NAFLD. Many risk factors such as systematic inflammation have been identified for abnormal bone turnover and osteoporosis. Chronic inflammation results in the systemic bone loss, one of the mechanisms of osteoporosis. The inflammatory cytokines, especially TNF-α and IL-1, have been implicated in osteoporosis. These inflammatory cytokines may play a crucial role in the development of osteoporosis. Thus, inflammation may be related both to NAFLD and to osteoporosis.

Several studies suggest NAFLD may be a risk factor for decreased BMD. In 1 study, NAFLD was significantly associated with a history of osteoporotic fractures in middle-aged and elderly Chinese men. However, in other studies, debate existed regarding the effect of BMD on NAFLD.

Based on the debates mentioned above and a few large-scale studies especially in Asia, we hypothesized that NAFLD is associated with osteoporosis. In response to the lack of national data and few longitudinal studies concerning this association, we designed a nationwide population-based study to investigate the possibility of higher risk of developing osteoporosis among patients with NAFLD.

2. Materials and methods

2.1. Data source

The National Health Insurance (NHI) program in Taiwan was instituted in 1995. In this compulsory program, health-related information such as medical data collected from outpatient, inpatient, and emergency is offered to all compatriots, with a coverage rate up to 98%. Prescription, physical and laboratory examinations and diagnostic codes based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) are obtained in the NHI Research Database (NHIRD). The NHIRD was originally managed by the National Health Research Institutes. However, the NHIRD has been transferred to the Health and Welfare Data Science Center, Ministry of Health and Welfare (MOHW) in Taiwan to merge more health-related databases and improve safety issues. In addition, interested researchers could still obtain the data through formal application to the MOHW. The database of the study was the Longitudinal Health Insurance Database 2000 (LHID 2000), which was constructed by systematic and random sampling from the NHIRD and includes data of one million individuals. According to the Taiwanese National Health Research Institutes reports, no significant differences were observed for the distributions of age and sex or the average monthly insurance amount between the data in the LHID 2000 and the original NHIRD.

2.2. Study population

For this retrospective cohort study patients selected from the LHID 2000 are newly diagnosed with NAFLD between January 1, 2000, and December 31, 2003. Patients with NAFLD were defined according to the ICD-9-CM code 571.8 by gastroenterologists. Exclusions included patients diagnosed with osteoporosis (ICD-9-CM code: 733.0, 733.1) between January 1, 1996, and December 31, 1999, and those diagnosed with osteoporosis before the NAFLD diagnosis. Age- and sex-matched patients without NAFLD were selected from the LHID 2000 as the control cohort. All participants were observed until one of the following occurred: diagnosis with osteoporosis (ICD-9-CM code: 733.0, 733.1), withdrawal from the NHI system, death, or study cessation (December 31, 2013). The primary reported clinical outcomes in patients were osteoporosis. Moreover, common comorbidities, including depressive disorder, hypertension, diabetes mellitus, dyslipidemia, cerebrovascular disease, chronic obstructive pulmonary disease (COPD), nephropathy, autoimmune disease, obesity, and congestive heart failure, were compared among the patients in the NAFLD and control cohorts. The study flow is presented in Fig. 1.

2.3. Statistical analysis

The primary outcome of this study was the incidence of newly diagnosed osteoporosis both in the NAFLD and control group. Independent t test and Chi-squared test were applied to compare the distributions of the demographic characteristics between the 2 groups. To examine potential surveillance bias, subgroups were stratified by duration since the NAFLD diagnosis. Furthermore, a Cox proportional hazard regression model was used to estimate the hazard ratios (HRs) of osteoporosis in the NAFLD and control cohorts. Age, sex, comorbidities relating to NAFLD and osteoporosis, urbanization, and income of the participants were the predictive variables for the analysis. The significance of variables (P < .05) on univariate analysis would be arranged multivariate analysis. We also performed gender subanalysis to estimate the HRs of risk factors for osteoporosis in patients with fatty liver. We calculated follow-up specific risk ratio, since the risk ratio for NAFLD was substantially higher in the first year after osteoporosis diagnosis.

2.4. Ethics

This study was approved by the Institutional Review Board of Kaohsiung Veterans General Hospital (VGHKS17-CT12-05). We did not apply written consent for this study because the data were obtained from the LHID 2000, which includes de-identified secondary data. Besides, the Institutional Review Board designed a formal written waiver for the need for consent.

