

## PEER-REVIEW REPORT

**Name of journal:** World Journal of Stem Cells

**Manuscript NO:** 40453

**Title:** Efficacy and safety of autologous stem cell transplantation for decompensated liver cirrhosis: A retrospective cohort study

**Reviewer's code:** 01213078

**Reviewer's country:** China

**Science editor:** Fang-Fang Ji

**Date sent for review:** 2018-06-25

**Date reviewed:** 2018-06-28

**Review time:** 3 Days

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input checked="" type="checkbox"/> Grade A: Priority publishing	<input checked="" 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 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 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

The authors reported the long-term efficacy and safety of SCT for decompensated liver cirrhosis by retrospectively analyzing a cohort of patients. The results demonstrated that SCT fails to increase the long-term survival rate and increase the incidence of HCC

in patients with decompensated liver cirrhosis. The results of this study is very important because it alert the medical field for the tumorigenicity of stem cells in specific condition as liver cirrhosis. Although it is not a RCT study, by it is from real world data and analyzed with proper biostatistics.

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

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

- ☐ The same title
- ☐ Duplicate publication
- ☐ Plagiarism
- ☐ [Y] No

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

- ☐ The same title
- ☐ Duplicate publication
- ☐ Plagiarism
- ☐ [Y] No

## PEER-REVIEW REPORT

**Name of journal:** World Journal of Stem Cells

**Manuscript NO:** 40453

**Title:** Efficacy and safety of autologous stem cell transplantation for decompensated liver cirrhosis: A retrospective cohort study

**Reviewer's code:** 02566952

**Reviewer's country:** Romania

**Science editor:** Fang-Fang Ji

**Date sent for review:** 2018-06-25

**Date reviewed:** 2018-06-30

**Review time:** 5 Days

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 checked="" 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

Comments for the authors Congratulation for the meaningful work, scientific and medical practitioner community needs more of there clinical studies and publishing of long term results. For the sake of keeping the manuscript concise but still informative, I

would suggest adding one or two phrases in the introduction about current stage of stem cell based therapy in treating liver cirrhosis? Is this a common practice procedure, do the cited studies perform stem cell transplantation of autologous or allogeneic origin, differentiated or non differentiated stem cells, what type of stem cells? In special condition in the lab BMMSCs were shown to differentiate to hepatocytes, however if this happens truly in vivo or if stem cells have rather a cytokine based regeneration potentiating effect it is not yet clear. **Methods** It is not clear for me from the methods description what was the exact formulation for stem cell therapy in the case of bone marrow derived source. It seems it was rather bone marrow aspirate that does contain a (very limited) amount of BMMSCs but is composed mostly of other monocytic cells of mesenchymal and endothelial origin. As the second "therapeutic branch was basically HSC transplantation, probably stem cells were obtained by apheresis. Please confirm if it is the case. Is there literature support for treating liver cirrhosis using HSCs? (non differentiated obviously) if so, please comment and cite. **Results** Results from table 1 and 3 would benefit from being shown in chart form I have a problem with this statement "bone marrow or HSCs transplantation was performed accordingly to patient willingness. First of all I am not sure it was BMMSCs transplantation or bone marrow aspirate (please document) and second on what bases could the patient choose, what they were offered in terms of informed consent as this manuscript does not offer clear information about result from previous studies comparing BMMSCs and HSCs effect, their comparative advantages and caveats. How many follow up visits were performed average per time unit (month, or year, how it is the case and on what criteria) What was the therapeutic regimen (cells per ml, how many ml, vehicle, timing, frequency of administration?) All these parameters are known to influence SCT efficiency and safety and need to be mentioned. **Discussion** I would argue that there were a limited amount of true mesenchymal stem cells in the case of bone marrow aspirate infusion.

Without proper preconditioning such cells they adopt a fate that is dictated by their environment therefore if a very early tumorigenic process was already undergoing in patients at the moment of injection or occurred early after this malignancies were only fuelled by cell cocktail administration. Maybe it is not a problem of the cell therapy in itself but of the cell type , modality of preconditioning and delivery. Moreover, all the treated cases seem to fail into the category of advanced complicated liver cirrhosis. Treated and non-treated patients seem to have similar mortality rate. As authors themselves state, it is hard to conceive that irreversible morphological and physiological alterations due to vascular and parenchymatous liver failure can be reversed by couple of circulating stem cells injected in a harsh environment. Rather the long term follow up in this study coincides with the natural history of the condition itself that might be indeed aggravated by injecting uncommitted progenitors within a tumor prone environment. Follow up of the fate of administered stem cells using combined Imagistics methods has been proposed as a method to discriminate tumorigenic transformation and should be maybe mentioned (Labusca, Herea, J Nanosci Nanotechnol 2018) What is the author opinion about eventual modalities to improve performance of SCT (such as vehicle based delivery to support hepatic development and anti-inflammatory activity, use of preconditioned cells, delivery on earlier stages of the disease to more carefully selected patients ) Overall this is an important information about long term follow up of cell treated patients following the mentioned therapeutic protocol and stage of the disease from which all clinical and scientific comunitu can benefit

