

Dear Editors and Reviewers:

Thank you for your letter and for the reviewers' comments concerning our manuscript entitled "Hepatic epithelioid hemangioendothelioma : clinical characteristics, diagnosis, treatment and prognosis" (Manuscript NO.: 73681, Retrospective Study). Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our researches. We have studied comments carefully and have made correction which we hope meet with approval. The main corrections in the paper and the responds to the reviewers comments are as flowing:

**Responds to the reviewer 1' s comments:**

**1. Response to comment:** (Please clarify the threshold of 0.05 set at two-tailed or one-tailed.)

Author Response:

All tests were two-sided, and P-values of  $\leq 0.05$  were considered significant.

**2. Response to comment:** (Please rephrase the conclusion instead of including short background and discussion)

Author Response:

We are sorry for the lack of focus in the conclusion, it is now corrected as follows: The clinical course of HEHE is rare and variable, and patients

with intrahepatic metastases and liver dysfunction may have a poorer prognosis than those without. Surgical intervention, whether liver resection or transplantation, might be warranted regardless of the disease stage. For patients without the option for surgery, clinicians should consider the use of TACE with antiangiogenic drugs in the treatment of HEHE.

**3. Response to comment:** (Materials and Methods: The description of methods is quite insufficient, particularly inclusion criteria subjects should be described in more details.)

Author Response:

We further describe the materials and methods in detail, it is now corrected as follows:

### **Materials and methods**

The clinical data of 2 patients diagnosed with HEHE at the Fourth Hospital of Hebei Medical University and 184 previously reported cases retrieved from the literature were combined and summarized.

### **Data search**

We searched the PubMed and China National Knowledge Infrastructure (CNKI) databases from January 2010 through December 2020 using search terms, including “hepatic epithelioid hemangioendothelioma (HEHE)” and “epithelioid hemangioendothelioma of liver.” The references of related studies and reviews were also retrieved, if

necessary.

### **Study inclusion and exclusion criteria**

The studies that met the following criteria were included: (1) tumor tissues obtained by liver biopsy or surgery were pathologically identified as HEHE; (2) accurate clinical statistical indicators were provided in the studies; (3) articles were published in English or Chinese.

Exclusion criteria: (1) epithelioid hemangioendothelioma from other sites with liver metastasis; (2) duplicate publications; (3) studies without sufficient data; and (4) case reports, meeting abstracts, meta-analysis, and reviews.

### **Data extraction**

We reviewed all titles and abstracts to identify potentially relevant articles. Two investigators reviewed all potentially relevant full texts for inclusion, with disagreements resolved through discussion and consensus. We used standardized data extraction forms to collect the following items: first author's name, geographical region and year of publication, study design, inclusion/exclusion criteria, size of the patient cohort, and clinical statistical indicators (age, sex, etiology, clinical features, laboratory tests, radiographic findings, pathological features, treatment, and survival).

**4. Response to comment:** (Did authors test whether the assumptions of Cox regression were met before applying it. The authors

should depict more clearly the main model of adjustments for regression analysis.)