3. Results

The eligible study participants comprised 4318 patients in the NAFLD and 17,272 in control cohorts, respectively. Table 1
shows the demographic and clinical data between the 2 groups. The median age of the patients was 44.94 (interquartile range, 35.60–54.94 and 35.60–54.92) years and the median follow-up duration was 10.7 and 10.83 years in the NAFLD and control groups, respectively. Hypertension, diabetes mellitus, dyslipidemia, and cerebrovascular disease were the 4 most common comorbidities in both groups.

During the follow-up period, the NAFLD group included 365 patients diagnosed with osteoporosis. The incidence was significantly higher in patients in the NAFLD cohort ($P < .001$) than in those in the control cohort. Moreover, the subanalysis in our study stratified by the duration of follow-up showed that the participants in the NAFLD cohort yielded the highest risk ratio for developing osteoporosis within 1 year of NAFLD diagnosis. Although the risk of developing osteoporosis decreased with time, it revealed statistically significant even more than 10 years after diagnosis (Fig. 2). Compared with patients in the control cohort, patients in the NAFLD cohort tended to have a higher risk of developing osteoporosis (RR = 1.46, 95% confidence interval [CI] = 1.30–1.65) (Table 2).

We applied Cox proportional hazard regression analysis to estimate the HR of newly diagnosed osteoporosis for patients in the NAFLD and control cohorts. We listed the results of the analysis after adjusting for confounding factors and noted the same association between NAFLD and osteoporosis (Table 3).

We also performed a Cox proportional hazard regression analysis to detect risk factors for osteoporosis in patients with NAFLD. Predictive variables in comorbidities showed a higher prevalence of diabetes mellitus and COPD among patients in the NAFLD cohort (Table 4). In the gender subanalysis, predictive variables in comorbidities revealed a higher prevalence of COPD among male (Table 5) and dyslipidemia among female (Table 6), respectively.

4. Discussion
The present study, based on a large-scale data set, indicated that NAFLD was significantly associated with an increased risk of subsequent osteoporosis. Furthermore, our analysis revealed that patients with NAFLD are prevalently comorbid with hypertension, dyslipidemia, COPD, and low income were significantly than in the patients without NAFLD.

Numerous studies tried to identify the association between NAFLD and osteoporosis.$^{[7,21,22,25]}$ However, few large-scale
cohort study could be found in the literature; therefore, we conducted a study to observe the incidence and subsequent risk of osteoporosis among patients with NAFLD. Our nationwide study benefited from a large cohort study, and the selection process of our study design was unbiased.

Proinflammatory cytokines (TNF-related-activation-induced cytokine) and IL-6 are related to osteoclast bone resorption.\[20\] Osteopontin acts both in osteoblastic and in osteoclastic functions by inhibiting bone mineral growth.\[28\] High serum osteopontin levels suggested a significant risk factor for menopausal osteoporosis.\[29\] These studies support that inflammation has a major impact on bone metabolism leading to osteoporosis. Vitamin D deficiency may result in osteoporosis. Roth et al\[30\] found that vitamin D deficiency exacerbates NAFLD and increases hepatic inflammation in rat pathways. In 1 case-control study patients with NAFLD tended to have a decrease in serum 25(OH)D levels.\[31\] A significant relationship between vitamin D deficiency and NAFLD was found in Korea.\[32\] Zhai et al\[33\] suggest that vitamin D levels have an association with NAFLD, especially in East China. Vitamin D deficiency leads to osteomalacia, thin or brittle bones, which increases risks for osteoporosis.\[34\]

### Table 1

Baseline characteristics of patients with and without fatty liver.

| Demographic data       | Patients with fatty liver n=4318 | Patients without fatty liver n=17,272 | P-value |
|------------------------|----------------------------------|--------------------------------------|---------|
| Age, y\(^*\)           | 44.94 (35.60–54.94)              | 44.94 (35.60–54.92)                  | .999    |
| ≥65                    | 552                              | 2208                                 |         |
| <65                    | 3766                             | 15,064                               |         |
| Sex                    |                                  |                                      |         |
| Male                   | 2815                             | 11,260                               | .999    |
| Female                 | 1503                             | 6012                                 |         |
| Comorbidities          |                                  |                                      |         |
| Depressive disorder    | 70                               | 158                                  | <.001   |
| Hypertension           | 1380                             | 3276                                 | <.001   |
| Diabetes mellitus      | 818                              | 1560                                 | <.001   |
| Dyslipidemia           | 1145                             | 1900                                 | <.001   |
| Cerebrovascular disease| 736                              | 1667                                 | <.001   |
| COPD                   | 575                              | 1442                                 | <.001   |
| Nephropathy            | 510                              | 1080                                 | <.001   |
| Autoimmune disease     | 145                              | 289                                  | <.001   |
| Obesity                | 63                               | 57                                   | <.001   |
| Congestive heart failure| 122                             | 276                                  | <.001   |
| Degree of urbanization |                                  |                                      | <.001   |
| Urban                  | 2750                             | 10,591                               | .61     |
| Suburban               | 1253                             | 5562                                 | .32     |
| Rural                  | 315                              | 1119                                 | .65     |
| Income group           |                                  |                                      | <.001   |
| High income            | 800                              | 2550                                 | 14.8    |
| Medium income          | 752                              | 3221                                 | 18.6    |
| Low income             | 1986                             | 8474                                 | 49.1    |
| No income              | 780                              | 3027                                 | 17.5    |
| Follow-up, y\(^*\)     | 10.70 (9.30–12.22)               | 10.83 (9.45–12.30)                   | <.001   |

