Conflict of interest

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Interaction between infection and hepatic encephalopathy

To the Editor:

We read with interest "The Hepatic Encephalopathy Practice Guidelines" published in the September issue of the *Journal of Hepatology* [1].

As underlined by the authors in Table 3, infections are extremely frequent as precipitating factors for overt hepatic encephalopathy (OHE). In our tertiary referral centre, with an ongoing project for the search of active infection at hospital admission, infection was the precipitating event in 56% of patients with OHE in a study performed in 2008 and 2009 [2]. This prevalence has increased to 64% in 2012 (personal data).

In the same article however, the authors claim that "patients with cirrhosis do not differ from patients without cirrhosis regarding their risk to develop brain dysfunction with sepsis". We disagree with this information. We have recently investigated the association between bacterial infections and cognitive dysfunction in 150 cirrhotic patients and 81 non-cirrhotic controls [3]. Signs of neurocognitive impairment were systematically looked for by means of standardized clinical examination or by the application of psychometric tests in both groups. Following a diagnosis of sepsis, neurocognitive alterations were significantly more frequent in cirrhotic patients than in controls (90% *vs.* 39% cirrhotic patients *vs.* non-cirrhotic controls). In cirrhotic patients, the probability to find neurocognitive alterations increased from patients without infection (42%) to patients with infection and no systemic inflammatory response syndrome (SIRS) (79%) to those with sepsis (90%). Efficaciously treated patients, in whom the infection subsided, improved their neurological symptoms. Both overt and covert hepatic encephalopathy were influenced by the presence of infection and by its resolution.

These results are in keeping with a role for inflammation in the pathogenesis of HE [4]. Other authors have supported this hypothesis: the administration of LPS has been found to alter consciousness and to exacerbate brain oedema only in rats with liver damage [5]; and ibuprofen restored the learning ability of rats with portacaval shunts and cognitive impairment [6]. In cirrhotic patients, serum levels of TNF-alfa [7], as well as of IL-6 and IL-18 [8,9] were associated with the presence and severity of overt and minimal HE. Indeed pro-inflammatory cytokines may contribute to HE in cirrhotic patients by acting synergically with hyperammonemia [10]. Interestingly, in our study [3] the mean ammonia plasma levels associated with OHE were lower in patients with concomitant infection/inflammation than in those without infection.

We would like to emphasize the importance of actively searching for infections, even if not clinically evident, in any cirrhotic patient with cognitive impairment.

Conflict of interest

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Partial hepatectomy *vs.* transcatheter arterial chemoembolization for resectable multiple hepatocellular carcinoma beyond Milan criteria: A RCT

To the Editor:

Yin and colleagues are to be congratulated on having performed an RCT in such a challenging study population [1]. The results are strongly supportive of surgery in preference to transarterial chemoembolization (TACE), in patients beyond Milan criteria at BCLC B. But, the findings must be viewed with caution before a similar approach is pursued in different patient populations. Firstly, the disease aetiology was almost exclusively due to chronic hepatitis B infection. A recent UK study showed that 70% of cases of HCC were due to alcoholic liver disease, fatty liver disease, and cryptogenic disease, so the patient groups between geographical locations are clearly very different and thus not comparable. Furthermore, the mean age in the far eastern population was 52 and 54 years for the partial hepatectomy patients and TACE patients, respectively. This compares with a median age of 69.9 years in the study from the Newcastle group [2]. Excluding patients 70 years or older is likely to have introduced a selection bias to the study, since older patients are more likely to have significant co-morbidities that would preclude major liver resection. The normal platelet counts may also hint at low levels of significant portal hypertension, which is known to be associated with poorer outcomes following partial hepatectomy. Moreover, 22% of the surgical patients and 13% of the TACE patients were not cirrhotic, but for those patients who were cirrhotic, more Child-Pugh B patients were in the TACE group (although this approached, but did not reach statistical significance). Finally, the authors highlight the poorer than anticipated outcomes from TACE and the lack of access to drug eluted beads [3–6]. The lack of access to these treatments is understandable, but the questions remain: "Would the outcomes have been different had this been available"? In summary, the fact that Yin and colleagues were able to perform and complete this study is a major achievement, but due to the understandable difficulties in the methodology, it would be too early to suggest that BCLC B patients outside Milan should be offered surgery before TACE.

Conflict of interest

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