



**PEER-REVIEW REPORT**

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

**Manuscript NO:** 49701

**Title:** Post-transplant infection improves outcome of hepatocellular carcinoma patients after orthotopic liver transplantation

**Reviewer’s code:** 03479537

**Reviewer’s country:** United Kingdom

**Science editor:** Jia-Ping Yan

**Reviewer accepted review:** 2019-06-17 03:34

**Reviewer performed review:** 2019-06-17 06:11

**Review time:** 2 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input checked="" type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input checked="" type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	(High priority)	<input type="checkbox"/> Anonymous
<input type="checkbox"/> Grade C: Good		<input type="checkbox"/> Accept	<input checked="" type="checkbox"/> Onymous
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of language polishing	(General priority)	Peer-reviewer’s expertise on the topic of the manuscript:
<input type="checkbox"/> Grade E: Do not publish	<input type="checkbox"/> Grade D: Rejection	<input checked="" type="checkbox"/> Minor revision	<input checked="" type="checkbox"/> Advanced
		<input type="checkbox"/> Major revision	<input type="checkbox"/> General
		<input type="checkbox"/> Rejection	<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

**SPECIFIC COMMENTS TO AUTHORS**

We extend our congratulations to the authors of this study. They have tackled a sensitive topic from a novel sceptical point of view. The authors found that in patients transplanted for HCC Particularly with MVI), the occurrence of post-transplant infection



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was linked to prolonged DFS and OS. Their hypothesis is that the infection stimulated a sustained immune response that had anticancer characteristics. The theory is applaudable albeit the controversial evidence. In fact, several authors have found a negative correlation between the occurrence of postoperative infection and disease-specific survival in cancer patients. Indeed, the postoperative infection was linked to higher rates for cancer recurrence. The proinflammation induced by infection is long thought to be a promotor for cancer development and recurrence. This does not negate the presence of evidence to suggest the role of innate immunity against cancer. Immune therapy has been proposed to be promising over other systemic therapies for HCC. Nonetheless, the mechanism behind the findings of the beforehand study cannot be verified due to the limited methodology. Besides, the study lacks the appropriate a posteriori power to link PTI to benefit seen in OS or DFS. This study is well written, despite that few details requires attention. For example, in the methods, the patient inclusion for transplant is defined by several well-known transplant criteria. It is possible that a patient is admitted to receive liver transplantation based on one or another of these criteria. It is not possible that the same patient will meet all the criteria (the authors used and in their description) as the inherited difference among the different criteria necessitates that if the patient meets one, will not meet the other at the same time. In the results: The survival figures given for patients with PTI per group need revising as the DFS is longer than OS at 3 and five years and should match the figure1. It is not clear why the authors provided a cutoff value for aAFP of 200. None of the criteria declared in the methods utilized this cutoff value as a prognostically determinant element. Some studies have identified a relationship between the grade of infection and the OS after cancer treatment. Others have linked the localization of infection to the latter parameter. Could the authors try to ascertain any of the findings? Due to the sensitivity of the topic, we suggest that the authors enrich their discussion with the



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counterargument. The current study findings are not immediately applicable in clinical practice. However, it might help further research to discuss the possible source of controversy with the main body of literature, which is against the findings of this study.

Kind regards

#### **INITIAL REVIEW OF THE MANUSCRIPT**

##### ***Google Search:***

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**PEER-REVIEW REPORT**

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

**Manuscript NO:** 49701

**Title:** Post-transplant infection improves outcome of hepatocellular carcinoma patients after orthotopic liver transplantation

**Reviewer's code:** 00051373

**Reviewer's country:** Taiwan

**Science editor:** Jia-Ping Yan

**Reviewer accepted review:** 2019-06-17 13:33

**Reviewer performed review:** 2019-06-18 13:15

**Review time:** 23 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language	(High priority)	<input checked="" type="checkbox"/> Anonymous
<input type="checkbox"/> Grade C: Good	polishing	<input type="checkbox"/> Accept	<input type="checkbox"/> Onymous
<input checked="" type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of	(General priority)	Peer-reviewer's expertise on the
<input type="checkbox"/> Grade E: Do not	language polishing	<input type="checkbox"/> Minor revision	topic of the manuscript:
publish	<input type="checkbox"/> Grade D: Rejection	<input type="checkbox"/> Major revision	<input checked="" type="checkbox"/> Advanced
		<input checked="" type="checkbox"/> Rejection	<input type="checkbox"/> General
			<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

**SPECIFIC COMMENTS TO AUTHORS**

This is a retrospective observation study to talk about post-transplant infection improves outcome of hepatocellular carcinoma patients after orthotopic liver transplantation. This manuscript is not well written. Too many citations in the section of methods. It is not a



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good written in this section. It seems to be a chart record or report of the paper reading. The topic is the post transplantation infection, which should be included not only in bacteria but also in viral infection particular in HBV and HCV. Infection category in the table is too compact and making a confusion.

