Dear Editor,

We are grateful to Grietje H. Prins et al for their interest in our recent article regarding the characteristics and mechanisms of liver damage caused by three highly pathogenic coronavirus infections and for their valuable insights on the liver injury among COVID-19.1,2

Grietje H. Prins et al2 came up with a link between non-alcoholic fatty liver diseases (NAFLD) and COVID-19. Ji et al3 analysed 202 consecutive COVID-19 patients and found that the patients with NAFLD had higher likelihood of abnormal liver function, longer viral shedding time, and a higher risk of disease progression to severe COVID-19 compared with non-NAFLD patients. On the other hand, progressive severe COVID-19 patients had higher body mass index (BMI) and percentage of comorbidity including hypertension, diabetes and cardiovascular disease. A large cohort study also confirmed that COVID-19 patients with abnormal liver function test results had a higher BMI and tended to have pre-existing liver diseases, including NAFLD.4 The high prevalence of NAFLD has been fuelled by unhealthy lifestyles worldwide; a large population might be at risk of severe COVID-19.

The role of NAFLD involving in severity of COVID-19 remains unclear. NAFLD has been associated with increased production of inflammatory cytokines which might contribute to severe clinical outcomes of COVID-19,2 further study is warranted. The usage of angiotensin-converting enzyme inhibitors (ACE-Is) in hypertension patients has been considered to increase the expression of ACE2 receptor in the liver and promoting SARS-COV-2 susceptibility and disease severity of COVID-19.2 However, the results from Cai’s5 study showed that the hypertension patients treated with ACE-Is/angiotensin receptor blockers (ARBs) drugs were not increased the incidence of progressing to severe COVID-19 compared to the patients taking other antihypertensive drugs.

It is worth noting that NAFLD was renamed as metabolic (dysfunction)-associated fatty liver disease (MAFLD) recently.6 The diagnosis criteria of MAFLD are independent of the amount of alcohol consumed and based on evidence of hepatic steatosis, in addition to one of the following criteria, overweight/obesity, the presence of type 2 diabetes mellitus or evidence of metabolic dysregulation. For establishing reliable cohort studies to investigate the role of MAFLD in COVID-19, it is strongly recommended to evaluate the hepatic steatosis with abdominal ultrasound or computed tomography examination when patients admitted to hospital.

KEYWORDS
COVID-19, liver injury, metabolic (dysfunction)-associated fatty liver disease

CONFLICT OF INTEREST
The authors disclose no conflict of interest.

AUTHOR CONTRIBUTIONS
Xin Zheng designed and planned the work, and revised the manuscript. Ling Xu and Jia Liu performed the literature search and interpretation, and manuscript drafting. Mengji Lu and Dongliang Yang helped revise the manuscript.

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Occult hepatitis B infection in vaccinated children with negative anti-HBc, true or not?

To the Editor:

I read with interest the article by Ghaziasadi and colleagues on the prevalence of occult hepatitis B infection (OBI) among healthy children who received standard hepatitis B vaccination during infancy.1 Of 1200 children at the age of 9-18 years, none was positive for hepatitis B surface antigen (HBsAg) and antibodies against hepatitis B core antigen (anti-HBc), yet 91 of 660 children (13.8%, rather than 16% stated in their article) were defined with OBI based on the detectable HBV DNA in sera.1 However, I concerned several issues in this article.

First, the authors considered that children with anti-HBs level <10 mIU/mL at 9-18 years of age were non-responders and the proportion of non-responders was as high as 54.3%.1 This is incorrect. Non-responders to hepatitis B vaccination refer to those who produce anti-HBs <10 mIU/mL within 1-6 months following the completion of three serial vaccine doses. Anti-HBs levels will decline with growing age. Actually, <5% infants are non-responders to hepatitis B vaccination.2

Second, the findings that as high as 13.8% children were defined with OBI but none of these 91 OBI children was anti-HBc positive1 raise a question of whether they had been truly infected. OBI is usually a unique consequence of resolved HBV infection, mainly caused by the long-lasting cccDNA of HBV in hepatocytes. Numerous investigations showed that 60%-80% OBI individuals are anti-HBc-positive because HBCAg is most antigenic and anti-HBc can persist for decades.3

Third, the authors stated that the dynamic range of the assay for quantifying HBV DNA was 10²-10⁹ IU/mL and the lower detection limit was 85 IU/mL; however, the HBV DNA levels in some OBI children were <85 IU/mL as the lowest HBV DNA level in table 1 is 5.7 x log₂.1 Thus, whether the assay was adequately used in the study is not clear.

Fourth, based on figure 2,1 some OBI children had identical HBsAg sequences, which is exceptional. Since different isolates of HBV usually have divergent sequences, it is less likely that different HBV-infected individuals have identical sequences except for infection with the same virus. Thus, the possibility of cross-contamination in the detection of HBV DNA could not be excluded.

In summary, OBI occurs in vaccinated children, but the prevalence is low.4 Any exceptionally high prevalence of OBI in vaccinated children should be cautiously interpreted and occult cross-contamination during detection of HBV DNA should be excluded.5

CONFLICT OF INTEREST
The author declare no competing interests.

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