

Answering reviewers

January 22 2015

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 15801-review.doc).

**Title:** Prognostic factors of spontaneously ruptured hepatocellular carcinoma

**Author:** Xiang-Jun Han, Hong-Ying Su, Hai-Bo Shao, Ke Xu

**Name of Journal:** *World Journal of Gastroenterology*

**ESPS Manuscript NO:** 15801

The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

(1) what is the cut off value for size? Should a ROC curve be done for that?  
(Revised in Methods, Results and Discussion)

Our result revealed that the size of ruptured tumor was a predictor to poor survival, and the 30-day mortality has been reported in the range of 30%-70%, so we conducted ROC analysis to identify the cut-off value for tumor size in patient with HCC rupture, and the parameter was whether the patients survival for 30 days or not. We revealed that the cut-off point for tumor size was 8.85 cm for 30-day mortality of HCC rupture patients, and the AUC was 0.813 ( $P < 0.001$ ), the sensitivity and specificity were 81.8% and 78.9%.

(2) English review should be performed in advance

For we are non-native speakers of English, so our manuscript was revised by the English language editing company- American Journal Experts

(3) why the presence of cirrhosis was not associated with a poor outcome? What are the bias involved and how should you proceed when facing such a scenario?

(Revised in Discussion)

Our result revealed that the presence of cirrhosis was associated with the poor survival in univariate analysis, but multivariate analysis showed that it was not an independent predictor. From our perspective there are two reasons. First the number of sample was small, and this small sample size

may produce bias. Second the presence of cirrhosis may affect the hepatic function, and we conducted the independent samples T test to reveal that the presence of cirrhosis was associated with lower ALB (28.4g/L VS 34.8 g/L,  $P<0.01$ ), higher Tbil (33.6 $\mu$ mol/L VS 19.6 $\mu$ mol/L,  $P<0.01$ ), but not associated with ALT (109 U/L VS 157 U/L,  $P=0.332$ ). So the parameters in multivariate analysis included ALB, Tbil and cirrhosis may produce bias, but they are the necessary parameters in our research. When facing such a scenario, large samples maybe helpful, if not necessary do not put the related parameters into multivariate analysis.

(4) The anti-tumor therapies before HCC rupture are variable. Does specific treatment play roles on prediction of HCC rupture?

(Revised in Discussion)

The anti-tumor therapies before HCC rupture in our cases included 19 TACE, 2 surgical treatments, 2 radiofrequency ablations, 2 TACE combined with oxaliplatin chemotherapy, and 1 TACE combined with sorafenib. Because the number of patients who underwent surgical treatment, radiofrequency, TACE combined with oxaliplatin or sorafenib is too small, they were counted as a variable to make analysis.

(5) The multivariate analysis showed that the HR of ALT was 1.00 with  $P < 0.05$ . This result is quite hard to understand. For some other factors such as WBC, the HR was very closed to 1, the clinical significance is limited, although the statistic significance is detected. This should be discussed.

(Revised in Discussion)

The HR of ALT was actually 1.003, our manuscript kept two decimal points and the HR of ALT was written as 1.00. In our result, the WBC was not an independent factor ( $P=0.375$ ), but four factors with statistic significance and limited clinical significance were Age, ALT, ALB, and  $\text{HCO}_3^-$ . The HR of age is similar to other studies. The library data such as ALT, ALB, and  $\text{HCO}_3^-$  can be easily and artificially corrected during the medical therapy, but other factors such as BCLC stage, treatment before rupture, and treatment after rupture can not be immediately changed. So factors such as ALT, the HR is close to 1, although the statistic significance is detected, the clinical significance is limited.

(6) The language should be extensively polished since there are lots of grammatical errors.

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3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

A handwritten signature in black ink, consisting of stylized Chinese characters, likely '徐克' (Xu Ke).

Ke Xu, Ph.D

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