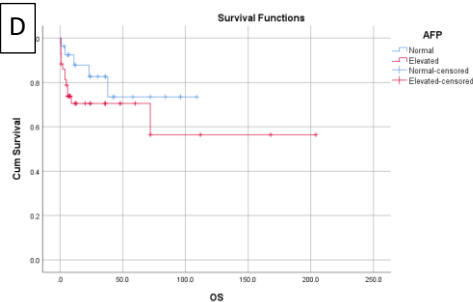
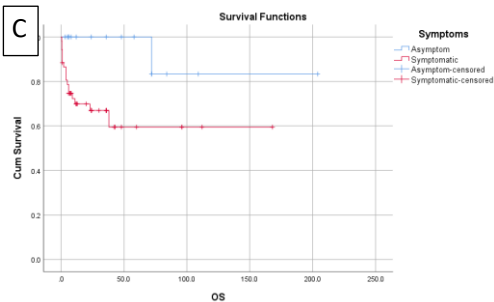
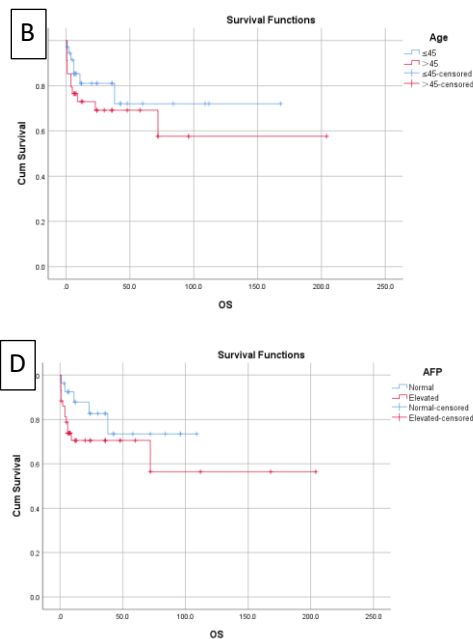
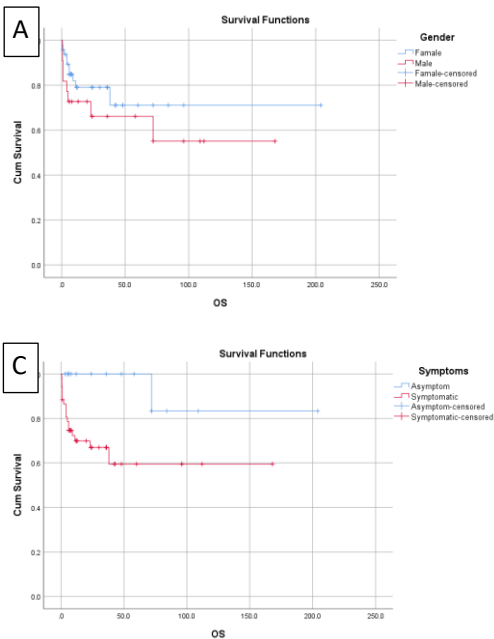
Author Response:

Time-Dependent Cox Regression Model and Kaplan – Meier survival curve were used to verify whether the proportional hazards assumption was satisfied. The interaction terms were not statistically significant (Table 1) and the Kaplan – Meier survival curve of categorization covariables had no obvious crossover (Figure 1). Hence, it could be considered that the proportional hazards assumption was satisfied.

Table 1 Time-Dependent Cox Regression Model

T_COV_	Gender	Age	Sympt oms	AFP	Liver function	diameter of tumor	Intrahepatic metastasis	Extrahepatic metastasis	Treat ments
P	0.371	0.333	0.396	0.272	0.052	0.999	0.967	0.486	0.757

