



PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 48771

Title: De novo malignancies after liver transplantation: The effect of immunosuppression – personal data and review of literature

Reviewer’s code: 00054465

Reviewer’s country: United States

Science editor: Jia-Ping Yan

Reviewer accepted review: 2019-05-04 16:08

Reviewer performed review: 2019-05-05 16:14

Review time: 1 Day

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 checked="" type="checkbox"/> Anonymous
<input type="checkbox"/> Grade C: Good		<input checked="" type="checkbox"/> Accept	<input 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 Grade E: Do not publish	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 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

This is an excellent review of the current literature regarding De-Nova malignancies occurring after liver transplantation in adults and children. The literature review is comprehensive and discussed appropriately. The authors include their own experience



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at the Tor Vergata Institute for weaning patients off immunosuppression drugs. The conclusion that an Immunosuppression Free State is a goal to go for makes sense with the medical knowledge at this time.

INITIAL REVIEW OF THE MANUSCRIPT

Google Search:

- The same title
- Duplicate publication
- Plagiarism
- No

BPG Search:

- The same title
- Duplicate publication
- Plagiarism
- No



PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 48771

Title: De novo malignancies after liver transplantation: The effect of immunosuppression – personal data and review of literature

Reviewer’s code: 02908399

Reviewer’s country: Pakistan

Science editor: Jia-Ping Yan

Reviewer accepted review: 2019-05-04 11:33

Reviewer performed review: 2019-05-07 02:41

Review time: 2 Days and 15 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 type="checkbox"/> Anonymous
<input checked="" type="checkbox"/> Grade C: Good	polishing	<input type="checkbox"/> Accept	<input checked="" 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

1 Title. Adequate 2 Abstract. Adequate 3 Key words. Adequate 4 Background. Adequate 5 Methods. Adequate 6 Results. The study increases our understanding of DNMs after liver transplant. There is promising evidence that patients can be



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suppression free at some stage in the post transplant period. It would be worthwhile to know if any particular blood levels of immunosuppression like TACROLIMUS and CYCLOSPORIN were linked with DNMS. It would also be interesting to know if immunosuppression increased the risk of HCC recurrence in patients within or outside Milan criteria. There are no tables in the manuscript. Perhaps the frequencies of DNMs in adult and pediatric patients can be represented in tables or graphs. 7 Discussion.
Adequate

INITIAL REVIEW OF THE MANUSCRIPT

Google Search:

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BPG Search:

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 48771

Title: De novo malignancies after liver transplantation: The effect of immunosuppression – personal data and review of literature

Reviewer’s code: 03021264

Reviewer’s country: China

Science editor: Jia-Ping Yan

Reviewer accepted review: 2019-05-05 12:06

Reviewer performed review: 2019-05-11 13:03

Review time: 6 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

De novo malignancies are serious complication that impairs the survival of transplant recipients. This review article examined about the DNMs and immunosuppression weaning both in adult and pediatric OLT recipients through literatures and clinical trials,



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revealed the incidence, main types, possible inducements and main treatment methods of DNMs after liver transplantation. It has a very positive reference value for clinical work. The paper cites a large number of effective references, rich in content, reasonable methods for processing data, and draws conclusions with high reliability. However, due to the relatively low incidence of DNM, the observation period is long, and it is difficult to provide large samples and prospective comparative studies in clinical practice. Therefore, observations of the effects of immunosuppression withdrawal on DNMs were only reported exclusively, and the data does not provide statistical comparison. Further improvement of related studies is required. In addition, liver-localised PTLN as a special type may be originating from the dono, the treatment effect is very different. The donor/host origin of PTLN may have prognostic significance because donor origin has different clinical and pathologic features compared with the case of host origin (as related report [Am J Surg Pathol,2000,24(5):733-41.]), authors may consider adding relevant content.

INITIAL REVIEW OF THE MANUSCRIPT

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BPG Search:

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[Y] No



PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 48771

Title: De novo malignancies after liver transplantation: The effect of immunosuppression – personal data and review of literature

Reviewer's code: 01221666

Reviewer's country: Taiwan

Science editor: Jia-Ping Yan

Reviewer accepted review: 2019-05-04 10:42

Reviewer performed review: 2019-05-12 01:47

Review time: 7 Days and 15 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 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 checked="" 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 systemic review aims to summary data regarding de novo malignancies after liver transplantation. Though the topics is not novel, it is still worth reporting in the era of growing field of transplant oncology. Comments The wordings throughout the



