Author’s response to reviews

Title: The Glasgow Prognostic Score, an inflammation based prognostic score, predicts survival in patients with hepatocellular carcinoma.

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Version: 3 Date: 28 November 2012

Author’s response to reviews:

Dear Dr. Christna Chap Nov 28, 2012

We greatly appreciate your suggestions. The following are our response to the suggestions and a description of the changes to the manuscript.

Answers to reviewer 1 (Ioannis Gioulbasanis):

Major Compulsory Revisions.

According to your suggestion, we performed a multivariate analysis evaluating each score (GPS and mGPS) at a time. The results are same.

Minor Essential Revisions.

1. According to your suggestion, we used the terms “GPS”, “mGPS” throughout the text.

2. According to your suggestion, we added the sentence “It was based on the observation that hypoalbuminaemia without an elevated CRP concentration was rare and that hypoalbuminaemia on its own was not associated with poor survival.”(Page5, line17) And we omitted the sentence “it had greater consistency and was more generally applicable”

3. According to your suggestion, we added some explanation on page 9, line 13.” We presumed that it is of importance to evaluate prognosis in patients with curative or non-curative treatment separately in an attempt to minimize the impact of different treatment modalities in the process of evaluating the prognostic model.”
4. According to your suggestion, we added a box plot indicating the distribution of CRP and albumin in the GPS and mGPS groups (Figure 1a, b).

5. According to your suggestion, we reported the number of patients received systemic therapy. (Page12, line3)

6. According to your suggestion, we added mGPS classification. (Table 2)

7. According to your suggestion, we omitted the direct correlations of these laboratory values (CRP, albumin).

8. According to your suggestion, we corrected the sentences. (Page13, line5-9)

9. According to your suggestion, we removed albumin and CRP from multivariate analysis. The results are same. Moreover, we added an explanation of the findings on page 15, line 2. “Due to the correlation between CRP, albumin and GPS and between GPS and mGPS, variables (AST, total serum bilirubin, Plt, AFP, GPS, CLIP score, JIS score, BCLC score, TNM stage, maximal tumor diameter, multiple nodules, vascular invasion and extrahepatic metastasis) were tested in multivariate analysis.”

10. According to your suggestion, we omitted the sentence “Moreover, the GPS might identify patients likely to have poor outcomes, allowing for more extensive tumor staging and follow-up and for assessing the need of adjuvant therapy”

11. According to your suggestion, we added “small sample size”. (Page20, line18)

Answers to reviewer 2 (Donald C McMillan):

Minor Essential Revisions.

According to your suggestion, we corrected some spelling mistakes in the supplementary Tables.

Answers to reviewer 3 (Elaine Leung):

Reviewer’s comment: “However, I was a bit confused as to how patients are allocated into curative”

According to your suggestion, we added an explanation of the findings on page 9, line 16. “Therefore, in this study, according to the current EASL-EORTC clinical practice guidelines [17], a curative treatment was defined as aggressive treatment, including surgical resection, RFA, PEI. By contrast, a non-curative treatment was defined as other palliative treatment (TACE, TAI, systemic chemotherapy, sorafenib or BSC).”

Reviewer’s comment: “In addition, I could not find information with regards to how many patients were deemed "curative" and "non-curative" respectively.”

According to your suggestion, we added an explanation of the findings on page 12, line 4. “Seventy seven (51.3%) patients received curative treatment and 73 (48.7%) patients received non-curative treatment.”

Reviewer’s comment: “Multiple statistical tests were used and the possibility of type I error increases significantly.”
As has been indicated by the reviewer, we also believe that consideration must be given to the fact that Type 1 errors increase when multiple statistical testing is carried out. However, the final conclusion was based on the results of analyzing the relation between the GPS and prognosis upon multivariate analysis. We simply set the level of significance upon univariate analysis to $P<0.05$ in order to select a variable to use upon multivariate analysis. Accordingly, we believe that an increase in Type 1 errors upon multiple statistical testing affecting the multivariate analysis, which is a concern of the reviewer, is unlikely to occur.

Reviewer’s comment: “In addition, the multivariate analysis did not specify which variables were entered to the analysis. This may mean the authors, for example, combined both mGPS and GPS in the analysis.”

According to your suggestion, we added an explanation of the findings on page 15, line 2. “Due to the correlation between CRP, albumin and GPS and between GPS and mGPS, variables (AST, total serum bilirubin, Plt, AFP, GPS, CLIP score, JIS score, BCLC score, TNM stage, maximal tumor diameter, multiple nodules, vascular invasion and extrahepatic metastasis) were tested in multivariate analysis.”

Reviewer’s comment: “I would suggest the editors or the authors to seek further statistical advice on whether there are any issues with the current analysis (I am afraid this is out of my area of expertise).”

Our manuscript was checked by a statistician (Masato Matsushima, co-author of my manuscript).

Reviewer’s comment: “Please comment on the limitations of the potential confounding relationships between liver function and inflammation. As progressive HCC patients would have poor liver function and reduced albumin, GPS in this group of patient is no longer only a marker of inflammation but also a marker of poorer liver function. What implications do the authors think this will have to their results?”

According to your suggestion, we added some explanation on page 21, line 8. “Fourth, there may be the potential causal relationships between liver function and inflammation. As progressive HCC patients would have poor liver function and reduced albumin, GPS in this group of patient is no longer only a marker of inflammation but also a marker of poorer liver function. However, Cervoni et al. have demonstrated that a systemic inflammation response, as evidenced by an elevated CRP concentration, is associated with poor survival in Child Pugh score > B8 cirrhotic patients independently of Model of End Stage Liver Disease [29]. We also have shown that CRP is an independent marker of poor prognosis in patients with HCC, irrespective of tumor stage and liver function [16].”

Thank you in advance for considering our paper for publication in the BMC Cancer.

Respectfully yours,

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