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##### ***Google Search:***

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- Plagiarism
- No



**PEER-REVIEW REPORT**

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

**Manuscript NO:** 49701

**Title:** Post-transplant infection improves outcome of hepatocellular carcinoma patients after orthotopic liver transplantation

**Reviewer’s code:** 00054275

**Reviewer’s country:** Italy

**Science editor:** Jia-Ping Yan

**Reviewer accepted review:** 2019-06-17 06:56

**Reviewer performed review:** 2019-06-22 15:33

**Review time:** 5 Days and 8 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language	(High priority)	<input checked="" type="checkbox"/> Anonymous
<input checked="" type="checkbox"/> Grade C: Good	polishing	<input type="checkbox"/> Accept	<input type="checkbox"/> Onymous
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of	(General priority)	Peer-reviewer’s expertise on the
<input type="checkbox"/> Grade E: Do not	language polishing	<input checked="" type="checkbox"/> Minor revision	topic of the manuscript:
publish	<input type="checkbox"/> Grade D: Rejection	<input type="checkbox"/> Major revision	<input type="checkbox"/> Advanced
		<input type="checkbox"/> Rejection	<input checked="" type="checkbox"/> General
			<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

**SPECIFIC COMMENTS TO AUTHORS**

Intriguing and accurate paper. Nevertheless some points need to be clarified: - Line 130: 3 patients from the 8 with negative microbiological cultures, were diagnosed with CMV infection; which type of PTI was present in the remaining 5 patients? - Lines 140-141:



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overall survival 3 and 5 years post LT seems to be less than recurrence free survival but obviously it cannot be... - Line 151: what does mean "cirrhotic background"? Perhaps seriousness of cirrhosis...? - Is there any relation between type of infection (bacterial or fungal, or site of infection...) and HCC recurrence? - Possibly immunosuppression therapy may has been reduced in case of PTI and it may influence HCC recurrence: an evaluation of this point shoulde be reported and discussed - which was the aetiology of cirrhosis before LT? Is there any relation between aetiology of cirrhosis and HCC recurrence?

#### **INITIAL REVIEW OF THE MANUSCRIPT**

##### ***Google Search:***

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##### ***BPG Search:***

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- Duplicate publication
- Plagiarism
- No



**PEER-REVIEW REPORT**

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

**Manuscript NO:** 49701

**Title:** Post-transplant infection improves outcome of hepatocellular carcinoma patients after orthotopic liver transplantation

**Reviewer's code:** 00182703

**Reviewer's country:** Romania

**Science editor:** Jia-Ping Yan

**Reviewer accepted review:** 2019-06-18 16:55

**Reviewer performed review:** 2019-06-22 18:04

**Review time:** 4 Days and 1 Hour

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input checked="" type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input checked="" type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language	(High priority)	<input checked="" type="checkbox"/> Anonymous
<input type="checkbox"/> Grade C: Good	polishing	<input checked="" type="checkbox"/> Accept	<input type="checkbox"/> Onymous
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of	(General priority)	Peer-reviewer's expertise on the
<input type="checkbox"/> Grade E: Do not	language polishing	<input type="checkbox"/> Minor revision	topic of the manuscript:
publish	<input type="checkbox"/> Grade D: Rejection	<input type="checkbox"/> Major revision	<input checked="" type="checkbox"/> Advanced
		<input type="checkbox"/> Rejection	<input type="checkbox"/> General
			<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

**SPECIFIC COMMENTS TO AUTHORS**

The article is very interesting and useful. There are numerous cases of neoplasms that have evolved favorably after infections with different germs and different localizations. The authors of this article had the excellent idea of studying the evolution of HHC



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patients undergoing OLT with and without post-transplant infection. The group of patients with post-OLT infection is not very large, but the results are statistically significant. The material and method are very clearly presented. The statistical analysis is correct, as well as the interpretation of the results and discussions with references to literature data. Further studies are needed to confirm the results and to find the clear pathophysiological mechanisms that intervene and make the evolution of the infected patients to be favorable.

