Author's response to reviews

Title: The prognostic role of preoperative serum albumin levels in glioblastoma patients

Authors:

Sheng Han (hansheng2001_x@aliyun.com)
Yanming Huang (liochristine@hotmail.com)
Zhonghua Li (80682749@qq.com)
Haipei Hou (814597256@qq.com)
Anhua Wu (cmuwuanhua@aliyun.com)

Version: 4
Date: 2 December 2014

Author's response to reviews: see over
Dear Editor:

(Manuscript number: MS: 1558305274141560)

We would like to thank you for giving us the opportunity to revise our manuscript. We have carefully taken reviewer’s comments into consideration in preparing our revision, which resulted in a paper that is clearer and more rigorous. Below is our point-by-point response to reviewer’s comments.

**Response to Reviewer Aaron Mammoser:**

Thanks for your careful review. We have revised our paper according to your comments.

1. As suggested by the reviewer, the inaccurate word “predictive” has been replaced by “prognostic” in the revised paper.

2. We agree with the reviewer that in some of our analyses, the serum albumin levels were actually described as categorical variables, while they were used as continuous variables in the Cox proportional hazards models. As categorical variables, the serum albumin levels were defined as: (0) <30 g/L, (1) ≥30 g/L; or (0) <30 g/L, (1) 30-40 g/L, (2) ≥40 g/L. This information has been added in the revised paper.

3. As suggested by the reviewer, we clarified that the tumor resection status was defined as (0) biopsy or subtotal resection with residual tumor ≥30%, (1) subtotal resection with residual tumor <30%, and (2)
4. We are sincerely sorry to say that, the 1-year and 2-year survival rates had been miscalculated. As presented in Figure 2C and D, in this series of patients the overall 1- and 2-year survival rates were 60.3% (129/214) and 8.9% (19/214), respectively. This error has been corrected in the revised paper. And in patients who completed all of their adjuvant treatment, 2-year survival rate was 19.2% (15/78). Anyway, it was still less than the approximately 27% reported by Stupp et al. Nowadays, there is no established standard regimen for patients progressing after prior radio-chemotherapy, and re-operation, re-irradiation or second-line chemotherapy has been suggested [1]. We think that, the heterogeneity of post-progression salvage treatment may result in the differences of survival rate. This information has been added in the revised paper.

5. The reviewer’s suggestion is very inspiring. And we tried to divide the patients in the partial adjuvant treatment group according to various reasons and serum albumin levels. However, we found that, the reasons why patients stopped adjuvant treatment were very complicated. Although as expected the main reasons were tumor progression, treatment intolerance and bad general status, other reasons (including financial problems, use of traditional Chinese medicine and emotional conditions) also involved, making the
analyses complex and inaccurate. Thus, we are collecting prospective
data to balance interference factors, and in the future study we will
analyze the data as the reviewer suggested.

Response to Reviewer Solmaz Sahebjam:

Thanks for your careful review. We have revised our paper according to
your comments.

1. We agree with the reviewer that tumor specific molecular markers
should be included in the multivariate analysis. For glioma, important
molecular markers include $MGMT$ promoter methylation, $IDH$
mutation and genetic loss on chromosomes $1p/19q$. $MGMT$ status has
been included in the multivariate analysis. However, mutations in the
$IDH$ gene are hallmarks of low-grade glioma, and less than 10% of
individuals with adult glioblastoma carry an $IDH$ mutation $^{[2, 3]}$. In
addition, genetic loss on chromosomes $1p/19q$ is more frequently
found in oligodendrogliomas and less than 5% in glioblastoma $^{[1]}$. In
this study, all the subjects were glioblastoma patients. Thus, $IDH$
mutation and genetic loss on chromosomes $1p/19q$ were not included.

2. We agree with the reviewer that the lack of serial dynamic serum
albumin levels is a limitation of this study, and we discussed this
limitation in the revised paper. However, studies of preoperative serum
prognostic markers are still clinically relevant and significant, which
may guide treatment and researches $^{[4, 5]}$. Moreover, since preoperative
albumin levels are not affected by medical interventions such as surgery, they are more objective and accurate. In this study, serum albumin levels were measured after an overnight fast before medical intervention as we described in the paper, therefore, the measurement was not interfered by the steroids. The reviewer’s suggestion of including ESR and CRP is very inspiring. However, for glioma patients, ESR and CRP were not commonly measured before surgery in our hospital. Thus, this information is unavailable in this retrospective study. In future prospective studies, we will include these factors.

3. The reviewer’s suggestion of including IL-6 levels is also very interesting. Again, IL-6 was not commonly measured before surgery in our hospital. Thus, the serum IL-6 levels are unavailable to us. Nevertheless, the objective of this study is to explore the prognostic role of preoperative serum albumin levels and to propose possible underlying mechanism using clinically available data. Further mechanism researches investigating the interaction among albumin, IGFBP-2 and IL-6 will be done in future studies.

4. As we discussed in the paper, the number of cases who completed standard therapy was not large enough and their serum albumin levels were high, which limits the power of this study. However, using 214 clinical cases, we clearly showed that serum albumin level is a
prognostic factor for glioblastoma patients. We further demonstrated that, the mechanism by which serum albumin levels predict clinical outcome is complex, not only because it is a nutritional indicator, but also because of its role in the inflammatory response. The finding of this study is relevant and significant for the understanding of the role of serum albumin in gliomas.

Thanks for the careful review and we are looking forward to your reply.

Best wishes.

Dr Anhua Wu

References