Hepatic Encephalopathy Increases the Risk of Hip Fracture: a Nationwide Cohort Study

CURRENT STATUS: UNDER REVIEW

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SUBJECT AREAS
Orthopedics

KEYWORDS
Aged, Cohort studies, Hepatic encephalopathy, Osteoporotic fractures
Abstract

Background

Osteoporotic hip fractures debilitate the patients and largely decrease their life quality. Early prevention of the fracture is essential in the recent decades by finding out the related risk factors as reference of further intervention. Hepatic encephalopathy, a major complication of liver cirrhosis, may increase the rate of falling down and weaken the bone quality. Few papers emphasized the association between hepatic encephalopathy and osteoporotic hip fracture.

Methods

This retrospective cohort study used data from Taiwan’s National Health Insurance Research Database between 2000 and 2012. Patients with and without hepatic encephalopathy were matched at a ratio of 1:4 for age, sex, and index year. The incidence and hazard ratios of comorbidities related to aging and poor lifestyle were calculated using Cox proportional hazard regression models.

Results

In total, 2496 patients with hepatic encephalopathy and 9984 patients without hepatic encephalopathy were enrolled. The average age of the patients was approximately 66.5 years. The incidence of comorbidities did not significantly differ between patients with and without hepatic encephalopathy. Patients with hepatic encephalopathy were 2.15-times more likely to develop osteoporotic hip fractures than patients without hepatic encephalopathy in the whole group and the risk ratio was significantly higher in female patients. Those who were aged 50–64 and 65–79 years were respectively 3.57- and 2.51-times more likely to develop osteoporotic hip fracture compared to their non-HE counterparts. The results were also similar in the comorbidity subgroups of hypertension, diabetes mellitus, hyperlipidemia, senile cataract, gastric ulcer and depression. The cumulative incidence of the fractures significantly differed between patients with and without hepatic encephalopathy.

Conclusions

Hepatic encephalopathy is significantly associated with an increased risk of osteoporotic hip fractures and the significance was not affected by the comorbidities. The risk cumulated steadily through time.
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**Background**

In patients with chronic liver disease, hepatic encephalopathy (HE) is one of the most common morbidities that disables patients and causes irreversible brain injury [1, 2]. The patients with liver cirrhosis and the complications of severe HE are associated with a very high mortality rate, even in the first year alone [3]. The life expectancy of patients with HE has grown due to familiarity with the mechanism of disease progression and the considerable improvements in the resuscitation and evolved support system [4].

Osteoporosis, a complication of liver cirrhosis, is strongly correlated with the incidence of osteoporotic fractures [5]. Osteoporotic hip fractures (OHFx) often occur due to low-energy mechanisms, such as falling on the ground due to sudden changes in position, in elderly people or women who undergo surgical menopause [6]. The occurrence of OHFx in patients with HE results in severe disability and a high mortality rate; HE increases treatment difficulty of OHFx, potentially placing a considerable economic burden on society [7, 8]. Due to the increasing life span of the patients with liver cirrhosis and HE, the association with osteoporosis-related fractures has become prominent in the recent decade. It will require more research because of the issue of its increasing prevalence and the needs of these patients with HE, which will over-exert the abilities of the health care system? However, few studies have investigated the relationship between HE and OHFx in a large sample size by comparing both patients with and without HE. The present retrospective cohort study aimed to investigate the correlation between the risk of OHFx and HE in people aged more than 50 years by using the big data of Taiwan’s National Health Insurance (NHI) program.

**Materials And Methods**

**Data sources**

The NHI Research Database (NHIRD) contains the health-related data of nearly the entire population of Taiwan. The NHI program, which was launched in 1995, provides all-round medical care, including outpatient and inpatient care, to approximately 99% of the 23.74 million citizens of Taiwan. The Longitudinal Health Insurance Database 2000 (LHID2000), a subset of NHIRD, contains the data of 1 million beneficiaries randomly selected from the Registry for beneficiaries of the year 2000. These
random samples found in LHID2000 have been confirmed by the NHIRD to be representative of Taiwanese residents. For each beneficiary, a unique identification number was used to link all insurance information and health care records. In the NHIRD, diseases are defined according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes. This study was approved by the Research Ethics Committee of China Medical University and Hospital in Taiwan (CMUH-104-REC2-115).

