Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2018.09.026.

George N. Ioannou[1,2,*]

[1]*Division of Gastroenterology, Department of Medicine Veterans Affairs Puget Sound Healthcare System and University of Washington, Seattle, WA, United States*

[2]*Research and Development, Veterans Affairs Puget Sound Healthcare System, Seattle, WA, United States*

Address: Veterans Affairs, Puget Sound Health Care System, Gastroenterology, S-111-Gastro, 1660 S. Columbian Way, Seattle, WA 98108, United States;
Tel.: +1 206 277 3136; fax: +1 206 764 2232.
E-mail address: georgei@medicine.washington.edu

Hip fracture risk in patients with alcoholic cirrhosis: Do comorbidities and complications matter?

To the Editor:

Patients with liver disease are particularly susceptible to osteoporosis, making them prone to bone fractures.[1,2] The 30-day mortality rate in patients with bone fractures was approximately 6.7% according to the data collected from the National Hip Fracture Database.[3] Moreover, cirrhosis following hip fracture was associated with higher 30-day in-hospital mortality.[4] Nevertheless, the absolute risk of hip fractures in individuals with alcoholic cirrhosis is still unclear.

Recently, we read with great interest the study by Otete *et al.*[5] Using the Clinical Practice Research Datalink, Hospital Episodes Statistics, and National Patient Registry database, this population-based study of a large sample suggested that patients with alcoholic cirrhosis had a significantly higher risk of hip fracture and post-hip fracture mortality compared to the general population. The research appears informative clinically. Thus, we addressed some issues regarding this study.

Firstly, the incidence rate of diabetes mellitus increased all over the world.[6] Additionally, nearly 30% of cirrhosis patients have diabetes mellitus.[7] Theoretically, patients with liver cirrhosis had a higher incidence of bone fracture compared to those without diabetes mellitus.[8] Additionally, hypoglycemic treatment could modulate the risk of fractures.[9] Accordingly, it is essential to consider concurrent diabetes mellitus as a risk factor when analyzing the incidence rate of hip fracture in patients with alcoholic liver cirrhosis. Otete *et al.* did not report the information on concurrent diabetes mellitus.[5] Can the authors provide the relevant data?

Secondly, we are confused about the detection method for the diagnosis of liver cirrhosis. Theoretically, the symptoms and signs would not be apparent in the early phase of liver cirrhosis. Many patients with early stage liver cirrhosis would have missed diagnosis without routine and detailed inspection. Patients with early stage cirrhosis had a lower risk of bone fracture than those with late stage cirrhosis. If the patients with early stage cirrhosis are included in the alcoholic cirrhosis group, the absolute rate of fracture risk may decrease. Therefore, the results would be inaccurate without knowledge of how many patients had early stage liver cirrhosis.

Thirdly, the Charlson comorbidity score was not balanced between the cirrhosis and control group in the UK database. More patients had zero scores in the control group, which suggested that the disease burden in the control group was lighter than in the alcoholic liver cirrhosis group. Therefore, the results may be inaccurate without knowledge of the balance of demographic characteristics.

Fourthly, surgery was the primary therapy for patients with hip fracture. Evidence showed that early surgery reduced the overall mortality compared with control therapy.[10] However, Otete *et al.* did not illustrate the relevant details.[5] Additionally, the surgery-associated complications that relate to prognosis are also critical when assessing the absolute rate of post-hip fracture mortality.

In summary, we suggest that comorbidities and complications in alcoholic liver cirrhosis should be considered when analyzing the risk of hip fracture and post-hip fracture mortality. Clarification regarding these issues would significantly solidify the conclusions of the study by Otete *et al.*[5]

Financial support

The authors received no financial support to produce this manuscript.

Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Dr Ling-Yue Zhao and Yi-Jun Luo: Design of the work and final approval of the manuscript for submission. Dr Ling-Yue Zhao: Drafting and revision of the manuscript. Dr Jing Zhu: Revision of the manuscript. Dr Hong-Yue Liu: Revision of the manuscript.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2018.09.012.

