Research Article

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Increased incidence of orthopedic fractures in cirrhotic patients: A nationwide population-based study

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Background & Aims: Hepatic encephalopathy (HE) is a reversible neuropsychiatric disorder in cirrhotic patients. The cognitive dysfunction and increased accidental falls in HE and osteodystrophy in cirrhotic patients may contribute to orthopedic fractures. This study investigated the fracture incidence and risk factors in cirrhotic patients with HE.

Methods: In total, 3764 cirrhotic patients with HE were identified from the Taiwan National Health Insurance database between 2000 and 2009. The fracture incidence of the HE patients was compared with that of 3764 age-, sex-, and comorbidity-matched cirrhotic patients without HE and non-cirrhotic controls. Cox proportional hazard models were used to estimate the risk of fracture in the HE patients.

Results: Cirrhotic patients with and without HE had comparable increased risks of fracture (p <0.05) and cumulative incidences of fracture than controls (log-rank p <0.001). The estimated fracture rates were 7.09% for the HE group, 7.72% for the cirrhosis without HE group, and 4.05% for the controls, during the 18-month follow-up. The HE group had a higher incidence rate of skull fractures (IRR = 2.61, 95% CI 1.04–6.57), but a lower rate of upper limb fractures (IRR = 0.45, 95% CI 0.29–0.70) than the cirrhosis without HE group. Alcoholism, heart failure, and cerebrovascular disease were associated with increased risk of fracture in HE patients.

Conclusions: Cirrhotic patients, with or without HE, are at an increased risk of orthopedic fractures. Skull fractures, rather than fractures in weight-bearing bones, are more frequently observed in HE patients, particularly those with comorbidities.

Keywords: Cirrhosis; Injury; Neuropsychiatric syndrome.

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Abbreviations: HE, hepatic encephalopathy; IRR, incidence rate ratio; CI, confidence interval; NHI, National Health Insurance; ICD, International Classification of Diseases; DM, diabetes mellitus; HR, hazard ratio.

Introduction

Hepatic encephalopathy (HE) is a serious neuropsychiatric complication, involving both acute and chronic liver disease that affects the health-related quality of life of patients, clinical management strategies, liver transplant priority, and patient survival [1,2]. HE includes a broad range of neuropsychiatric abnormalities of varying severity, from minimal/subclinical neurological changes to coma. Patients with HE may exhibit altered psychomotor, intellectual, cognitive, emotional, behavioral, and motor-coordination functions, resulting in confusion, disorientation, and poor coordination [1,2]. Persistent and cumulative impairment in cognition may remain even after a complete resolution of overt HE [3]. The interest in accidental events, such as motor vehicle crashes and falls, among minimal HE patients has intensified in recent years. Patients with minimal HE are more likely to suffer from traffic accidents and accidental falls and are at a greater risk of requiring health care and hospitalization [4–7]. However, patients with minimal HE are not easily detected clinically since these patients seem to be clinically unimpaired, but have subtle deficits and psychomotor abnormalities that can only be elicited by specialized tests [8].

In addition, hepatic osteodystrophy, including osteomalacia and osteoporosis, is extremely common in patients with chronic liver disease. There is an approximately 2-fold relative increase in the risk of fracture among patients with cirrhosis, regardless of the etiology of the liver disease, and the prevalence of overall fractures in patients with chronic liver diseases ranges from 3% to 22% [9,10]. These bone diseases are one of the major complications of chronic liver disease and are reported to significantly affect the morbidity, quality of life, and even survival of patients with chronic liver disease and those waiting for, or who have already received liver transplants [9–13]. Therefore, fractures and falls have negative consequences not only for patients but also for their families, communities, and society, creating an economic and social burden [14,15]. However, previous studies regarding fracture risks were mainly small-scale case-control studies lacking information on incidence rates and details on the sites of fracture [6,7,9,10].

HE patients may be at an increased risk of fracture because of weak bones or an increased risk of accidents. Further information

regarding the fracture incidence, fracture location, and related medical costs might help in the design of better preventive strategies. We thus conducted a population-based study using the National Health Insurance (NHI) database in Taiwan to examine the incidence of fractures and medical costs in HE patients and compare them with matched cirrhotics without HE and non-cirrhotics. We also attempted to identify independent factors for predicting fracture occurrence in cirrhotic patients with HE.

Materials and methods

Data sources

Taiwan began the NHI program in 1995 to provide health care for all citizens, and the program currently has a coverage rate of up to 98% [16]. The NHI is a mandatory universal health insurance program that offers comprehensive medical care coverage to all Taiwanese residents. The program includes coverage for outpatient, inpatient, emergency, and dental care in addition to traditional Chinese

Table 1. The ICD-9-CM code and ATC code to identify diseases and medication category.

Definition of diseases/medication category	ICD-9 CM code or ATC code
Chronic hepatitis	571.40 Chronic hepatitis, unspecified 571.41 Chronic persistent hepatitis 571.49 Other chronic hepatitis
Hepatic encephalopathy	572.2 Hepatic encephalopathy
Liver cirrhosis	571.2 Alcoholic cirrhosis of liver 571.5 Cirrhosis of liver without mention of alcohol 571.6 Biliary cirrhosis
Malignant neoplasm of liver	155.0 Malignant neoplasm of liver, primary
Alcoholism	291.X Alcohol-induced mental disorders 303.X Alcohol dependence syndrome 305.0X Non-dependent alcohol abuse 357.5 Alcoholic polyneuropathy 425.5 Alcoholic cardiomyopathy 571.0X Alcoholic fatty liver 571.1X Acute alcoholic hepatitis 571.2X Alcoholic cirrhosis of liver 571.3X Alcoholic liver damage, unspecified 980.0 Toxic effect of ethyl alcohol V11.3 Personal history of alcoholism
Skull fractures	800 Fracture of vault of skull 801 Fracture of base of skull 802 Fracture of face bones 803 Other and unqualified skull fractures 804 Multiple fractures involving skull or face with other bones
Spine and trunk fractures	805 Fracture of vertebral column without mention of spinal cord injury 806 Fracture of vertebral column with spinal cord injury 807 Fracture of rib(s) sternum larynx and trachea 808 Fracture of pelvis 809 Ill-defined fractures of bones of trunk
Upper limb fractures	810 Fracture of clavicle 811 Fracture of scapula 812 Fracture of humerus 813 Fracture of radius and ulna 814 Fracture of carpal bone 815 Fracture of metacarpal bone 816 Fracture of one or more phalanges of hand 817 Multiple fractures of hand bones 818 Ill-defined fractures of upper limb 819 Multiple fractures involving both upper limbs and upper limb with rib(s) and sternum
Lower limb fractures	820 Fracture of neck of femur 821 Fracture of other and unspecified parts of femur 822 Fracture of patella 823 Fracture of tibia and fibula 824 Fracture of ankle 825 Fracture of one or more tarsal and metatarsal bones 826 Fracture of one or more phalanges of foot 827 Other multiple and ill-defined fractures of lower limb 828 Multiple fractures involving both lower limbs lower with upper limb and lower limb(s) with rib(s) and sternum 829 Fracture of unspecified bones
Diabetes mellitus	250.X Diabetes mellitus

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