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manuscript needs a great revision. Specific words are suggested. For example, Methods in Abstract In addition, the review assesses the differences in adult and pediatric recipients by describing the adopted immunosuppression regimens, the different type of diagnosed solid and blood "tumors" as well as "the clinically tolerant cases". 1. blood malignancy is a better term for blood tumor 2. the clinically tolerant cases are not clear here. Page 8 3.2.1 PTLT Most PTLTs are due to EBV. Even if a clear cut-off range of EBV-DNA levels has not been well recognized, virus detection may be sufficient to reveal early "lymphoma". Do your "lymphoma" mean all lymphoma or just "PTLT"? Line 9-10 The survival rate was significantly better in patients "treated" with Tacrolimus compared to CsA (81.2% against 50% after 5 years from the PTLT diagnosis). It can be misleading that tacrolimus and CsA are drugs that "treat" PTLT. Page 14 Line 8-10 In fact, physicians, in order to treat or avoid the rejection set the blood levels to the up threefolds,; this can lead to an impairment of the immune system and "expose recipients to DNMs". Do you mean expose recipients to the risk of getting DNM? Figure 2 is missing.

INITIAL REVIEW OF THE MANUSCRIPT

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BPG Search:

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[Y] No



PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 48771

Title: De novo malignancies after liver transplantation: The effect of immunosuppression – personal data and review of literature

Reviewer’s code: 02734287

Reviewer’s country: Croatia

Science editor: Jia-Ping Yan

Reviewer accepted review: 2019-05-05 14:57

Reviewer performed review: 2019-05-15 04:30

Review time: 9 Days and 13 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 polishing	(High priority)	<input checked="" type="checkbox"/> Anonymous
<input type="checkbox"/> Grade C: Good		<input checked="" type="checkbox"/> Accept	<input 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 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

This is a good review on the association of immunosuppression and malignancies. The part discussing the effects of weaning of immunosuppression on malignancies is especially valuable since there is not much data published dealing with this



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phenomenon.

INITIAL REVIEW OF THE MANUSCRIPT

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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: 48771

Title: De novo malignancies after liver transplantation: The effect of immunosuppression – personal data and review of literature

Reviewer’s code: 03372021

Reviewer’s country: China

Science editor: Jia-Ping Yan

Reviewer accepted review: 2019-05-04 11:18

Reviewer performed review: 2019-05-19 07:50

Review time: 14 Days and 20 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 type="checkbox"/> Grade B: Minor language polishing	(High priority)	<input checked="" type="checkbox"/> Anonymous
<input type="checkbox"/> Grade C: Good		<input type="checkbox"/> Accept	<input type="checkbox"/> Onymous
<input type="checkbox"/> Grade D: Fair	<input checked="" 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 type="checkbox"/> Minor revision	<input checked="" type="checkbox"/> Advanced
		<input type="checkbox"/> Major revision	<input type="checkbox"/> General
		<input checked="" type="checkbox"/> Rejection	<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

With the wide application of orthotopic liver transplantation in patients with end-stage liver disease, the number of long-term survival recipients is increasing, and the de novo malignancies (DNMs) are gradually receiving widespread attention. This article



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reviewed the incidence and the characteristics of DNMs in the adult and pediatric populations of orthotopic liver transplants (OLTs). Then the authors evaluated the role of immunosuppression minimization and withdrawal in liver transplant patients. However, there is currently insufficient evidence to confirm that immunosuppression withdrawal can reduce the incidence of DNMs. There have been some similar studies on DNMs after liver transplantation. This review provides limited new ideas for this field. In addition, some major issues need to be clarified. 1. In the ABSTRACT, the authors argued that ‘the reconstitution of the immunological pathway could decrease the incidence of DNMs and may also help in treating liver transplanted patients suffering from cancers’, this conclusion lacks sufficient research evidence and needs to be confirmed by further high-quality researches. 2. The structure of the article is unreasonable, and there are a few mistakes, for example, there is no 3.1 in part 3. The reviewer suggest it be divided into six major parts: introduction, literature research, de novo malignancies in the OLT population, the role of IS minimization and withdrawal in liver transplant patients, discussion, and conclusion and future prospects. 3. ‘Several studies have demonstrated that the tolerogenic potential of the liver allows IS discontinuation and a permanent IS-free state (IFS)...’ What is the tolerogenic potential of the liver? The authors should explain this sentence in detail and annotate relevant references. 4. The authors should describe Figure 1 in detail. How many studies and patients were included in this article, and how many of them were about adult or pediatric OLT recipients. What were the age and sex distribution of these patients? 5. Abbreviations in the text should be noted where they first appeared, such as ALD, HNC, and LFTs. 6. In Page 6, the ‘2.4 Aim’ should be introduced in the INTRODUCTION part, and this article is a review, the ‘primary end point’ and the ‘secondary end points’ are mainly used for clinical trials. 7. In Page 7, ‘OLT recipients experience the highest onset rate of lymphomas (57%)’, ‘Overall, skin cancers are the most diagnosed DNMs’, these