COPD = chronic obstructive pulmonary disease.

\(^*\) Median (interquartile range).

### Table 2

The incidence of osteoporosis in patients with and without fatty liver.

|                      | Patients with fatty liver | Patients without fatty liver | Risk ratio (95% CI) | P-value |
|----------------------|----------------------------|------------------------------|----------------------|---------|
|                      | No of osteoporosis | Per 1000 person-years | No of osteoporosis | Per 1000 person-years |                     |                     |
| Total                | 365                  | 37.9                        | 1034                 | 30.3                        | 1.46 (1.30–1.65)   | <.001               |
| Age \(≥65\)          | 114                  | 106.7                       | 409                  | 108.6                       | 1.47 (1.01–1.53)   | .040                |
| Age \(<65\)          | 251                  | 31.1                        | 625                  | 21.9                        | 1.65 (1.42–1.92)   | <.001               |
| Sex                  |                      |                             |                      |                             |                     |                     |
| Male                 | 100                  | 16.2                        | 312                  | 14.7                        | 1.31 (1.03–1.64)   | .020                |
| Female               | 265                  | 81.9                        | 722                  | 60.2                        | 1.57 (1.36–1.82)   | <.001               |
| Follow-up            |                      |                             |                      |                             |                     |                     |
| 0–1                  | 79                   | 450.1                       | 124                  | 347.0                       | 1.72 (1.28–2.30)   | <.001               |
| 1–5                  | 149                  | 423.7                       | 407                  | 374.2                       | 1.20 (0.98–1.45)   | .061                |
| 5–10                 | 99                   | 70.9                        | 399                  | 68.0                        | 1.02 (0.81–1.27)   | .089                |
| ≥10                  | 38                   | 13.8                        | 104                  | 8.9                         | 1.53 (1.03–2.24)   | .023                |

CI = confidence interval.
vitamin D levels in NAFLD and patients with osteoporosis needs more investigation. NAFLD might be a risk factor for subsequent osteoporosis because of increased insulin resistance and leptin levels. Pirgon et al\(^7\) reported that NAFLD cohorts had a lower BMD than the non-NAFLD cohorts through the mechanism of increased insulin resistance. Activation of inflammatory pathways both in NAFLD and insulin resistance is discussed in a study\(^35\); another study suggested elderly patients with type 2 diabetes mellitus and metabolic syndrome as risk factors for osteoporosis. These overlapping risk factors can be due to hyperinsulinemia and increased leptin levels, which is also a potential risk factor for osteoporosis in patients with NAFLD. 

