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# ESPS PEER-REVIEW REPORT

**Name of journal:** World Journal of Transplantation
**ESPS manuscript NO:** 24035
**Title:** Higher plasma bilirubin predicts veno-occlusive disease in early childhood undergoing hematopoietic stem cell transplantation with cyclosporine
**Reviewer's code:** 02446204
**Reviewer's country:** Japan
**Science editor:** Xue-Mei Gong
**Date sent for review:** 2016-01-03 18:11
**Date reviewed:** 2016-01-04 14:07

| CLASSIFICATION | LANGUAGE EVALUATION | SCIENTIFIC MISCONDUCT | CONCLUSION |
|---|---|---|---|
| [ Y] Grade A: Excellent | [ ] Grade A: Priority publishing | Google Search: | [ Y] Accept |
| [ ] Grade B: Very good | [ Y] Grade B: Minor language polishing | [ ] The same title | [ ] High priority for publication |
| [ ] Grade C: Good | [ ] Grade C: A great deal of language polishing | [ ] Duplicate publication | [ ] Rejection |
| [ ] Grade D: Fair | [ ] Grade D: Rejected | [ ] Plagiarism | [ ] Minor revision |
| [ ] Grade E: Poor | | [Y ] No | [ ] Major revision |
| | | BPG Search: | |
| | | [ ] The same title | |
| | | [ ] Duplicate publication | |
| | | [ ] Plagiarism | |
| | | [Y ] No | |

## COMMENTS TO AUTHORS

This review is well written, presenting a very significant issue of "an increased risk for developing VOD after cyclosporine treatments in younger (< 8 years old) generations". Authors also claimed that the plasma BILmax levels being ≥ 1.4 mg/dL would provide a useful indicator to recognize the development of VOD in those generations. The information provided by the authors I believe that this report will contribute to the establishment of an up-graded protocol in cyclosporine-based immunosuppressive therapies for children. I hope that similar studies will be performed in other countries to confirm the reproducibility of the finding shown by the current study. This manuscript is worth-publishing in World Journal of Stem Cells. Nevertheless, there are some errors or reader-unfriendly expressions that should be corrected or up-graded before publication. Minor concerns 1) In line 45 (in page 3), the words "G#1≥ 8" should be corrected as "G#1≥ 18". 2) In lines 69-70 (in page 5), the phrase "… differences between neonate, children and adult populations … " would better be replaced by "… differences between neonate, child and adult populations … " or "… differences between neonates, children and adults … ". 3) In line 151 (in page 9), the phrase " …

seemed to be a risk factor … " would better be replaced by " … would be a possible risk factor …". 4) In line 152 (in page 9), the phrase "… in these patients who …" should be corrected as "… in those patients who …". 5) In lines 170-172 (in page 10), the sentences "When we set a BILmax cutoff of 2.0 mg/dL, there was an obvious difference in overall VOD incidences. However, the difference was not seen in G#1, whereas highly significant differences were found in G#2 and G#3" are too complicated. They can be replaced by, for example, "Setting the BILmax cutoff level at 2.0 mg/dL demonstrated an obvious increment in VOD incidences in high BILmax groups when G#2, G#3 or the total population was analyzed, although it failed in demonstrating increased VOD incidences when G#1 was solely analyzed (data not shown)." 6) In lines 172-175 (in page 10), the sentences "More importantly, the result of two by two analyses provided strong evidence that a level of 1.4 mg/dL (a minimal significant value obtained empirically) or higher of BILmax might provide a good indicator of VOD incidence by cyclosporine therapy in G#3 ($p<0.0001$) (Table 3). The other groups did not reach statistical significance." would better be replaced by, for example, "More importantly, setting the BILmax cutoff level at 1.4 mg/dL (a minimal significant value obtained empirically) revealed an augmented incidence of VOD in the high BILmax group in G#3 ($p<0.0001$), but not in G#1 or G#2, as determined by two-by-two analyses (Table 3)". 7) In line 231 (in page 13), the word "both" should be deleted.