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two sentences contradict each other. 8. In Page 8, 'Over the years, albeit the mortality remains high (up to 85% and 69% respectively after one and five years) PTLDs are decreasing'. The mortality after one year was higher than that after five years? What is the reason for the decrease of PTLDs? 9. In Page 10, 'Despite being identified at earlier stages amongst OLT patients, the prognosis of colorectal metastasis is still worse than the general population', why the prognosis of OLT patients with colon cancer is reduced. 10. In Page 12, 'Data from...children with post-transplant non-PTLDs DNMs are older than recipients developing PTLDs malignancies (7.9 vs. 13.2 years of age, $P < 0.0001$)', the age was 13.2 vs. 7.9? 11. In Page 13, mTORi, CNIs, antilymphocyte medications and corticosteroids play different roles in the development of DNMs, and mTORi might play a slight protective role, so why should the patients stop all drugs, rather than selectively stop carcinogenic drugs? 12. In Page 13, 'IS drugs activate different pathways in the immune system and need to be carefully selected.' It would be better for the authors to list the pathways that are activated by IS and explain their relationship to DNMs. 13. Figure 2 is poorly organized, the resolution was low, and it was easily confused. It may be better to use a percentage for each malignancy, not the number of cases, and each malignancy should be arranged in the same order, such as the US, Swden, and Israel. In addition, the incidences of DNMs vary greatly among different registries. What are the possible reasons? 14. Table 2 listed the incidence of malignancies after pediatric Solid Organ Transplantation, but this study mainly focused on the malignancies after liver transplantation, so I think table 2 is useless and meaningless for the conclusion of this article.

INITIAL REVIEW OF THE MANUSCRIPT

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Duplicate publication

Plagiarism

Y] No

BPG Search:

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Duplicate publication

Plagiarism

Y] No



PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 48771

Title: De novo malignancies after liver transplantation: The effect of immunosuppression – personal data and review of literature

Reviewer’s code: 00052926

Reviewer’s country: Greece

Science editor: Jia-Ping Yan

Reviewer accepted review: 2019-05-07 17:04

Reviewer performed review: 2019-05-19 21:11

Review time: 12 Days and 4 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 checked="" type="checkbox"/> Anonymous
<input type="checkbox"/> Grade C: Good		<input type="checkbox"/> Accept	<input 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 type="checkbox"/> Advanced
		<input type="checkbox"/> Major revision	<input checked="" 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

The authors conducted an interesting review and reported their personal observations about the De novo malignancies development after liver transplantation. The manuscript is written concisely and the data are convincing. I have the following minor



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issues with the manuscript: 1. mTOR inhibitors might play a slight protective role reducing the incidence of DNMs compared to calcineurin inhibitors in patients with OLT. However, many patients take mycophenolate mofetil in combination with CNI. What is the role of mycophenolate in DNM development? Are there any data? Please comment. 2. Alcohol abuse, smoking and PSC diagnosis correlates with increased risk of developing DNMs. How do the authors explain the high probability of developing DNMs in these 3 groups? 3. PTLD are the second most prevalent DNMs after skin carcinoma in adults with OLT. What types of PTLD do the adults develop? What is the time mediating from OLT to the development of PTLD? 4. Skin cancer is the most prevalent DNM in adults with OLT. What is the prevalence of skin cancer? What is the time mediating from OLT to the diagnosis of skin cancer? 5. Please do not use acronyms like "IS" in the title of chapters. 6. Please make correct use of commas throughout the manuscript.

INITIAL REVIEW OF THE MANUSCRIPT

Google Search:

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BPG Search:

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- No



PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 48771

Title: De novo malignancies after liver transplantation: The effect of immunosuppression – personal data and review of literature

Reviewer’s code: 00050232

Reviewer’s country: Brazil

Science editor: Jia-Ping Yan

Reviewer accepted review: 2019-05-09 16:12

Reviewer performed review: 2019-05-27 15:22

Review time: 17 Days and 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 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

The subject of the article is the one with the greatest problems concerning liver transplantation. The review was performed using good and extensive bibliographic references. The Discussion Section is objective as well as the suggested perspectives. For



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these reasons the manuscript deserves publication.

INITIAL REVIEW OF THE MANUSCRIPT

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