Sample Design
From the NHIRD, we identified and enrolled people aged ≥ 50 years between 2000 and 2012 in this cohort study. Patients with HE (ICD-9-CM code 572.2) and those without HE were included in the case and control cohorts, respectively. The study outcome was the diagnosis of OHFx (ICD-9-CM codes 733.00–733.09, and 820.0–820.9). The index date was the first date of HE diagnosis for the case cohort and a random date and the index year for the control cohort. We excluded patients who were diagnosed with OHFx before the index date, had multiple injuries (ICD-9-CM code 959.99), or had missing information on sex or age. A follow-up period on the patients lasted until the diagnosis of OHFx, death, withdrawal from the insurance, or the end of 2013. According to the logistic regression model, we matched age, sex, index year, and comorbidities between the case and control cohorts by using propensity scores at a ratio of 1:4. We examined the distribution of sex, age, and comorbidities, namely hypertension (HTN; ICD-9-CM codes 401–405), diabetes mellitus (DM; ICD-9-CM code 250), hyperlipidemia (ICD-9-CM code 272), senile cataract (ICD-9-CM codes 366.10–366.19), gastric ulcer (ICD-9-CM codes 531.0–531.9), cholangitis (ICD-9-CM code 576.1), and depression (ICD-9-CM codes 296.2, 296.3, 296.82, 300.4, 309.0, 309.1, and 311), between the case and control cohorts. The entire design and screening process are presented as a flowchart in Fig. 1.

Statistical analysis
The standardized mean difference (SMD) on strata of sex, age, comorbidity, and means of age and follow-up period were applied for further analysis. The incidence rate (IR) was defined as the number of events divided by person-years. Crude hazard ratios, adjusted hazard ratios (aHRs), and 95% confidence intervals (95% CIs) were calculated based on the multivariable Cox proportional hazard
regression model adjusted for sex, age, and comorbidities. The Kaplan–Meier method was used to
determine the cumulative incidence of OHFx in patients with and without HE, and the log-rank test
was used to examine its significance. Statistical analysis was performed using SAS 9.4 software (SAS
Institute, Cary, NC, USA). $P < 0.05$ was considered statistically significant.

Results
A total of 2496 patients with HE and 9984 patients without HE were included. The demographic data
had great similarity between the two groups, including the distributions of sex, age, and the related
comorbidities according to the very small values of standardized mean difference, which made them
very comparable (Table 1). As shown in Table 2, patients with HE were 2.15-times more likely to
develop OHFx compared to those without HE (IR per 1000 person-years = 20.4 vs. 9.8). Female and
male patients with HE were respectively 2.25- and 2.00-times more likely to develop OHFx compared
with female and male patients without HE. HE patients aged 50–64 and 65–79 years were respectively
3.57- and 2.51-times more likely to develop OHFx compared to their non-HE counterparts. The
comorbidity subgroups of HTN, DM, hyperlipidemia, senile cataract, gastric ulcer, and depression all
developed the similar aHRs compared with their non-HE counterparts (Table 2). Figure 2 shows that
the cumulative incidence of OHFx differed significantly between patients with and without HE (log-
rank test: $P < 0.001$).

| Table 1 |
|---|

| Baseline characteristics in the patients with and without hepatic encephalopathy | Hepatic encephalopathy | Standardized mean difference |
|---|---|---|
| | No (n=9984) | Yes (n=2496) | |
| Sex | | | |
| Female | 3708 (37.1) | 943 (37.8) | 0.01 |
| Male | 6276 (62.9) | 1553 (62.2) | 0.01 |
| Age, years | | | |
| 50-64 | 4427 (44.3) | 1163 (46.6) | 0.05 |
| 65-79 | 4425 (44.3) | 1081 (43.3) | 0.02 |
| 80+ | 1132 (11.3) | 252 (10.1) | 0.04 |
| Mean (SD) | 66.5 (10.4) | 66.7 (10.1) | 0.02 |
| Comorbidity | | | |
| HTN | 6125 (61.4) | 1473 (59.0) | 0.05 |
| DM | 4446 (44.5) | 1073 (43.0) | 0.03 |
| Hyperlipidemia | 2847 (28.5) | 685 (27.4) | 0.02 |
| Senile cataract | 2832 (28.4) | 666 (27.5) | 0.02 |
| Gastric ulcer | 4285 (42.9) | 1053 (42.2) | 0.02 |
| Cholangitis | 342 (3.43) | 114 (4.57) | 0.06 |
| Chronic renal failure | 0 | 0 | |
| Depression | 1019 (10.2) | 261 (10.5) | 0.01 |
| Alcohol-related illness | 2131 (21.3) | 537 (21.5) | 0.004 |