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**Name of journal:** World Journal of Transplantation
**ESPS manuscript NO:** 24035
**Title:** Higher plasma bilirubin predicts veno-occlusive disease in early childhood undergoing hematopoietic stem cell transplantation with cyclosporine
**Reviewer's code:** 02446119
**Reviewer's country:** China
**Science editor:** Xue-Mei Gong
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| CLASSIFICATION | LANGUAGE EVALUATION | SCIENTIFIC MISCONDUCT | CONCLUSION |
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| [Y] Grade C: Good | [ ] Grade C: A great deal of language polishing | [ ] Duplicate publication | [ ] Rejection |
| [ ] Grade D: Fair | [ ] Grade D: Rejected | [ ] Plagiarism | [Y] Minor revision |
| [ ] Grade E: Poor | | [Y] No | [ ] Major revision |
| | | BPG Search: | |
| | | [ ] The same title | |
| | | [ ] Duplicate publication | |
| | | [ ] Plagiarism | |
| | | [Y] No | |

## COMMENTS TO AUTHORS

The continual use of cyclosporine and especially the maintainance of drug concentration is critical in controlling the incidence of GVHD, but reverse drug reaction exists. Present retrospective study reveal BIL as a possible indicator for VOD incidence, which holds a potential application in monitoring the VOD risk of patients. There should be a table showing the detail information of VOD patients, especially the age, BIL level, cyclosporine concentration. Physiologically, there may be no clear difference in the metabolism of cyclosporine below and above age of 8 years old. Because the authors arbitarily assigned patients into groups according to their ages, this may limit the application of BIL levels to young patients. It will be helpful if more statistical analysis could be performed using age as a factor and one year as a step to test the relationship between age of VOD patients and BIL level and to adjust the cutoff value of BIL. Considering the physiological difference among individuals, the net change of BIL level before and after the use of cyclosporine might be a better indicator in stead of absolute value of BIL. The index of liver function should be included in tables. The discussion should be limited to the results of present data. Going through the discussion, I still

do not know if the quick fall of cylcosporine concentration or the increased burden to liver metabolism cause VOD problem in younger children. " the incidences of VOD increased in childhood age, with patients exhibiting higher plasma concentrations of cyclosporine ", here, the authors should translate the meaning of "higher" compared with present study, otherwise, this citation may cause confusing.

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# ESPS PEER-REVIEW REPORT

**Name of journal:** World Journal of Transplantation
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**Title:** Higher plasma bilirubin predicts veno-occlusive disease in early childhood undergoing hematopoietic stem cell transplantation with cyclosporine
**Reviewer's code:** 00505755
**Reviewer's country:** Japan
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| CLASSIFICATION | LANGUAGE EVALUATION | SCIENTIFIC MISCONDUCT | CONCLUSION |
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| | | BPG Search: | |
| | | [ ] The same title | |
| | | [ ] Duplicate publication | |
| | | [ ] Plagiarism | |
| | | [Y] No | |

## COMMENTS TO AUTHORS

General comments It is the important study about correlation of plasma bilirubin level and prediction of VOD. Some part of the manuscript as below is misleading, which requires revision. Specific comments Title: From the conclusion of this study, it may be suitable to change the title into higher plasma bilirubin….. Please check it carefully. Abstract: The description about G#1 should be as G#1≧18, not as G#1≧8, please check it again. Introduction: Cyclosporine therapy is introduced well in the section. Methods: The description about Duncan test may be added in statistical analysis. Results: It contains the explanation of Tables, the details may be further added. Discussion: In this study, the concentration of cyclosporine seems to be lower in childhood group than in adult group, although the reference showing the higher plasma concentrations of cyclosporine in childhood age has been described in discussion in page 12. The differences between this study and previous studies exhibiting higher plasma concentrations of cyclosporine may be discussed. References: Please check reference citations carefully. Tables: In Table 1, please check donor types. In Table 2, oral dose of cyclosporine in G#2 is the same as in G#1, and significantly lower than in G#3. The "others" may be

specified as “G#1 and G#2” in the text in page 9.