

**ESPS Peer-review Report**

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

**ESPS Manuscript NO:** 8095

**Title:** Metformin Does Not Improve Survival in patients with Hepatocellular Carcinoma

**Reviewer code:** 02855671

**Science editor:** Ma, Ya-Juan

**Date sent for review:** 2013-12-16 10:56

**Date reviewed:** 2014-01-08 08:34

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A (Excellent)	<input checked="" type="checkbox"/> Grade A: Priority Publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B (Very good)	<input type="checkbox"/> Grade B: minor language polishing	<input type="checkbox"/> Existed	<input type="checkbox"/> High priority for publication
<input checked="" type="checkbox"/> Grade C (Good)	<input type="checkbox"/> Grade C: a great deal of language polishing	<input type="checkbox"/> No records	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D (Fair)	<input type="checkbox"/> Grade D: rejected	BPG Search:	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade E (Poor)		<input type="checkbox"/> Existed	<input checked="" type="checkbox"/> Minor revision
		<input type="checkbox"/> No records	<input type="checkbox"/> Major revision

**COMMENTS TO AUTHORS**

In the article "Metformin does not improve survival in patients with Hepatocellular carcinoma" the authors performed a retrospective analysis on the impact of this antidiabetic drug on HCC survival. Although the main limitation of the study is the retrospective nature and the limited population, the data presented shed some light on the role and use of metformin in liver patients with HCC in a real-life clinical scenario. Some minor points to be addressed: - to add one or two phrases in the "Background and aim" of the Abstract section - to expand the "Results" section - the fifth reference number in the " Discussion" is 11 and not 1 - what kind of HCC therapies did the patients undergo? May this have some relevance in the discussion (see paper by Chen TM 2011 J Gastroenterol Hepatol on metformin after RFA)? - in table 1 the cumulative number of BCLC patients is 514 and not 701. Please address



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Name of Journal: World Journal of Gastroenterology

ESPS Manuscript NO: 8095

Title: Metformin Does Not Improve Survival in patients with Hepatocellular Carcinoma

Reviewer code: 00742517

Science editor: Ma, Ya-Juan

Date sent for review: 2013-12-16 10:56

Date reviewed: 2014-01-11 15:26

Table with 4 columns: CLASSIFICATION, LANGUAGE EVALUATION, RECOMMENDATION, CONCLUSION. It lists various grades (A-E) and corresponding evaluation criteria, search results (Google/BPG), and final conclusions (Accept, High priority, Rejection, Minor revision, Major revision).

COMMENTS TO AUTHORS

The article is a retrospective study of metformin effect on HCC patients between Jan 2005 and June 2011 and shows no survival benefit to the use of metformin in DM patients with HCC. Overall the paper is well designed. My specific comments are as follows. Virus, alcoholic and fat are main etiologies of HCC. As we know, metformin works in overweighted patients who suffered insulin resistance. It is common used in fatty liver disease. So, it will be better if author could add BMI/HOMA-IR result in table 1, and divide HCC into fatty-liver group and non-fatty-liver group. Metformin might affects more in HCC induced by fatty liver disease.

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

**ESPS Manuscript NO:** 8095

**Title:** Metformin Does Not Improve Survival in patients with Hepatocellular Carcinoma

**Reviewer code:** 00068278

**Science editor:** Ma, Ya-Juan

**Date sent for review:** 2013-12-16 10:56

**Date reviewed:** 2014-01-19 19:47

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A (Excellent)	<input type="checkbox"/> Grade A: Priority Publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B (Very good)	<input type="checkbox"/> Grade B: minor language polishing	<input type="checkbox"/> Existed	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C (Good)	<input type="checkbox"/> Grade C: a great deal of language polishing	<input type="checkbox"/> No records	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D (Fair)	<input type="checkbox"/> Grade D: rejected	BPG Search:	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade E (Poor)		<input type="checkbox"/> Existed	<input type="checkbox"/> Minor revision
		<input type="checkbox"/> No records	<input type="checkbox"/> Major revision