A standardized mean difference ≤ 0.10 indicates a negligible difference between the two cohorts.
Table 2
Incidence and hazard ratios of osteoporotic hip fracture between the patients with and without hepatic encephalopathy

|       | Hepatic encephalopathy |       |
|-------|-------------------------|-------|
|       | No Event | PY | Event | PY | rate* | No Event | PY | Event | PY | rate* | CHR (95% CI) |
| Overall | 575 | 58393 | 9.8 | 68 | 3337 | 20.4 | 2.15 | 1.67, 2.78 |
| Sex |       |       |       |       |       |       |       |       |       |       |       |
| Female | 332 | 22154 | 15.0 | 41 | 1278 | 32.1 | 2.25 | 1.62, 3.13 |
| Male   | 243 | 36239 | 6.7 | 27 | 2058 | 13.1 | 2.00 | 1.34, 3.00 |
| Age, years |       |       |       |       |       |       |       |       |       |       |       |
| 50-64 | 105 | 28340 | 3.7 | 24 | 1972 | 12.2 | 3.57 | 2.27, 5.60 |
| 65-79 | 350 | 25837 | 13.5 | 34 | 1144 | 29.7 | 2.51 | 1.76, 3.60 |
| 80+   | 120 | 4216 | 28.5 | 10 | 221 | 45.3 | 1.52 | 0.79, 2.92 |
| Comorbidity |       |       |       |       |       |       |       |       |       |       |       |
| HTN   | 408 | 32778 | 12.4 | 49 | 1910 | 25.7 | 2.18 | 1.62, 2.95 |
| DM    | 277 | 23738 | 11.7 | 30 | 1348 | 22.3 | 1.96 | 1.34, 2.87 |
| Hyperlipidemia | 145 | 14205 | 10.2 | 25 | 1081 | 23.1 | 2.38 | 1.55, 3.65 |
| Senile Cataract | 204 | 13964 | 14.6 | 21 | 828 | 25.3 | 1.77 | 1.13, 2.80 |
| Gastric Ulcer | 289 | 23761 | 12.2 | 36 | 1432 | 25.1 | 2.07 | 1.46, 2.95 |
| Cholangitis | 27 | 1595 | 16.9 | 2 | 109 | 18.4 | 1.18 | 0.27, 5.07 |
| Depression | 66 | 5053 | 13.1 | 11 | 443 | 24.8 | 2.02 | 1.06, 3.84 |
| Alcohol-related illness | 79 | 10429 | 7.6 | 13 | 1117 | 11.6 | 1.57 | 0.87, 2.83 |

Abbreviations: aHR, adjusted hazard; cHR, crude hazard ratio; DM, diabetes mellitus; HTN, hypertension; PY, person-years; rate, per 1,000 person-years.

Discussion
This study revealed that the incidence of OHFx was significantly higher in patients with HE aged > 50 years than in elderly patients without HE. The cumulative incidence of OHFx was also significantly higher in patients with HE although the follow-up period was shorter in the HE group than in the non-HE group, which may be due to a shorter life span related to HE as a comorbidity.

Many studies have found that patients with hepatic failure have an increased risk of osteoporosis; the pathogenesis of bone loss and osteoporosis in patients with hepatic failure is complex and multifactorial [7, 9]. A study reported that low levels of insulin-like growth factor 1 in patients with advanced liver cirrhosis may aggravate bone remodelling and maintenance of bone mass in elderly patients, causing fragility fractures [10, 11]. In addition, patients with HE have demonstrated poor cognitive function and are often afflicted by psychiatric illnesses, which may increase the risk of sustaining an injury due to a fall [5].

In this study, patients with HE were 2.15-times more likely to develop OHFx than patients without HE. Patients without the comorbidities listed in Table 2 had a similar risk of OHFx, but patients with cholangitis, senile cataract, alcohol-related illness, and DM in the case group had a lower risk of OHFx.
(less than 2 times) than those in the control group. This result indicates that these four comorbidities may exert a significant effect on the increase of the incidence of OHFx. Hyperbilirubinemia can be found in cholangitis and has been shown to impair osteoblast proliferation and result in decreased bone formation [12–14]. A recent study found senile cataract was independently associated with an increased risk of osteoporosis and fractures, and that the reasons for this association are multifactorial, mainly relating to aging and a high possibility of sustaining a fall injury [15].

