

Format for ANSWERING REVIEWERS



January 19, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 6924-revised.doc).

Title: STAGING SYSTEMS OF HEPATOCELLULAR CARCINOMA: A REVIEW OF LITERATURE

Author: Marcello Maida, Emanuele Orlando, Calogero Cammà, Giuseppe Cabibbo.

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 6924

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 reviewers:

- **REVIEWER #1**

Major points

Although this paper is a well organized review, several points should be corrected. First of all, most of the cited papers regarding staging or scoring system of HCC in this paper were finally resulted to be negative in various reasons. Authors should summarize the reason in the different table for convenient understanding.

Answer: An overview Table summarizing all the studies has been added for convenient understanding (Table 3)

Minor points

Page 7, Staging systems in Eastern countries, line 5, Tokyo score is not described in Table 1.

Answer: Tokyo score has been added in Table 1.

- **REVIEWER #2**

In this study, the authors briefly reviewed the staging systems for hepatocellular carcinoma (HCC). This issue is important because selecting an appropriate staging system is crucial to predict the outcome of patients with HCC or to determine the appropriate interventions (e.g. to identify the best candidates for liver transplantation, to select the best treatment, etc). The authors arrive to the conclusion that none of these systems is universally accepted and should be used only as a general guide. Therefore, they explain why the optimal system is still under intense debate. Also, they conclude that the current prognostic models need to be improved. In my opinion, the Discussion section would be enriched if authors discuss the following articles:

A) Prognosis of hepatocellular carcinoma: comparison of 7 staging systems in an American cohort. Marrero JA et al Hepatology. 2005; **B)** Selecting an optimal staging system for hepatocellular carcinoma: comparison of 5 currently used prognostic models. Hsu CY et al Cancer 2010; **C)** What is the best staging system for hepatocellular carcinoma in the setting of

liver transplantation? Olthoff KM et al Liver Transpl. 2011. D) Applicability of BCLC stage for prognostic stratification in comparison with other staging systems: single centre experience from long-term clinical outcomes of 1717 treatment-naive patients with hepatocellular carcinoma. Kim BK et al. Liver Int. 2012

Answers: All the suggested articles has been included and discussed in the paper (see references 34, 35, 36, 55) and enclosed in new Table 3.

• **REVIEWER #3**

Major Points

a. It would be better to change the title of this article into “Staging Systems of Hepatocellular Carcinoma” since this article mainly dealt with staging systems and the prognosis of HCC accounts for only a small part of this article.

Answer: title has been changed, according to reviewer suggestion.

b. In the “STAGING SYSTEM OF HEPATOCELLULAR CARCINOMA” section, it is strongly recommended to discuss on “which staging system is the best one?” rather than in the DISCUSSION section. It would be the most important and interesting part in this article.

Answer: a new paragraph entitled “Staging Systems For Hcc: Which Is The Best One?” has been added for a better discussion of the topic in a separate section.

c. This article needs to include TNM staging systems including modified UICC system, 6th edition of AJCC/UICC staging system, and 7th edition of AJCC staging system since these staging systems are still widely applied for anatomical staging in daily clinical practice and clinical trials.

Answer: 6th and 7th edition of AJCC/UICC staging system have been added in the paper (see references 11, 12).

d. It would be necessary to mention that since survival outcomes can be inevitably confounded by treatment strategies that may be quite different from one center to another (Huo TI, et al. Hepatology 2005;41:678.), external validation using natural history of untreated HCC cohorts might be the most useful way to compare the prognostic value of each staging system (Ryder S, et al. Gut 2005;54:328-9.; Llovet JM, et al. Hepatology 1999;29:62-7.).

Answer: this important sentence and related suggested references, have been included at Page 10, line 26.

e. I am afraid that GRETCH scoring system is not a well validated or a widely used staging system. Therefore, this staging system would be better to be classified as “Other Staging Systems” together with Tokyo score, CUPI score, and JIS score. In addition, the sentence “Between all, the BCLC, CLIP and GRETCH are most commonly used in Western countries, with a good geographical variability” (page 9, lines 7-9) needs to be modified.

Answer: GRETCH score was moved to “Other Staging systems in western countries” (page 7, line 12) and the sentence at page 9 has been deleted.

Minor Points

a. Extensive English editing is required.

Answer: as suggested, an Extensive English editing has been done.

b. In BCLC staging system, 5-year survival rate for stage 0 or A exceeds 40-70%, not 50-70%.

Answer: this data has been corrected according to reviewer suggestion.

c. Recently, serum IGF-1 level was found to reflect time-to-progression as well as overall

survival of HCC patients after curative treatment (Cho EJ, et al. Clin Cancer Res. 2013;19(15):4218-27.). It would be better to add this reference.

Answer: the reference has been enclosed and discussed in the paper (see reference 29). Please note that in this study IGF-1 level was found to reflect time-to-recurrence and not time-to-progression.

- d. It would be better for “New Prognostic Markers” part to include estrogen receptor classification of HCC.

Answer: estrogen receptor classification has been moved to “New Prognostic Markers” section, as requested.

3) References and typesetting were corrected

Sincerely yours,

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