**COMMENTS TO AUTHORS**

In the presented study, the authors assessed the effect of metformin on the survival of 701 patients with newly diagnosed HCC. They did not find a statistically significant survival advantage of metformin among 3 groups (diabetic patients on metformin, not on metformin and non-diabetic patients). Minor points: 1-Page 4, paragraph 2; organic cation transporter 1 (OCT1) transporter (must be deleted)... 2-Some abbreviations were not defined on first mention in the text (mTOR, VEGF, etc). 3-Discussion section, paragraph 2; the reference number of Chen et al must be corrected as "11". 4- The manuscript has not been written in accordance with the Journal's rules (references within the text and in the references, style, tables, etc). Major points: 1-Although it has been stated that metformin decreased HCC risk among diabetic patients in a dose-dependent manner (reference #11, and Yi G, et al. Int J Oncol. 2013 Nov;43(5):1503-10. doi: 10.3892/ijo.2013.2077), no data given about the dose of metformin. 2-On Table 1, the BCLC stage distribution shows only 514 patients (no information about 187 patients). 3- Overall the length of the discussion is short. It would be helpful to state that the failure to find a difference may be secondary to a Type II statistical error. It has been found that age and BCLC stage were associated with increased risk of death (HR>1.0). It would be helpful to present data and comment on age groups and BCLC stage differences between the groups. 4- Is there any explanation about higher mortality rate and shorter median survival in patients with stage C compared to those with stage D? 5-Metformin may act differently in HCC patients who have different causes (Yilmaz Y, et al. Tumori. 2013 Jan-Feb;99(1):10-6. doi: 10.1700/1248.13781.). It would be helpful to present data on etiologic groups.

**ESPS Peer-review Report**

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

**ESPS Manuscript NO:** 8095

**Title:** Metformin Does Not Improve Survival in patients with Hepatocellular Carcinoma

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**Science editor:** Ma, Ya-Juan

**Date sent for review:** 2013-12-16 10:56

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CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A (Excellent)	<input type="checkbox"/> Grade A: Priority Publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B (Very good)	<input type="checkbox"/> Grade B: minor language polishing	<input type="checkbox"/> Existed	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C (Good)	<input type="checkbox"/> Grade C: a great deal of language polishing	<input type="checkbox"/> No records	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D (Fair)	<input type="checkbox"/> Grade D: rejected	BPG Search:	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E (Poor)		<input type="checkbox"/> Existed	<input type="checkbox"/> Major revision
		<input type="checkbox"/> No records	

**COMMENTS TO AUTHORS**

The paper ‘Metformin Does Not Improve Survival in patients with Hepatocellular Carcinoma’ by Bhat M et al. is an original article to assess whether metformin has any chemotherapeutic effect in newly diagnosed hepatocellular carcinoma.

The major points that authors must be clarified are listed below:

1. The main factors related to the HCC survival are treatment strategies, including surgery, radiofrequency ablation (RFA), liver transplant, TACE and chemotherapeutic agents (Figure 1). The aim of this article is to evaluate the metformin exposure at least 90 days for newly diagnosed HCC patients and the result is that metformin exposure does not improve one -year survival. The result is not persuasive, because of the authors neglect the effects of the aforementioned treatments play a critical role in HCC survival than a single drug exposure.

<b>BCLC STAGING SYSTEM<sup>4</sup></b>				
BCLC Stage	PS	Tumor Features	Liver Function	Treatment Options
A1	0	Single <5 cm	No PH	Surgery, RFA
A2	0	Single <5 cm	PH, normal bili	Surgery, RFA, transplant
A3	0	Single <5 cm	PH, abnormal bili	RFA, transplant
A4	0	3 tumors <3 cm	Not applicable	Transplant, TACE
B	0	Large multinodular	CP A-B	TACE
C	1-2	Vascular invasion or metastases	CP A-B	sorafenib
D	3-4	Any	CP C	Supportive care

bili=total bilirubin; CP=Child-Pugh class;  
PH=portal hypertension; RFA=radiofrequency ablation; TACE=transarterial chemoembolization.  
Adapted with permission from O'Neil et al (2007).

Figure 1

2. The methodology of this article is not rational. Case-matched method is suitable for this study and the outcome is capable of convincing the readers.
3. The total numbers of BCLC stage is incorrect to overall patients (Table 1)