#### **INITIAL REVIEW OF THE MANUSCRIPT**

##### ***Google Search:***

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##### ***BPG Search:***

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- Plagiarism
- No



**PEER-REVIEW REPORT**

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

**Manuscript NO:** 49701

**Title:** Post-transplant infection improves outcome of hepatocellular carcinoma patients after orthotopic liver transplantation

**Reviewer's code:** 02444864

**Reviewer's country:** Greece

**Science editor:** Jia-Ping Yan

**Reviewer accepted review:** 2019-06-19 19:48

**Reviewer performed review:** 2019-06-23 22:45

**Review time:** 4 Days and 2 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language	(High priority)	<input type="checkbox"/> Anonymous
<input type="checkbox"/> Grade C: Good	polishing	<input type="checkbox"/> Accept	<input type="checkbox"/> Onymous
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of	(General priority)	Peer-reviewer's expertise on the
<input type="checkbox"/> Grade E: Do not	language polishing	<input type="checkbox"/> Minor revision	topic of the manuscript:
publish	<input type="checkbox"/> Grade D: Rejection	<input type="checkbox"/> Major revision	<input type="checkbox"/> Advanced
		<input type="checkbox"/> Rejection	<input type="checkbox"/> General
			<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input type="checkbox"/> No

**SPECIFIC COMMENTS TO AUTHORS**

Comments to Authors The submitted manuscript (no 49701) provides strong evidence for the beneficial impact of infection on tumor recurrence, overall survival and post-recurrence survival in transplant HCC patients. The results revive Coley's



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important observations one century ago, which suggested that the host immune response against bacterial infection might exert a tumor suppressive effect. It seems possible that a novel conception of immunotherapy may ensue based on new pathways and therapeutic agents. The study is well designed, well documented and well written, only minimal corrections are needed. Minor comments Line 128: “ pathogens” instead of “pathogen”. Line 129: “However” should be omitted. Lines 149 and 152: lymph nodes (two words). Lines 157 and 181: “absence of” instead “without”. Lines 204-206: The virus-related carcinogenesis doesn’t have to be mentioned. Thus “likewise” (line 207) should be also deleted. Line 251-253: the possible role of innate immunity should be mentioned.

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**PEER-REVIEW REPORT**

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

**Manuscript NO:** 49701

**Title:** Post-transplant infection improves outcome of hepatocellular carcinoma patients after orthotopic liver transplantation

**Reviewer’s code:** 00077376

**Reviewer’s country:** Japan

**Science editor:** Jia-Ping Yan

**Reviewer accepted review:** 2019-06-17 05:28

**Reviewer performed review:** 2019-06-27 09:26

**Review time:** 10 Days and 3 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input checked="" type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language	(High priority)	<input checked="" type="checkbox"/> Anonymous
<input type="checkbox"/> Grade C: Good	polishing	<input type="checkbox"/> Accept	<input type="checkbox"/> Onymous
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of	(General priority)	Peer-reviewer’s expertise on the
<input type="checkbox"/> Grade E: Do not	language polishing	<input type="checkbox"/> Minor revision	topic of the manuscript:
publish	<input type="checkbox"/> Grade D: Rejection	<input checked="" type="checkbox"/> Major revision	<input checked="" type="checkbox"/> Advanced
		<input type="checkbox"/> Rejection	<input type="checkbox"/> General
			<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

**SPECIFIC COMMENTS TO AUTHORS**

This retrospective study in a single institution demonstrated that early post-transplant Infection occurring with 30 days after LT for HCC significant improved the long-term survivals, compared to those without infection. The study results are interesting;



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however, however, the following thing should be taken into consideration. (1) In the abstract, there are no data on exact number of patients analyzed, including PTI and non-PTI groups. This is mandatory. (2) The exact follow-up schedule should be described to determine recurrence-free survival. For example, enhanced CT scan after operation is performed every 3 months until one year, and every 6 months thereafter. (3) According to the data shown in Table 1, the incidence of vascular invasion was very high, reaching over 50% of the recipient in each group. Major vascular invasion was contraindication for LT, and thus this high incidence means that microscopic vascular invasion was very high. Is this correct? You should explain the reason why the incidence of microvascular invasion was very high, compared with those of the previous reports. (4) In Table 1, there are no data on HCV virus infection. Are there any patients with HCV virus infection? (5) In the present study, you demonstrated an improved OS and PRS in patients who suffered tumor recurrence with PTI compared to those without PTI, indicating a sustained anti-tumor effect of PTI transplant HCC patients after cancer relapse. This finding is very interesting; however, how do you explain the reason why early postoperative event of infectious complication after LT highly influence the survival benefit even when tumor recurrence occurs. What kind of factors do you imagine or speculate?

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