

Reviewed by 00505755

Title: From the conclusion of this study, it may be suitable to change the title into higher plasma bilirubin..... Please check it carefully.

→ **Page 1: The title was corrected to “higher plasma bilirubin...”.**

Abstract: The description about G#1 should be as $G\#1 \geq 18$, not as $G\#1 \geq 8$, please check it again.

→ **Page 3, line 45: The description about $G\#1 \geq 8$ was corrected to $G\#1 \geq 18$.**

Introduction: Cyclosporine therapy is introduced well in the section.

Methods: The description about Duncan test may be added in statistical analysis.

→ **Page 8, line 140: Duncan test was mentioned in statistical analysis.**

Results: It contains the explanation of Tables, the details may be further added.

→ **Page 9, lines 153-156: The further details of Tables were added in the result section as you advised.**

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.

→ **Page 12, lines 217-226: The descriptions for higher plasma concentrations of cyclosporine in childhood age were incorrectly referred and it was corrected in the discussion section. If anything, the plasma concentration of cyclosporine in childhood age was lower than adult because of the faster clearance of cyclosporine.**

References: Please check reference citations carefully.

→ **The references were checked again as the reviewer suggested.**

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.

→ The donor types in Table 1 were checked again and appropriate.

→Page 9, line 160: The “others” in the text in page 9 was appropriately edited.

Reviewed by 02446119

The continual use of cyclosporine and especially the maintenance 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.

→Tables 1 and 2: The detail information of VOD patients such as the age, BIL level, and cyclosporine concentration were already shown in Tables 1 and 2.

Physiologically, there may be no clear difference in the metabolism of cyclosporine below and above age of 8 years old. Because the authors arbitrarily 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.

→Before assigning patients into three groups in this manuscript, the statistical analysis was conducted in subgroups of patients divided by one year difference. The ages of 8 and 18 years were chosen as the cutoffs to show the differential relationship between age of VOD patients and BIL level.

Considering the physiological difference among individuals, the net change of BIL level before and after the use of cyclosporine might be a better indicator instead of absolute value of BIL.

→ There was no significant difference in BIL level before cyclosporine treatment among three groups of patients. Also the criteria of hyperbilirubinemia and bilirubin for McDonald's VOD-Seattle Criteria are usually determined by the absolute value of BIL. Therefore, the relationship of absolute BIL value and VOD occurrence was evaluated in this study.

The index of liver function should be included in tables.

→In the result section, we mentioned that there was no difference in ALT or AST value among three groups of patients, which was used as the indicator of liver function. According to the reviewer's comment, these parameters were added in Table 1.

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 cyclosporine 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.

→ The description and the reference about VOD incidence and cyclosporine concentration were incorrectly written and it was revised. The key finding in this part is that higher VOD incidence is strongly associated with the higher bilirubin level in younger childhood group. The sentences were edited as follows: our finding showing the lower plasma cyclosporine level with the higher occurrence of VOD in G#3 differs from the previous report that the higher plasma concentrations or high doses of drugs in pediatric HSCT patients were usually associated with the frequent and severe VOD even in the different therapy in HSCT patients.^[34] In the present study, low plasma cyclosporine levels may reflect its high turnover rate in G#3.

Reviewed by 02446204

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 \geq 8” should be corrected as “G#1 \geq 18”.

→ **Page 3, line 45: “G#1 \geq 8” was corrected as “G#1 \geq 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 ... ”.

→ **Page 5, lines 69-70: The sentence was revised by “... differences between neonate, child and adult populations”.**

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 ... ”.

→ **Page 9, line 151: The phrase was revised as suggested.**

4) In line 152 (in page 9), the phrase “... in these patients who ...” should be corrected as “... in those patients who ...”.

→ **Page 9, line 152: The phrase was revised as recommended.**

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).”

→**The authors agree to the comment and the sentences were revised as suggested.**

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)”.

→**The sentences were edited as suggested.**

7) In line 231 (in page 13), the word “both” should be deleted.

→ **Page 13, line 229: The word “both” was deleted.**