Author’s response to reviews

Title: White cell count and platelet count associate with histological alcoholic hepatitis in jaundiced harmful drinkers

Authors:

Timothy Hardy (timothy.hardy@ncl.ac.uk)
Christopher Wells (chris.wells@nth.nhs.uk)
Stuart Kendrick (stuart.kendrick@ncl.ac.uk)
Mark Hudson (Mark.Hudson@nuth.nhs.uk)
Christopher P Day (Chris.day@ncl.ac.uk)
Alistair Burt (alistair.burt@ncl.ac.uk)
Steven Masson (steven.masson@nuth.nhs.uk)
Stephen F Stewart (sstewart@mater.ie)

Version: 3 Date: 19 December 2012

Author’s response to reviews: see over
Re-submission date: 19.12.12

Address to Editor-in-Chief:
BCM Gastroenterology

Dear Sir/Madam,

We would like to thank both reviewers for their insightful critique of our paper; we will respond to them in turn.

Reviewer 1:

Major comments

1. The authors need to include in the references and to discuss the recent published EASL Clinical Practical Guidelines on Alcoholic Liver Disease [J Hepatol 2012;57:399-420]

We have added:

‘...and this is reflected in practice guidelines where precise indications for liver biopsy are not well established [16,17,18]. Recent EASL Guidance recognises that many centers rely on clinical criteria, and do not consider biopsy as routine practise. However, the guidance includes biopsy in the therapeutic algorithm and recommend that it should be considered in high risk patients according to prognostic assessment with Maddrey’s discriminant function for example [18].’

‘Had the group not undergone biopsy, 25% (n=15) of the total number would have undergone specific treatment without having the clinical condition the treatment was specifically targeted to. This supports the conclusions of the EASL guidance for the use of liver biopsy in the setting of alcoholic hepatitis.’

2. The authors need to provide all details on histological analysis on overall patients: a/What are the histological features for patients without biopsy-proven alcoholic hepatitis? b/ What are the histological features of patients with biopsy-proven alcoholic hepatitis? Do the pathologist use a histological grading of severity of alcoholic hepatitis in terms of hepatocyte ballooning and of
inflammatory infiltrate?

We have added an extra table (Table 2) Our pathologist didn’t use a grading of severity in terms of hepatocyte ballooning.

3. Although the presence of Mallory-Denk’s bodie is not considered as necessary, it would be interesting to specify the percentage of patients disclosing this histological feature.

This has been added into Table 2

4. The authors state on page 7: “There was no difference in the mean age, Child’s score, DF, prothrombin time or serum concentrations of creatinine, bilirubin, albumin, alkaline phosphatase and alanine transaminase between the group with histological alcoholic hepatitis and those without.” This sentence is inaccurate when considering the limited sample size. As an example, the lack of significance for bilirubin (431 vs 307 μmol/l) is probably attributed to a type II error consisting in the failure to reject a false null hypothesis.

This statement has been withdrawn.

5. In table 1, p values need to be provided for all comparisons including the non significant.

P values where stated as NS have been amended.

6. The authors need to clearly discuss their results in terms of the use of liver biopsy in the setting of trials. How can we accept the possibility of 25% of false inclusions if we are testing therapy with an expect impact of 20-30% in terms of
short-term survival? I suggest emphasizing this point in the conclusion of the
abstract, as well. This is a crucial point for the development of future therapies
aiming to improve the outcome of patients suffering from this life-threatening
disease.

We have added

‘Our results suggest that in future clinical trials where biopsy is not mandated, 25% of patients may be falsely
included. This clearly has implications for the validity and reliability of data testing specific therapies in patients
who may not suffer from the disease they are targeted to; this is reflected in the EASL Clinical Practise Guideline
in Alcohol whereby performing liver biopsy prior to trial commencement is recommended.’

Abstract:

‘This is critically important when deciding on specific therapies such as corticosteroids and interpretation of data
from future trials where biopsy is not mandated’
Reviewer 2:

Major compulsory revisions:

1. ASAT (GOT) values are not reported - thus is very unusual given alcoholic liver disease is investigated.

2. A logistic regression model using ASAT as a conventional activity marker as a baseline model +/- platelet count and the appropriate backward selection models should be used to formally look for the superiority of either (also WBC and platelet count parameters)

Unfortunately, at the time of entry into the original study AST was not routinely measured at our hospital. We therefore cannot (a) provide values for AST and (b) cannot provide a logistic regression model using AST.

3. Only scarce information on the histological severity is available: one could for instance do a direct pair-wise correlation analysis of histological inflammation versus clinical predictors and look for groups based on histological inflammation grade etc.

We did not score the liver biopsies according to the severity of histological alcoholic hepatitis; just whether it was present or not. To stratify the group with proven alcoholic hepatitis into sub-groups and then compare them would leave us with very small numbers in each group. In addition, given that there is no statistically significant difference between those with and without histological features, we feel that it will not change the main message of the paper; that the major laboratory markers of liver dysfunction are inadequate at determining which patients have alcoholic hepatitis on biopsy.

4. What about fibrosis: do patients with histological fibrosis also show this pattern of laboratory abnormalities?

This is a very good point, which we neglected to mention in the original paper. We have fibrosis scores for each of the patients. We have now analyzed these and found interesting results, which we now present and interpret. We have now included the sections below and Table 2 and Table 3.
‘Fishers exact test was non significant (p=0.08) in determining an association between fibrosis stage and presence of AH on biopsy. Only WCC remained statistically significant (p=0.0084) when groups were analysed according to fibrosis stage.’

‘The majority of the patients in our study were cirrhotic 50/58 (86%). As expected, all 15 of the patients that were found to not have alcoholic hepatitis on liver biopsy were cirrhotic. These are the patients that progressed to decompensation due to very advanced liver disease rather than superimposed hepatitis. 8/44 patients with AH were non-cirrhotic; all of these were F3. When we compared laboratory indices between the cirrhotic patients and the non-cirrhotic patients we found the only statistically significant finding to be the difference in average WCC. This is largely due to the fact that the F4 cohort contained all the patients that did not have histological alcoholic hepatitis.’

Minor: multiple small typos, missing spaces etc.

We have made every attempt to correct any typos or missing spaces.

Sincerely,

**Corresponding author**

Dr. Stephen F Stewart
The Centre for Liver Disease
Mater Misericordiae University Hospital
55 Eccles Street
Dublin 7
Ireland
Email: sstewart@mater.ie
Tel- 0035318032048