AFP: Alpha fetoprotein



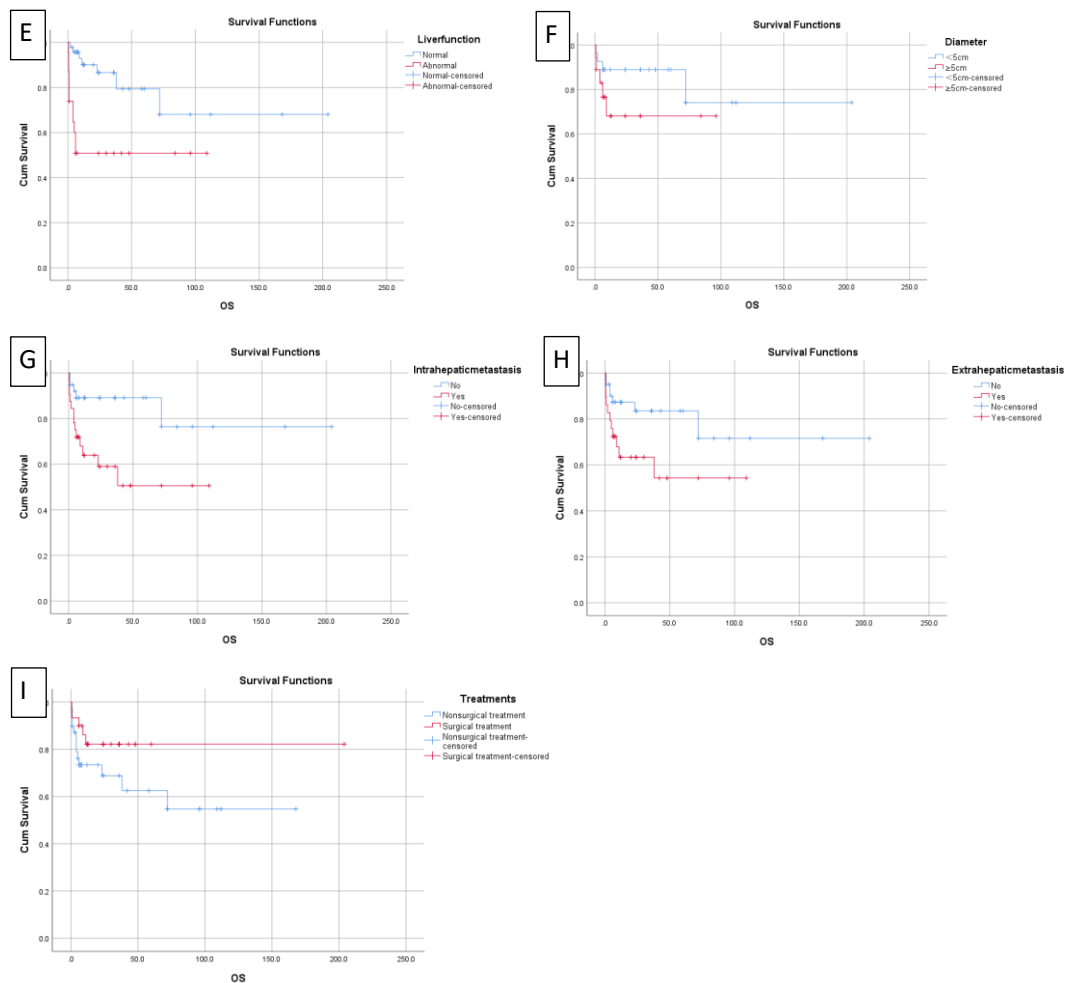


Figure 1 Overall survival of patients with hepatic epithelioid hemangioendothelioma.

A according to gender; B according to age; C according to symptoms; D according to AFP; E according to liver function; F according to diameter of tumor; G according to intrahepatic metastasis; H according to extrahepatic metastasis; I according to treatments.

AFP: Alpha fetoprotein

**5. Response to comment:** (The authors should depict more clearly the main model of adjustments for regression analysis.)

Author Response:

Statistical analysis

Statistical analyses were performed using SPSS 26.0. Distributions of

patients' characteristics (age, sex, clinical features, laboratory tests, radiographic findings, pathological features, treatment, and survival) were explored and summarized using descriptive statistics. Survival analysis was performed using the Kaplan–Meier method. The differences between the survival curves were compared using the logrank test. Multivariate Cox hazard regression analysis was performed on the factors shown to be significant on univariate analysis. All tests were two-sided, and P-values of  $\leq 0.05$  were considered significant.

**6. Response to comment:** ( I was wondering how authors deal with the extreme ages, i.e. 3 and 80?.)

Author Response:

In the process of collecting patients' information, data of patients aged 3 – 80 years were collected. Due to the low incidence of the disease, extremely aged patients were also included in the study and described to further understand the scope of the disease. The age, sex, clinical characteristics, laboratory examination findings, imaging findings, and pathological characteristics of the patients were analyzed. However, no specific information on treatment and prognosis was collected. Therefore, the choice of treatment methods and the judgment of prognosis in the extreme age groups warrant further investigation.

**7. Response to comment:** ( Pregnantad is a typo? )

Author Response:

I'm sorry that pregnantad is a typo and it has been corrected.

**8. Response to comment:** (What is the Table 1 names as “Reference” for ? )

Author Response:

Table 1 lists the analyzed literature sources. We have added the analyzed literature sources to References.

**9. Response to comment:** (Ultivariate is a typo? )

Author Response:

I'm sorry that ultivariate is a typo and it has been corrected.

**10. Response to comment:** (Please add abbreviations to Table 3)

Author Response:

Thank you for your reminding, abbreviations have been added to Table 3.

**11. Response to comment:** (Please add strengthen of your study. I would suggest authors to rephrase the logics of the discussion, mainly focus on 1-2 findings)

Author Response:

Thank you for your valuable advice. This advice is very helpful for revising and improving our paper. We have rephrased the logics of the discussion, mainly focus on treatment and prognosis of the disease.

**Responds to the reviewer 2' s comments:**

**1. Response to comment:** (After a comprehensive review of the

literature performed in 2006 by A. Mehrabi et al. (DOI: 10.1002/cncr.22225) there are only single case reports in the literature. The authors tried to correct this shortcoming.)

Author Response:

Dear reviewer, We have re-examined the literature performed by A. Mehrabi et al. This is a literature review of 402 patients with primary HEHE from reports. The study showed that HEHE mainly occurs in middle-aged women, which is consistent with our findings.

**2. Response to comment:** ( I strongly recommend that the authors to describe in detail the methods of statistical analysis as well as adding the analyzed literature sources to References.)