## INITIAL REVIEW OF THE MANUSCRIPT

### *Google Search:*

- ☐ The same title
- ☐ Duplicate publication



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[ ] Plagiarism

[Y] No

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[ ] Duplicate publication

[ ] Plagiarism

[Y] No

## PEER-REVIEW REPORT

**Name of journal:** World Journal of Stem Cells

**Manuscript NO:** 40453

**Title:** Efficacy and safety of autologous stem cell transplantation for decompensated liver cirrhosis: A retrospective cohort study

**Reviewer's code:** 03203589

**Reviewer's country:** China

**Science editor:** Fang-Fang Ji

**Date sent for review:** 2018-06-25

**Date reviewed:** 2018-07-06

**Review time:** 10 Days

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 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

There are a number of points about this work not clear and perhaps not done in the way they should be done. Some of my concerns are following: 1. In the Stem cell transplantation, CD34+ stem cells were obtained at a density of  $(2.81 \pm 1.03) \times 10^6/\text{kg}$ , Is

the cell density unit in kilograms? 2. In the Impact of stem cell transplantation on the incidence of HCC, 11 cases with development of HCC in the SCT group, what is the number of cases with development of HCC among BMSC transplantation group and HSC transplantation group in the SCT group? 3. In the Impact of stem cell transplantation on the incidence of HCC, Can you compare the incidence of HCC between BMSC transplantation group with non-SCT group, and the incidence of HCC between in HSC transplantation group with non-SCT group, and whether the incidence of HCC of stem cell transplantation from two different sources is statistically different? And whether you can draw a conclusion that the incidence of HCC was higher in the SCT group than in the non-SCT group?

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

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**Manuscript NO:** 40453

**Title:** Efficacy and safety of autologous stem cell transplantation for decompensated liver cirrhosis: A retrospective cohort study

**Reviewer's code:** 01213078

**Reviewer's country:** China

**Science editor:** Fang-Fang Ji

**Date sent for review:** 2018-08-07

**Date reviewed:** 2018-08-07

**Review time:** 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 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
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		<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

I think the revised manuscript addressed my comments and improved a lot.

### INITIAL REVIEW OF THE MANUSCRIPT



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## PEER-REVIEW REPORT

**Name of journal:** World Journal of Stem Cells

**Manuscript NO:** 40453

**Title:** Efficacy and safety of autologous stem cell transplantation for decompensated liver cirrhosis: A retrospective cohort study

**Reviewer's code:** 02566952

**Reviewer's country:** Romania

**Science editor:** Fang-Fang Ji

**Date sent for review:** 2018-08-07

**Date reviewed:** 2018-08-18

**Review time:** 11 Days

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
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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

I am grateful for your patience and sorry again for my late response for which I apologize.



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I have read the current version of the manuscript and the author answer to reviewer. The authors have thoroughly answered each and every question and the resubmitted form of the manuscript reads indeed very good.

I appreciate the effort given in conducting the study as well as in presenting an important result about the long term follow up of stem cell treatment for liver cirrhosis. This study rise an important problem about the importance of patient stratification in choosing a therapeutic method signaling that in advanced stages of this condition stem cell treatment can increase the incidence of malignant transformation. The stem cell based therapies are on the rise, however in order to establish clear guideline for their use, high quality clinical studies need to pile up. In this line of thought, the present manuscript brings an important contribution, supporting both advancement of safe stem cell therapies as well as enlarging the therapeutic options for patients with liver cirrhosis hopefully in a more efficient and safe manner.

I congratulate the authors for their work and diligence and wish them good luck in further clinical and scientific developments

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☐ No

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**Reviewer's code:** 03203589

**Reviewer's country:** China

**Science editor:** Fang-Fang Ji

**Date sent for review:** 2018-08-07

**Date reviewed:** 2018-08-15

**Review time:** 8 Days

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

I think the revised manuscript has been greatly improved and is worthy of publication.

### INITIAL REVIEW OF THE MANUSCRIPT



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*BPG Search:*

- ☐ The same title
- ☐ Duplicate publication
- ☐ Plagiarism
- ☐ No