References

[1] Ninkovic M, Love SA, Tom B, Alexander GJ, Compston JE. High prevalence of osteoporosis in patients with chronic liver disease prior to liver transplantation. Calcif Tissue Int 2001;69:321–326.
[2] Diamond T, Stiel D, Lunzer M, Wilkinson M, Roche J, Posen S. Osteoporosis and skeletal fractures in chronic liver disease. Gut 1990;31:82–87.
[3] Royal College of Physicians. National Hip Fracture Database annual report 2017. London: RCP; 2017.
[4] Chen TL, Lin CS, Shih CC, Huang YF, Yeh CC, Wu CH, et al. Risk and adverse outcomes of fractures in patients with liver cirrhosis: two nationwide retrospective cohort studies. BMJ Open 2017;7 e017342.
[5] Otete H, Deleuran T, Fleming KM, Card T, Aithal GP, Jepsen P, et al. Hip fracture risk in patients with alcoholic cirrhosis: a population-based study using English and Danish data. J Hepatol 2018;69:697–704.
[6] Andries M, Glintborg D, Kvistborg A, Hagen C, Andersen M. A 12-month randomized crossover study on the effects of lanreotide Autogel and octreotide long-acting repeatable on GH and IGF-I in patients with acromegaly. Clin Endocrinol (Oxf) 2008;68:473–480.
[7] Bloodworth Jr JB. Diabetes mellitus and cirrhosis of the liver. Arch Intern Med 1961;108:695–701.
[8] Janghorbani M, Van Dam RM, Willett WC, Hu FB. Systematic review of type 1 and type 2 diabetes mellitus and risk of fracture. Am J Epidemiol 2007;166:495–505.
[9] Gilbert MP, Pratley RE. The impact of diabetes and diabetes medications on bone health. Endocr Rev 2015;36:194–213.
[10] Simunovic N, Devereaux PJ, Sprague S, Guyatt GH, Schemitsch E, Debeer J, et al. Effect of early surgery after hip fracture on mortality and complications: systematic review and meta-analysis. CMAJ 2010;182:1609–1616.

Ling-Yue Zhao
Yi-Jun Luo*
Jing Zhu
Hong-Yue Liu
Department of Ambulatory Surgery, Shenzhen Nanshan District People's Hospital, Shenzhen, Guangdong 518052, PR China
*Corresponding author. Address: Department of Day Surgery, Shenzhen Nanshan District People's Hospital, 89 Taoyuan Road, Shenzhen, Guangdong 518052, PR China.
Tel.: +86-755-5131121; fax: +86-755-5131121.
E-mail address: nsluoyijun@yeah.net

Reply to: "Hip fracture risk in patients with alcoholic cirrhosis: Do comorbidities and complications matter?"

To the Editor:

We thank Luo and colleagues for their interest and comments on our study.[1]

While we agree that diabetes may influence hip fracture risk, we have not presented specific estimates for patients with diabetes (nor for patients with any other comorbidity likely to affect the risk of bone fracture). Rather, we acknowledge the impact of comorbidity by adjusting our risk estimates for the Charlson comorbidity index, an established scoring system for comorbidity. The Charlson index includes diabetes in its scoring system, and is a reasonable way of accounting for the effect of diabetes and up to 20 other comorbidities at the same time.[2] Regarding the effect of antidiabetic medication specifically mentioned, the cited review[3] concluded that a small increased fracture risk is apparent among patients on Glitazones (Hazard ratio across reviewed studies ranged from 1.35 to 1.71). Less than 5% of type 2 diabetes patients in England and Denmark are reported to be on these medications, hence this is unlikely to have affected our estimates of risk unduly.[4,5]

We agree that fracture risk may be lower in patients with compensated as opposed to decompensated cirrhosis. However, our study did not aim to explore the differences in risk among people with "early stage" cirrhosis as implied by Luo and colleagues. Rather we focused on patients with clinically diagnosed cirrhosis in both England and Denmark. Our approach to identifying cirrhosis cases was based on a method that has been previously validated,[6] to identify the mix of cirrhosis cases in both countries. Consequently, our study includes clinically diagnosed patients with either compensated or decompensated cirrhosis, and our cohort therefore represents the case mix seen in clinical practice in the UK and in Denmark.

Finally, with reference to the authors' request to further understand the balance of demographic characteristics between the cirrhosis and control group, we would suggest they look at Table 1 of our manuscript in which both demographic and clinical characteristics of all Danish and English patients included in our study are displayed.

Financial support

The original article was supported by a Nottingham University Hospitals NHS Trust and University of Nottingham Senior Clinical Research fellowship for JW.

Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

Please refer to the accompanying ICMJE disclosure forms for further details.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2018.10.007.