Author Response:

We further describe the materials and methods in detail, it is now corrected as follows:

Statistical analysis

Statistical analyses were performed using SPSS 26.0. Distributions of patients' characteristics (age, sex, clinical features, laboratory tests, radiographic findings, pathological features, treatment, and survival) were explored and summarized using descriptive statistics. Survival analysis was performed using the Kaplan–Meier method. The differences between the survival curves were compared using the logrank test. Multivariate Cox hazard regression analysis was performed on the factors



shown to be significant on univariate analysis. All tests were two-sided, and P-values of  $\leq 0.05$  were considered significant.

We have added the analyzed literature sources to References.

### **Responds to the Science editor' s comments:**

**1. Response to comment:** (Please enrich the inclusion criteria of subjects, supple the description of statistical analysis methods.)

Author Response:

We have enriched the inclusion criteria of subjects and described the statistical analysis methods in detail, it is now corrected as follows

#### **Study inclusion and exclusion criteria**

The studies that met the following criteria were included: (1) tumor tissues obtained by liver biopsy or surgery were pathologically identified as HEHE; (2) accurate clinical statistical indicators were provided in the studies; (3) articles were published in English or Chinese.

Exclusion criteria: (1) epithelioid hemangioendothelioma from other sites with liver metastasis; (2) duplicate publications; (3) studies without sufficient data; and (4) care reports, meeting abstracts, meta-analysis, and reviews.

#### **Statistical analysis**

Statistical analyses were performed using SPSS 26.0. Distributions of patients' characteristics (age, sex, clinical features, laboratory tests,

radiographic findings, pathological features, treatment, and survival) were explored and summarized using descriptive statistics. Survival analysis was performed using the Kaplan–Meier method. The differences between the survival curves were compared using the logrank test. Multivariate Cox hazard regression analysis was performed on the factors shown to be significant on univariate analysis. All tests were two-sided, and P-values of  $\leq 0.05$  were considered significant.

**2. Response to comment:** (Whether the test meeting the hypothesis of Cox regression has been conducted.)

Author Response:

Time-Dependent Cox Regression Model and Kaplan – Meier survival curve were used to verify whether the proportional hazards assumption was satisfied. The interaction terms were not statistically significant and the Kaplan – Meier survival curve of categorization covariables had no obvious crossover. Hence, it could be considered that the proportional hazards assumption was satisfied.

**3. Response to comment:** (The discussion part will be further revised.)

Author Response:

We have rephrased the logics of the discussion, mainly focus on treatment and prognosis of the disease.

**Responds to the Company editor-in-chief' s comments:**

I have prepared and arranged the figures using PowerPoint and provide standard three-line tables.

We tried our best to improve the manuscript and made some changes in the manuscript. We appreciate for Editors/Reviewers' warm work earnestly, and hope that the correction will meet with approval.

Once again, thank you very much for your comments and suggestions.

With best regards,

Sincerely Yours,

Dr. Man Zhao

Dear Editor Thank you for your letter and the comments concerning our manuscript entitled "Hepatic epithelioid hemangioendothelioma: clinical characteristics, diagnosis, treatment and prognosis" (Manuscript NO.: 73681). We have studied comments carefully and have made correction which we hope meet with approval. The main corrections in the paper are as flowing: 1. Response to comment: (The texts in figure 6 are not movable and editable.Please provide the text in your figure in text boxes, we need to edit the words in the figures.) Author Response: I have provided the text in my figure in text boxes. 2. Response to comment: (Please revise the references list according to the attached file "73681 references", and the reference number should be revised in the file "73681\_Auto\_Edited) Author Response: We searched PubMed and China National Knowledge Infrastructure (CNKI) databases to screen and summarize suitable cases for this study to explore the clinical characteristics, diagnosis, treatment and prognosis of hepatic epithelioid hemangioendothelioma. In order to ensure the comprehensiveness of literature retrieval and the accuracy of this study, some cases were from the same journal. The references in the literature search results are not suitable for replacement, and I have listed these references separately in the supplementary materials. References in the introduction and discussion have been modified accordingly and the reference number have been revised in the file "73681\_Auto\_Edited. We tried our best to

improve the manuscript and made some changes in the manuscript. We appreciate for Editors' warm work earnestly, and hope that the correction will meet with approval. Once again, thank you very much for your comments and suggestions. With best regards, Sincerely Yours, Dr. Man Zhao