

WJG 34460.R1 Response to Reviewers

To reinforce their interesting data, Authors are suggested that they should present data on the severity of patients suffering from liver cirrhosis using modern criteria of the Child-Pugh classification as evidenced in....What are the implications of the spontaneous spleno-renal shunts in liver cirrhosis? BMC Gastroenterol. 2009 Nov 24;9:89. and....Blood ammonia levels in liver cirrhosis: a clue for the presence of portosystemic collateral veins. BMC Gastroenterol. 2009 Mar 17;9:21. Finally, Authors should highlight that the low adherence is probably linked to the perception that all in all the therapy for the advanced stages of liver cirrhosis is ineffective or at the best palliative, prolonging only the survival time, not necessarily in good health conditions (think about depression). A hope could lie, unfortunately only for virus-linked cirrhosis, on the use of new antivirals to prevent serious complications if prescribed on early stages.

The 'slightly modified' Child-Pugh classification suggested by the reviewer is not used at our centre. Grade of encephalopathy and ascites at recruitment was determined by the reviewing hepatologist and thus it is not possible to retrospectively re-grade these using suggested definitions. Furthermore, PT % of activity is not routinely reported by our pathology service and thus INR is the coagulation parameter used at our site for CTP score calculation.

We agree that some patients perceive that therapy for advanced liver disease is largely palliative and this may be linked with lower levels of adherence. This is possibly reflected by the relationship between 'Low' adherence and lower patient perception of treatment helpfulness in terminal stages (Treatment Control, Table 3) and stronger concerns relative to necessity medication beliefs (Table 2). However, all patients in this study were essentially palliative at review as they were ineligible for OLT, any many had positive perceptions of treatment helpfulness and a high Necessity-Concerns differential. We have expanded upon potential changes to patients' beliefs and perceptions in palliative stages of illness in the discussion (page 15, line 406 to 421).

We share the reviewer's postulation regarding "hope" and the use of new antivirals in patients with HCV. This group (n=35) perceived that their liver disease would last for a shorter duration of time compared to non-HCV patients (p=0.010), despite the possibility of persisting complications of cirrhosis after HCV DAA therapy. Having HCV or low Brief IPQ-Timeline scores were not associated with medication adherence. We have expanded on the relationship between HCV and illness perceptions on page 12 to 13, line 340 to 349, and elaborated upon this in the discussion within the context of symptom control and disease impact on quality of life (page 15 to 16, line 422 to 442).

A more clear information about the relationship between the response to questionnaires and some patients' characteristics need to be better explained in the manuscript. In particular the association between stage of cirrhosis (child), aetiology, age, gender and level of education with the level of adherence. also the expectation of life (OLT vs non-OLT) and the influence of concomitant chronic comorbidities should be investigated.

As shown in Table 1, patient age (p=0.787), aetiology of liver disease (all p>0.05), disease severity in terms of Child-Pugh score (p=0.684) and MELD score (p=0.936), level of education (p=0.215), employment status (p=0.602) and sociodemographic status (all p>0.05) were not associated with medication adherence. Male gender was associated with lower levels of adherence (p=0.015) however this variable did not predict 'Low' adherence on bivariate analysis (Table 5). Least absolute shrinkage and selection operator (LASSO) and stepwise backwards regression techniques did not

identify any clinical or demographic variable to have significant impact on adherence and thus these were not included in the final multivariable regression model.

As all patients enrolled in the study were ineligible for OLT at recruitment, we have used the presence of primary liver cancer (HCC) as a proxy expectation of life measure. The association between adherence and the presence of HCC was not significant (neither was the presence of any cancer, data not shown). We have now included the presence of HCC and the number of comorbidities in Table 1. We have also elaborated on the relationship between patients' medication beliefs, illness perceptions and relevant clinical / demographic variables throughout the manuscript (pages 6 to 7, line 327 to 332, line 340 to 349, and line 359 to 372).

The study is interesting and scientific. However, it should be better and more convincing if selection bias could be eliminated. Moreover, the discussions of results are too simple.

We agree that there is selection bias in our sample, and have elaborated on this further within the limitations section of the manuscript (page 17, line 469 to 477). We have also expanded the discussion section to further elaborate on the possible link between 'Low' adherence and perceptions of palliative disease management, perceptions of symptom control and impact on quality of life (page 14 to 16, line 397 to 442).

To the Editor,

Author addresses have been corrected with post codes, as requested. The Scientific Research Process report has also been adapted to the preferred format (separate document).