Reply to: "The importance of prognostic factors in cirrhosis"

To the Editor:
We appreciate the interest of Dr. Thalheimer and Dr. Burroughs in our study [1]. It is true that the baseline characteristics of our patients showed a slightly greater percentage of previous spontaneous bacterial peritonitis, variceal bleeding, and hepatocellular carcinoma in the saline arm, but without significant differences. We agree that the presence of renal failure in the saline group could be a confounding factor that might help explain the differences in survival between both groups. However, the MELD score, used to predict survival, had no differences in both arms.

The findings in survival were, as is reflected in the article, a secondary endpoint. The study was not designed to evaluate mortality. Nevertheless, we thought that the results had sufficient clinical relevance to be highlighted. The development of hepatic encephalopathy in advanced cirrhosis has been related to a worse prognosis and high mortality [2]. It is possible that the presence of hepatic encephalopathy identifies a group of patients that can benefit from the administration of albumin.

We agree that the hypothesis should be tested in subsequent studies with an adequate design and optimized sample size to accomplish this goal. The current study sets the basis for exploring the value of albumin in advanced cirrhosis identified by the development of hepatic encephalopathy.

Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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Macarena Simón-Talero*
Liver Unit, Department of Internal Medicine, Hospital Universitari Vall d'Hebron, Institut de Recerca (VHIR), Universitat Autònoma de Barcelona, Barcelona, Spain
*Corresponding author.
E-mail address: msimon@vhebron.net

Rafael Esteban
Juan Córdoba
Liver Unit, Department of Internal Medicine, Hospital Universitari Vall d'Hebron, Institut de Recerca (VHIR), Universitat Autònoma de Barcelona, Barcelona, Spain
Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), Instituto de Salud Carlos III, Madrid, Spain

Fatigue and liver transplantation in patients with primary biliary cirrhosis

To the Editor:
We read with great interest the paper of Carbone *et al.* [1] on fatigue in patients with primary biliary cirrhosis (PBC) and the role of liver transplantation. They performed a prospective, longitudinal study investigating fatigue in 49 adult cirrhotic patients with PBC at listing and at 6, 12, and 24 months after transplantation. They found that fatigue scores, as assessed by means of the PBC-40 questionnaire, improved substantially following transplantation but remained higher compared to community controls two years post-transplant [1]. In all, 89% of patients had moderate to severe fatigue before transplantation, which was also true for 48% and 44% at one and two years post-transplant respectively [1].

We have recently reported that although fatigue improves following transplantation in unselected cirrhotic patients, 37% are physically fatigued 1 year post-transplant [2], which is in accordance with previous studies [3,4]. In this prospective longitudinal study [2] no patients with hepatic encephalopathy grade >I were included as they could not complete the study questionnaires. Encephalopathy was assessed clinically (West-Haven criteria) and by means of the number connection tests A and B [2]. We found that fatigue severity in unselected cirrhotic patients worsened with worsening encephalopathy (from none to minimal and overt) [2]. Only 12 patients included in this paper had PBC (median age 54 (interquartile range 39–60); 9 female) and 10 reached 1 year post-transplant (1 patient died on the transplant list and another during the first post-transplant year). Fatigue was assessed by means of the fatigue impact scale, a 40-item questionnaire, which has been validated in PBC [5]. Fatigue data from these patients (not reported separately in the initial report) in comparison to non-PBC cirrhotic patients are shown in Table 1. Fatigue scores across all domains did not differ significantly between the two groups neither pre- nor post-transplant

Table 1. Fatigue scores at pre-transplant evaluation and 12 months following liver transplantation in patients with cirrhosis due to PBC and those with cirrhosis without PBC.

	Pre-transplant			One-year post-transplant		
	PBC (n = 12)	non-PBC (n = 96)	*p* value	PBC (n = 10)	non-PBC (n = 50)	*p* value
Physical FIS score	18 (15-24)	22 (10-29)	0.434	12 (0-21)[a]	11 (0-39)[e]	0.729
Psychosocial FIS score	37 (29-48)	31 (13-48)	0.609	14 (1-31)[b]	12 (1-23)[e]	0.817
Cognitive FIS score	19 (7-24)	15 (4-23)	0.609	5 (0-14)[c]	4 (0-16)[e]	0.908
Total FIS score	75 (61-93)	65 (29-101)	0.759	40 (1-64)[d]	30 (2-77)[e]	0.729

Data are presented as median (interquartile range).
FIS, fatigue impact scale.
The *p* values of Mann-Whitney tests are reported in the table.
[a]$p = 0.092$ *vs.* pre-transplant.
[b]$p = 0.114$ *vs.* pre-transplant.
[c]$p = 0.021$ *vs.* pre-transplant.
[d]$p = 0.047$ *vs.* pre-transplant.
[e]$p < 0.05$ *vs.* pre-transplant (related-samples Wilcoxon signed rank test).

(Table 1). All domain and total fatigue scores improved in both groups at 1 year post-transplant, but in the PBC group, this was mainly due to an improvement in the cognitive fatigue domain score (Table 1). Carbone and colleagues also found that the cognitive domain of the PBC-40 improved post-transplant [1], which may have been due to an improvement in hepatic encephalopathy. Although they identified two patients with moderate encephalopathy (both with severe fatigue one of whom improved post-transplant), there was no formal assessment of (minimal) hepatic encephalopathy. This is surprising as encephalopathy in patients with cirrhosis is a well-known cause of lethargy and fatigue. It is also unclear whether any patients were excluded due to inability to fill in the study questionnaire as a result of hepatic encephalopathy [1]. As the authors argue, fatigue severity may not be related to non-cirrhotic PBC severity at a group level [1] but it appears to be related to liver disease severity in cirrhosis in general [2]. Also, our data showing that improvement in fatigue post-transplant in PBC patients was attributed mainly to improvement in cognitive fatigue, and the fact that the two patients with moderate encephalopathy in the current study had severe fatigue with one improving post-transplant [1], indicate that encephalopathy could be an important factor leading to fatigue at least for some cirrhotic patients with PBC.

