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Dear reviewers,

Thank you for revision.

All corrections were performed

REVIEWER 1

The idea of the study is good and interesting, however it should be clearly stated the message from this study regarding only to show the relation of folate metabolism gene. What is the impact in clinical practice? Why folate metabolism gene is very important other than possible factor?

Answer:

Dear Reviewer, we add a paragraph showing the importance of folate metabolism in the clinical practice:

"As much as HCC is a very aggressive disease and discovered in the late stage in which the treatment chances are decreased is important research molecular biomarkers related to disease development. Thus, early diagnosis based on the detection of specific biomarkers such as polymorphisms in genes involved in the folate pathway is important. Once folate metabolism is associated to control of gene expression, genomic stability and regulation of chromatin structure and thus cell growth. The presence of gene polymorphisms involved in the pathway of folate may cause an uncontrolled cell cycle and lead to cancer."

REVIEWER 2

Dear colleagues, Your manuscript "Polymorphisms of folate metabolism genes in patients with cirrhosis and Hepatocellular Carcinoma" is an interesting study touches upon actual field of Hepatology. Manuscript should be accepted after minor revision. My remarks are following: ? Consideration of alcohol consumers, as "those who drink more than 4 drinks weekly, corresponding 30 mL of liquor, 102 mL of wine, and 340 mL of beer" is could be point of speculation. Current definitions "safe drinking" depend on gender and age, consumption during the meal, "binge drinking" etc. are more appropriate, than term "alcohol consumers" ?

ANSWER: Dear rewiever, we changed the "alcohol consumers" to "Binge drinking"

In paragraph "Statistical analysis" you mentioned, that the association between the clinical parameters (as far as I understand, besides clinical stages by BCLC also alpha fetoprotein, hepatitis B and C, diabetes mellitus and death) and polymorphisms with HCC development were also analysed by multiple logistic regression. But in "Results" paragraph there is not precise information about influence of all clinical parameters by results of multiple logistic regression, just one sentences "There was no association in the multiple logistic regression analysis of the analysed clinical parameters and polymorphisms in patients with HCC stratified into tumours in stages 0 and A, and tumours in stages B, C and D, according to the BCLC criteria" with Table 6. It will be better to noticed results of multiple regression with alpha fetoprotein, hepatitis B and C, diabetes mellitus and death in separate sentences or table. ?

Answer: Dear reviewer, we noticed results of multiple regression with alpha fetoprotein, hepatitis B and C, diabetes mellitus and death in table 6

In “Discussion” paragraph data of two studies (Varela et al. and Raphe et al.) about prevalence of different stages of HCC according to BCLC is meaningless. Thank you for understanding. Best regards

Answer: Dear reviewer, we changed the paragraph. Thank you :

“Our data showed that 7% of patients in stage 0, 29.6% in stage A, 22.5% in stage B, 31% in stage C and 9.8% in stage D according the study of Raphe et al. that reported that 32.7% were in stage A, 22% in stage B, 30.4% in stage C, and 14% in stage D. [40] The study of Varela et al., 2010 reported that 49.8% of 705 cases were in the initial stage (A), different of our results and 19.8% in the intermediate stage (B), 18.8% in the advanced stage (C) that also different of our findings and 11.6% in the terminal phase (D) as our results [25]. Regarding the alpha fetoprotein, hepatitis B and C, diabetes mellitus and death we found a positive association between patients in advanced stage (B,C and D) and death as current published that show that patients who are in stage A are asymptomatic and have preserved liver function have a 5-year survival of 50-75%. Patients who are in stage B have a median survival of 20 months; those who are already in the C and D stages have severe liver dysfunction and extrahepatic metastases reach an 11-month survival, and only 10% of patients in the D stage survive more than a year with an average survival of 3-4 months [26].”