A study reported that women aged between 67 and 90 years who consumed an average of more than 3 ounces of alcohol per day (the equivalent of six drinks) had higher bone loss than did women who had minimal alcohol intake [16]. In an animal study, older animals who were administered alcohol were found to have deficiencies in bone volume and density. Both type 1 and type 2 DM are associated with decreased bone strength, and alterations in bone quality play a major role in the pathogenesis of fragility fractures [17]. The insulin growth factor pathway, one of the complex pathways involved in the relationship between DM and bone fragility, mediates the accumulation of advanced glycation end products in bone collagen. This results in microangiopathy and increased fat content in the bone marrow. The mechanism underlying the interaction between HE and DM and senile cataract should be investigated in the future.

The advantage of our study is the large sample size. Selection and nonresponse biases may have been minimized due to the comprehensive coverage of the NHI system (> 95% of the Taiwanese population). This study also has some limitations. First, we could not determine the severity of hepatic damage because the NHIRD does not provide information regarding symptoms. Second, lifestyle factors, personal characteristics, and biochemical data, which may be important sources of bias, could not be obtained. Third, because our results are based on data from Taiwan’s NHI, the findings of this study may not be directly generalizable to Caucasian or African populations.

HE appears to be a crucial risk factor for OHFx in people aged > 50 years (especially those aged 50–64 years) based on the findings of this nationwide cohort study and this significance can be found similarly in the subgroups of HTN, DM, hyperlipidemia, senile cataract, gastric ulcer and depression, which all play an important role in the pathogenesis of OHFx; in addition to HE, the interaction
between these factors should be studied in the future. Aggressive treatment of osteoporosis and complete geriatric care strategies for older patients with HE should be routinely considered.

Abbreviations
95% CIs: 95% confidence intervals; aHRs: adjusted hazard ratios; cHR: crude hazard ratio; DM: diabetes mellitus; HE: hepatic encephalopathy; HTN: hypertension; ICD-9-CM: International Classification of Diseases, Ninth Revision, Clinical Modification; IR: incidence rate; LHID2000: Longitudinal Health Insurance Database 2000; NHI: National Health Insurance; NHIRD: NHI Research Database; OHFx: Osteoporotic hip fractures; PY: person-years; SMD: standardized mean difference

Declarations
Acknowledgments
This study is supported in part by Taiwan Ministry of Health and Welfare Clinical Trial Center (MOHW108-TDU-B-212-133004), China Medical University Hospital, Academia Sinica Stroke Biosignature Project (BM10701010021), MOST Clinical Trial Consortium for Stroke (MOST 107-2321-B-039 -004- ), Tseng-Lien Lin Charitable Foundation, Taichung, Taiwan, and Katsuzo and Kiyo Aoshima Memorial Funds, Japan. This manuscript was edited by Wallace Academic Editing.

Authors’ contributions
Conception and design of study: KTY, TCY, HWC, and IHC.
Acquisition of data: CYH, KLL, and CHP.
Analysis and/or interpretation of data: JHW.
Drafting the manuscript: KTY.
Revising the manuscript critically for important intellectual content: WTW, RPL.
All authors read and approved the final manuscript.

Funding
Taiwan Ministry of Health and Welfare Clinical Trial Center (MOHW108-TDU-B-212-133004), China Medical University Hospital, Academia Sinica Stroke Biosignature Project (BM10701010021), MOST Clinical Trial Consortium for Stroke (MOST 107-2321-B-039 -004- ), Tseng-Lien Lin Foundation, Taichung, Taiwan, and Katsuzo and Kiyo Aoshima Memorial Funds, Japan.

Availability of data and materials
All data generated or analysed during this study are included in this published article.
Ethics approval and consent to participate
This study was approved by the Research Ethics Committee of China Medical University and Hospital in Taiwan (CMUH-104-REC2-115).

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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Flow chart of the process for establishing the hepatic encephalopathy cohort and control group on the basis of the National Health Insurance Research Database.
Figure 2

Cumulative incidence of OHOx of patients with and without hepatic encephalopathy.