### Table 3

| Predictive variables | Univariate analysis | Multivariate analysis |
|----------------------|---------------------|----------------------|
|                      | HR (95% CI)         | P-value              | HR (95% CI)         | P-value |
| Fatty liver          | 1.46 (1.30–1.65)    | <.001                | 1.35 (1.20–1.53)    | <.001   |
| Age (<65 = 0, ≥65 = 1) | 5.56 (4.86–6.38)  | <.001                | 3.37 (2.94–3.85)    | <.001   |
| Sex (male = 0, female = 1) | 4.64 (4.14–5.20) | <.001                | 4.18 (3.71–4.70)    | <.001   |
| Comorbidities        |                     |                      |                     |         |
| Depressive disorder  | 1.22 (0.76–1.97)    | .412                 |                     |         |
| Hypertension         | 2.94 (2.64–3.27)    | <.001                | 1.36 (1.19–1.56)    | <.001   |
| Diabetes mellitus    | 2.27 (1.99–2.59)    | <.001                | 0.97 (0.84–1.13)    | .714    |
| Dyslipidemia         | 2.30 (2.04–2.59)    | <.001                | 1.31 (1.14–1.51)    | <.001   |
| Cerebrovascular disease | 2.95 (2.56–3.40) | <.001                | 1.21 (1.03–1.41)    | .019    |
| COPD                 | 2.53 (2.21–2.90)    | <.001                | 1.47 (1.27–1.70)    | <.001   |
| Nephropathy          | 1.92 (1.64–2.26)    | <.001                | 1.06 (0.90–1.26)    | .483    |
| Autoimmune disease   | 1.58 (1.26–1.99)    | <.001                | 1.20 (0.95–1.51)    | .124    |
| Obesity              | 0.65 (0.27–1.56)    | .332                 |                     |         |
| Congestive heart failure | 3.61 (2.80–4.65) | <.001                | 1.04 (0.80–1.35)    | .778    |
| Degree of urbanization |                   |                      |                     |         |
| Urban                | Reference           |                      |                     |         |
| Suburban             | 1.19 (1.06–1.34)    | .003                 | 1.12 (1.00–1.26)    | .060    |
| Rural                | 1.77 (1.48–2.12)    | <.001                | 1.20 (1.00–1.45)    | .051    |
| Income group         |                     |                      |                     |         |
| High income          | Reference           |                      |                     |         |
| Medium income        | 1.67 (1.29–2.16)    | <.001                | 1.22 (0.94–1.57)    | .139    |
| Low income           | 2.98 (2.39–3.71)    | <.001                | 1.48 (1.18–1.86)    | .001    |
| No income            | 4.15 (2.69–5.22)    | <.001                | 1.26 (0.99–1.61)    | .064    |

CI = confidence interval, COPD = chronic obstructive pulmonary disease, HR = hazard ratio.

Figure 2. Cumulative incidence comparison of newly diagnosed osteoporosis for patients with (solid line) and without (dashed line) nonalcoholic fatty liver disease.
diabetes mellitus are prone to develop osteoporosis. The serum osteocalcin, which expresses mainly by osteoblast, increases insulin secretion. However, osteocalcin was decreased in patients with NAFLD. In summary, the results of these previous studies implies that patients with NAFLD with insulin resistance may have associated risk for osteoporosis.

In our study, the results of multivariate analysis among the patients with NAFLD revealed that COPD could be seen as potential risk factors for the subsequent development of osteoporosis. As for the association with COPD and osteoporosis, studies have shown that COPD is associated with osteoporosis. The possible mechanisms may be related to the release of inflammatory cytokines and growth factors.

| Table 4 | Analyses of risk factors for osteoporosis in patients with fatty liver. |
|---------|---------------------------------|
| Predictive variables | Univariate analysis | Multivariate analysis |
| | HR (95% CI) | P-value | HR (95% CI) | P-value |
| Age (<65 = 0, ≥65 = 1) | 4.28 (3.43–5.38) | <.001 | 2.70 (2.06–3.53) | <.001 |
| Sex (male = 0, female = 1) | 5.30 (4.21–6.67) | <.001 | 4.72 (3.72–6.00) | <.001 |
| Comorbidities | | | |
| Depressive disorder | 1.49 (0.74–3.01) | .263 | |
| Hypertension | 2.12 (1.73–2.61) | <.001 | 1.14 (0.89–1.45) | .318 |
| Diabetes mellitus | 1.87 (1.48–2.35) | <.001 | 1.01 (0.78–1.30) | .888 |
| Dyslipidemia | 1.79 (1.45–2.22) | <.001 | 1.53 (1.22–1.93) | .636 |
| Cerebrovascular disease | 2.29 (1.76–2.98) | <.001 | 1.13 (0.84–1.51) | .418 |
| COPD | 2.06 (1.61–2.64) | <.001 | 1.44 (1.10–1.88) | .008 |
| Nephropathy | 1.63 (1.23–2.15) | <.001 | 1.02 (0.77–1.36) | .886 |
| Autoimmune disease | 1.08 (0.70–1.66) | .736 | |
| Obesity | 0.36 (0.09–1.44) | .148 | |
| Congestive heart failure | 3.26 (2.15–4.93) | <.001 | 1.31 (0.84–2.03) | .233 |
| Degree of urbanization | | | |
| Urban | Reference | | |
| Suburban | 1.14 (0.90–1.43) | .278 | 1.14 (0.90–1.43) | .287 |
| Rural | 1.55 (1.09–2.21) | .015 | 1.04 (0.72–1.51) | .825 |
| Income group | | | |
| High income | Reference | | |
| Medium income | 0.20 (0.13–0.31) | <.001 | 1.49 (0.90–2.46) | .119 |
| Low income | 0.64 (0.33–0.65) | <.001 | 1.77 (1.13–2.77) | .013 |
| No income | 0.74 (0.58–0.94) | .014 | 1.57 (0.97–2.55) | .066 |