In line with our findings in the whole cirrhotic cohort [1], we found that physical fatigue scores of PBC patients also improved but this failed to reach statistical significance (Table 1). In all, 5 out of 12 PBC patients (42%) had significant physical fatigue (physical fatigue scores >2 SD of controls) at pretransplant evaluation, which was also true in 3/10 (30%) of PBC patients and 37% of all cirrhotic patients [1] at 1 year post-transplant. Two out of 4 physically fatigued PBC patients pretransplant who survived 1 year following transplantation continued to be physically fatigued post-transplant (50%) compared to 46% in the whole cirrhotic cohort [1]. Out of 6 PBC patients without significant physical fatigue pre-transplant who survived 1 year following transplantation, 1 (17%) developed significant physical fatigue post-transplant, compared to 22% in the whole cirrhotic cohort [1]. Thus, persistent fatigue following liver transplantation does not appear to be characteristic of PBC and a certain proportion of PBC and non-PBC cirrhotic patients appear to develop physical fatigue post-transplant [1–4]. The latter suggests that unidentified transplantation-related factors may be of importance for post-transplant fatigue in general. It is unclear, in the cohort of Carbone and colleagues [1] whether any patients developed fatigue *de novo* after transplantation.

In conclusion, taken together our findings and those of Carbone and colleagues [1] indicate that fatigue remains a problem following liver transplantation in cirrhotic patients with PBC as well as in patients transplanted for other indications. Some patients appear to develop physical fatigue post-transplant while persistent fatigue following liver transplantation does not appear to be characteristic of PBC as it is also noted in patients with cirrhosis transplanted for other indications. Hepatic encephalopathy could be of importance for fatigue in these patients pre-transplant and it would be important to include assessment of encephalopathy by appropriate testing in future studies.

Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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Evangelos Kalaitzakis*
Department of Gastroenterology, Skåne University Hospital, University of Lund, Lund, Sweden
*Corresponding author.
E-mail addresses: evangelos.kalaitzakis@medicine.gu.se, kalvag@hotmail.com

Einar Björnsson
Department of Gastroenterology and Hepatology, Landspitali University Hospital, Reykjavik, Iceland

Reply to: "Fatigue and liver transplantation in patients with primary biliary cirrhosis"

To the Editor:

We would like to thank Kalaitzakis *et al.* [1] for the comments on our article on the effect of liver transplantation (LT) on fatigue in patients with primary biliary cirrhosis (PBC) [2]. They confirm in an independent PBC cohort that fatigue remains a problem after LT. They also address some important issues, such as the need for an accurate assessment of hepatic encephalopathy (HE) before LT in patients with PBC, and that fatigue may not be specific to PBC.

Kalaitzakis *et al.* [1] showed that fatigue improved after LT although fatigue scores remained higher than in controls from the general population. Of note, they found that the median fatigue impact score (FIS) after LT was 40, which is identical to the median FIS in a non-transplant PBC cohort, reported by Goldblatt *et al.* [3]. In our study [2] fatigue score, assessed using the PBC-40, was 26 ± 10 at two years after LT, which was lower compared to a 'non transplant' PBC control cohort (31 ± 12; $p = 0.03$); however, the fatigue score was higher than a 'normal' age- and sex-matched control group (18 ± 6; $p < 0.0001$).

The work of Kalaitzakis *et al.*, along with our data, casts some light on the pathophysiology of fatigue, as they suggest the abnormalities that result in fatigue are either irreversible or that they do not arise in the affected liver. These findings also are helpful in identifying the role of transplantation in symptomatic patients with PBC.

Chronic fatigue is a feature of HE and the relationship between fatigue and HE in patients with PBC and other chronic liver conditions is complex and not fully understood. Emerging data suggest that continued cognitive impairment post-transplant is seen in particularly in patients with recurrent encephalopathy pre-transplant. This suggests that the neuropsychiatric abnormalities of encephalopathy, as the fatigue of PBC, do not fully revert post-transplant [4]. Larger, longitudinal studies are required to address this issue.

In the Birmingham liver unit, HE is routinely assessed using the Number Connection Test and graded clinically from 0–4 (West Haven criteria). In our study no patient was excluded because of overt HE. In the final cohort analyzed, only two had clinically evident HE who had grade 2 HE before LT. In one patient the fatigue persisted after transplant with the same severity (PBC-40 score of 45 and 46, before and two-years after LT). In the other, the fatigue improved but remained of moderate severity (falling from 46 before transplant to 30 two-years after LT). Therefore we do not believe the high fatigue scores before LT were suggestive of HE-related fatigue. Furthermore, we did not find any correlation between the severity of the liver disease and the severity of the fatigue, in keeping with previous literature. Minimal HE can only be determined by a comprehensive neurological assessment of consciousness, cognitive, and motor function and this has not been part of our routine pre-transplant assessment.

Kalaitzakis *et al.* have shown the persistence of fatigue after LT in those with other indications. However, data from more than half of the patients was excluded from the final analysis. As suggested by Kalaitzakis *et al.* unidentified transplantation-related factors may be relevant for post-transplant fatigue. However, as shown in Fig. 3 of our paper [2], no patient developed fatigue *de novo* after transplantation.

Further studies are needed to establish if the changes seen here are unique to PBC and to identify the mechanisms responsible for this symptom, and so develop appropriate treatments.

Conflict of interest

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