which may be confounding the reported data. There is also a well-established overlap between these two primary liver cancers and an estimated 5–15% of primary liver cancers could be combined iCCA/HCC (Cholangiocellular Ca).[3] A historical lack of biopsy data has not helped with diagnostic certainty and classification. There may also be issues with misdiagnosis as carcinoma of unknown primary.

In summary, bile duct cancers should be clearly sub-classified as intrahepatic, perihilar or distal (extrahepatic (ECC)). These three types of CC are anatomically distinct, have differing epidemiology, pathobiology, clinical presentations and management.[2] The term "Klatskin" is historic, unclear and should be abandoned in subsequent versions of the ICD and ICD-O classification systems.

Diagnostic data needs to be recorded uniformly and accurately. The responsibility to do so lies with both clinicians and cancer registries. ICD-11 and subsequent iterations of ICD-O should have clearly separate topography and morphology codes for iCCA, pCCA and dCCA. Until then, epidemiological trends in cholangiocarcinoma/biliary tract cancer need to be interpreted with caution. Nonetheless, however CC is classified, its overall incidence seems to be rising and urgent studies into its causes and effective therapies are needed.

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.2019.07.024.

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Reply to: "Global trends in mortality from intrahepatic and extrahepatic cholangiocarcinoma"

To the Editor:

We thank Dr. Khan *et al.* for their interest in our work.[1] They are right in pointing out that trends in extrahepatic cholangiocarcinoma (ECC) mirror the long-term declines in gallbladder cancer,[2,3] due to the increase in cholecystectomy. Gallbladder cancer mortality rates in the European Union, in fact, have been declining in women from 2.52/100,000 (world standard) in 1990 to 1.24 in 2015 (−51%). Comparable figures in men were 1.65 in 1990 and 1.24 in 2015 (−25%).[4]

We agree that misclassification in cancer registration, death coding and certification may have affected the incidence and mortality rates of intrahepatic cholangiocarcinoma (ICC), ECC and, mainly, their subsites. The WHO dataset did not enable the subsites of ECC to be distinguished, and the complex of hilar and perihilar CC is a larger proportion than the "historic Klatskin's tumors".[5] However, due to the small overall proportion of Klatskin's tumors reported using current methodology, this misclassification is not likely to materially affect the overall ICC/ECC trends.[6]

We also agree with the plea by Dr. Khan *et al.* that further attention should be given to the diagnosis, classification and registration of ICC and ECC, and their subsites, by hepatologists, pathologists, cancer registration and death certification systems.

Conflict of interest

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

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Supplementary data

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Early initiation of antiviral therapy contributes to a rapid and significant loss of serum HBsAg in infantile-onset hepatitis B

To the Editor:

One article with impressive results was published in a recent issue of this *Journal*. Zhu *et al.* presented us with a study on infantile-onset hepatitis B, which was successfully treated with early antiviral treatment, resulting in the highest HBsAg seroconversion rate we have ever witnessed.[1] We believed that this result is vital for the ulterior management of infantile chronic hepatitis B (CHB), but we have some concerns about this paper.

First of all, we find it hard to distinguish whether these infants with onset hepatitis are in the acute infection period or reactivation stage of chronic infection. We understand that these 2 types of HBV infection have disparate outcomes. Generally, CHB is defined as persistence of HBsAg or being HBV DNA positive for at least 6 months, with a preceding incubation period of 6 weeks to 6 months after infection. In this study, the earliest time at which treatment was started was 6 months of age and we are not sure if all the infants were infected at birth. Besides, Yotsuyanagi *et al.* have previously reported that the clearance of HBV in adulthood can happen between 6 to 12 months from the onset of acute infection.[2] Though a similar scenario was not reported in infancy, we still suggest not to neglect this possibility, and we supposed that some infants in this study were still in the acute infection period when HBsAg clearance occurred.

In addition, infants in group 2, before 1 year of age, are categorized as the no-treatment control with balanced baseline characteristics. However, several confounding factors were not fully justified as the grouping was determined by the parents but not randomization. The standard deviation of alanine aminotransferase (ALT) in group 1 was extremely large (357 ± 303 IU/L). We speculate that many more infants in group 1 presented with ALT over 10 times the upper limit of normal (40 IU/L), which is associated with a high chance of spontaneous clearance. The mean ALT in group 1 was also higher than that in group 2, although the p value did not reach statistical significance due to the limited sample size. The specific HBV DNA and HBsAg titers during screening, prior to treatment initiation, were not described in this article. Any decrease of HBsAg or HBV DNA during this period might also indicate spontaneous clearance and should be balanced between groups.

In brief, the high efficacy of antiviral treatment in group 1 can be partially explained by the possible high percentage of patients in the acute infection period.

The second question is about the outcome of infants who choose not to start antiviral treatment. As the flowchart in this study did not provide a clear procedure for patient screening, selection bias cannot be totally ruled out. We are not sure if there are some patients who fulfilled the inclusion criteria but were not included in the study as their parents did not agree to start antiviral treatment at such a young age.

Collectively, we fully support that this is an important study. However, at this stage, it is too early to adjust the guideline recommendations based on the inspiring results from this study. Further prospective, randomized, controlled studies are urgently needed.

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.