Response to Reviewer 1 Comments

Point 1: Unfortunately, the authors do not give any information about the status of the liver disease. Especially, it is not known if there are patients with cirrhosis included and if there are patients with cirrhosis how many patients at what stage of cirrhosis are included.

Response 1: We agree with the reviewer's opinion. In order to assess the liver status of the patients, histopathology data (n = 93) were added to the analysis (Table 1 and Supplementary Table 2.). To compare the liver status of various etiology, we used the fibrosis and activity stage based on the New Inuyama Classification. Moreover, we added and analyzed the data of 52 patients who underwent liver stiffness measurement examination by transient elastography performed within one year. These examinations were added in the section *2.5.* of **Material and Methods** (in page 3, line 152). The analysis data of correlation between the liver status and GHQ scores or arginase-1 were added in Table 3.

We diagnosed liver cirrhosis based on liver biopsy and liver stiffness measurement. Four patients were histologically confirmed cirrhosis (F4) and 5 patients had liver stiffness measurement more than 12.5 kPa, which is the standard value for the diagnosis of cirrhosis [Castéra L et al., Gastroenterology 2005]. Since one patient met both of criteria, a total of 8 patients could be diagnosed as cirrhosis. These results were mentioned in **Results** section in page 4, line 387. In addition, 3 more patients were diagnosed as suspected cirrhosis if any one of the following criteria was met; PT% less than 70% or albumin concentration less than 3.5 g/dL, or total bilirubin concentration more than 2 mg/dL (more than 4 mg/dL for PBC), or platelet count less than 100,000 /μL. Since we did not confirm the presence of hepatic encephalopathy and ascites, it was not a correct assessment, but in total 11 patients were thought to be suspected cirrhosis in this study.

When we compared the two groups (11 cirrhosis or suspected cirrhosis group and others group) statistically, there was no significant differences for arginase-1 and GHQ-scores. This data is not shown because Child-Pugh classification was not fully calculated, but we added these explanations in the section of **Discussion** in page 7, line 1133.

Point 2: It is known that cirrhosis of the liver impairs the mental status due to hepatic encephalopathy. There are established tests to check for even subclinical encephalopathy and it would be of interest if These tests actually correlate with the plasma levels of Arginase 1 and the health questionnaire.

Response 2: We were unable to analyze the association of GHQ socore or arginase-1 with hepatic encephalopathy because lack of evaluation in this study. However, considering that all outpatients were examined by two hepatologists, wrote a statement of understanding and consent for the study, and answered the GHQ questionnaire, they did not have at least overt hepatic encephalopathy. Hence, the patients could be considered as either subclinical hepatic encephalopathy or normal. As you pointed out, the relationship between subclinical encephalopathy and arginase-1 is an important topic. Therefore, I would like to discuss in the future, and it may be related to GHQ. In fact, various mental health questionnaires have been tested for screening subclinical encephalopathy [Koziarska et al. BMC Gastroenterology 2013]. I have added these explanations in the section of **Discussion** in page 7, line 1126.

Point 3: Related questions would be: Is there a correlation to the fibrosis; is there a correlation to disease activity, duration of disease ,treatments of the disease?

Response 3: The results of Table 3 showed that the fibrosis stage and liver stiffness measurement did not significantly correlated with any score of GHQ nor plasma arginase-1. These results mentioned in page 5, line 683.

As for disease activity, Table 3 showed that there was no significant correlation between activity stage of liver biopsy and arginase-1 nor GHQ score. We also did not find significant correlation arginase-1 nor GHQ score with ALT, which are representative enzymes of liver injury.

We are unable to comment on the relationship between arginase-1 or GHQ score and duration or treatment of liver disease in this study, as further data tracking is needed. In other literature, these factors have been found to affect the mental status and quality of life of patients with chronic liver disease [Kleinman L et al., Health Qual Life Outcomes 2012; Stewart SM et al., Pediatrics. 1988], and studies including investigation of the relationship with arginase-1 are desirable, as reviewer described.

Point 4: In order to make this study valuable an analysis of cirrhotic patients and encephalopathy should be included and discussed.

Response 4: As I already mentioned in **response 1**, the analysis and discussion about cirrhotic patients and hepatic encephalopathy were mentioned in the section of **Discussion**, in page 7, line 1117.