CI = confidence interval, COPD = chronic obstructive pulmonary disease, HR = hazard ratio.

| Table 5 | Analyses of risk factors for osteoporosis in patients with fatty liver (male). |
|---------|---------------------------------|
| Predictive variables | Univariate analysis | Multivariate analysis |
| | HR (95% CI) | P-value | HR (95% CI) | P-value |
| Age (<65 = 0, ≥65 = 1) | 7.38 (4.93–11.04) | <.001 | 4.01 (2.37–6.79) | <.001 |
| Sex (male = 0, female = 1) | | | |
| Comorbidities | | | |
| Depressive disorder | 2.01 (0.64–6.34) | .234 | |
| Hypertension | 2.82 (1.91–4.18) | <.001 | 1.25 (0.77–2.03) | .368 |
| Diabetes mellitus | 1.68 (1.06–2.66) | .026 | 0.85 (0.52–1.39) | .508 |
| Dyslipidemia | 1.78 (1.19–2.67) | .005 | 1.39 (0.90–2.23) | .137 |
| Cerebrovascular disease | 3.32 (2.06–5.33) | <.001 | 1.45 (0.85–2.44) | .170 |
| COPD | 3.63 (2.39–5.52) | <.001 | 1.72 (1.06–2.77) | .027 |
| Nephropathy | 2.21 (1.34–3.64) | .002 | 1.23 (0.27–2.07) | .442 |
| Autoimmune disease | 1.43 (0.66–3.08) | .363 | |
| Obesity | 0.05 (0.03–0.36) | .507 | |
| Congestive heart failure | 5.91 (3.07–11.38) | <.001 | 1.61 (0.79–3.30) | .190 |
| Degree of urbanization | | | |
| Urban | Reference | | |
| Suburban | 1.16 (0.75–1.77) | .510 | |
| Rural | 1.36 (1.05–2.65) | .410 | |
| Income group | | | |
| High income | Reference | | |
| Medium income | 0.93 (0.54–1.62) | .809 | 1.05 (0.60–1.82) | .876 |
| Low income | 0.47 (0.22–0.99) | .048 | 0.93 (0.42–2.04) | .855 |
| No income | 0.345 (0.166–0.717) | .004 | 0.65 (0.30–1.41) | .279 |

CI = confidence interval, COPD = chronic obstructive pulmonary disease, HR = hazard ratio.
of proinflammatory factors (e.g., IL-1, IL-6, CRP, and TNF-α) caused by chronic inflammation and imbalance between proteases and their inhibitors in patients with COPD.\textsuperscript{[40]} Additionally, frequent glucocorticoid use and vitamin D deficiency are also possible risks of osteoporosis development in patients with COPD.\textsuperscript{[41]} Therefore, we observed that patients with NAFLD comorbid with COPD have a higher risk of developing osteoporosis.

Further analyses considering genders showed that, among the male patients with NAFLD, COPD was a significant risk factor for the subsequent development of osteoporosis. Jaramillo et al.\textsuperscript{[42]} found that male smokers with COPD have a significant risk of low BMD and vertebral fractures than female smokers as our finding.

Dyslipidemia could be seen as potential risk factors for the subsequent development of osteoporosis among the female patients with NAFLD. Under the NHII program in Taiwan, almost all patients diagnosed with dyslipidemia would be treated. Statin treatment was widely used. A meta-analysis showed that statin treatment may be associated with an increased BMD at the total hip and the lumbar spine and may have a greater effect on male patients than on female patients.\textsuperscript{[43]} Statins may play a role in gender differences.

Several limitations to our study have been identified. Although NHIRD included a large amount of data, it does not include personal information on patients, such as smoking, lack of sun exposure and calcium supplements, body mass index, and family history of osteoporosis, which are contributing factors to the development of osteoporosis. Therefore, we could not survey these potential confounding variables. Second, a diagnostic delay of osteoporosis may be present in our study. Thus, the outcome of our study might not back up the hypothesis that NAFLD leads to osteoporosis.

Conclusion about the association between NAFLD and osteoporosis is positive in our study. NAFLD is prevalent in developed countries. Further long-term and well-designed prospective studies are needed to address the association between NAFLD and osteoporosis. For earlier detection, screening for osteoporosis in patients with NAFLD might be recommended and should be considered in future public health policy planning.

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Author Contributions

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