Author's response to reviews

Title: Invasive fungal infection among hematopoietic stem cell transplantation patients with mechanical ventilation in the intensive care unit

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Author's response to reviews: see over
Dear Dr. Nikolaos Markou:
Thanks you for the opportunity to revise our manuscript. We had revised our manuscript in light of the reviewer’s concern and comments. We resubmit the revision of detailed discussion and response to the reviewer’s concern and comments. Please reconsider it for publication.
Thank you once again for the opportunity to revise this manuscript.

Sincerely,

Chen-Yiu Hung
Reviewers' comments:

1. General comment: it would be very interesting to have data on IFI for all HSCT patients admitted to the ICU regardless of mechanical ventilation. The conclusion of the study is simply that HSCT patients who are mechanically ventilated have a uniformly dismal prognosis, regardless of the presence or absence of IFI. What is the impact of IFI in ICU patients who are not in need of mechanical ventilation? Major compulsory revision.

Response:

On the page 14, Discussion section: We added one paragraph after 4th paragraph.

During the study period, there were 7 HSCT patients were admitted to ICU without mechanical ventilation. Among these 7 non-ventilated critically ill patients, four patients had IFI (57%). All of these 4 IFI patients were diagnosed possible IFI and were infected by Aspergillus species at late ICU admission after HSCT (>40 days). The ICU mortality rate was 50% in these 4 IFI non-ventilated critically ill patients. Because of the small sample size (n=4), large scale study is warranted to clarify the influence of IFI on the outcome of non-ventilated critically ill HSCT patients.

2. Abstract - results section: instead of ‘longer duration of ICU admission’ I suggest ‘late ICU admission’. Minor essential revision

Response:

(1) On the page 2, Result section, 3th line:

Revised as:
The identified risk factors for IFI included longer duration of ICU admission after HSCT (>40 days after HSCT), GVHD and high dose corticosteroid (p<0.01).

(2) On the page 2, Conclusion section, 2nd line:

Revised as:
The identified risk factors for IFI include longer duration of ICU admission after HSCT, GVHD and high dose corticosteroid use.

3. Abstract - Conclusion: ‘Early intervention ... therapeutic direction’. This is more a wishful thought than a conclusion firmly based in data presented in the paper. I would suggest deleting it. Minor essential revision

Response:

On the page 3, Conclusion section, 3rd line:

We deleted the following sentence “Early intervention and adequate prescription with.
mold-active azoles or echinocandins may provide future therapeutic direction.”

4. Introduction 3rd Paragraph: the statement that ‘more than 60% of HSCT recipients require mechanical ventilation ... very poor prognosis’ should be re-examined. Possibly the authors refer only to patients admitted to the ICU? Minor essential revision

**Response:**
On the page 4, Introduction section, 2nd paragraph, 2nd line :
More than 60% of HSCT recipients require mechanical ventilation, which is associated with a very poor prognosis [4,5].

**Revised as:**
More than 60% of HSCT recipients require mechanical ventilation admitted to the ICU, which is associated with a very poor prognosis [4,5].

5. 3rd paragraph: I would suggest updating the references on the impact of mechanical ventilation in HSCT patients. Minor essential revision

**Response:**
We have updated the reference on the impact of mechanical ventilation in HSCT patients. We exchanged the current reference [4] as below.


6. In the 1st paragraph the authors start discussing about critical illness in HSCT patients. They return to the same subject in paragraph 3. I believe that paragraph 2 (on IFI in HSCT patients) should follow paragraph 3. Minor essential revision

**Response:**
On the page 4 and 5,Introduction section, we exchanged the order of paragraph 2 and paragraph 3. The order of references also changed as below.

**Revised as:**
Some post transplantation complications may be life-threatening and require ICU admission. More than 60% of HSCT recipients require mechanical ventilation, which is associated with a very poor prognosis [4,5]. Although the mortality rate of HSCT recipients admitted to the ICU has declined over the last two decades, it still exceeds 80% for those receiving mechanical ventilation [5]
Invasive fungal infections are increasingly recognized in critically ill HSCT patients, with the main risk factors being age, unmatched donor, neutropenia, acute GVHD, underlying disease, corticosteroid therapy, and duration of fungemia [6]. Other risk factors for serious fungal infections are related to critical illness, including immunosuppressive therapy, neutropenia, multiple broad-spectrum antibiotics, total parenteral nutrition, and indwelling catheters [6]. Despite advances in performing HSCT procedures, in prophylactic antifungal agents, and in ICU care, high mortality and morbidity are still major concerns for HSCT patients suffering IFI [7].

7. Patient information and data collection 1st paragraph: Data about number of patients enrolled in the study, should be removed in the results section. Minor essential revision

Response:
On the page 10, Result section, 1st paragraph, 4th line, we delete the sentence “A total of 60 HSCT patients admitted to ICU with mechanical ventilation were enrolled.”

8. 3rd paragraph: recorded the diagnostic criteria (?). perhaps clinical characteristics? Minor essential revision

Response:
On the page 7, Patient information and data collection section, 3rd paragraph, 1st line:
Revised as:
For patients with an IFI, we recorded the diagnostic criteria, clinical characteristics, the cytology or histology results, the mean duration of diagnosis after ICU admission, and the treatment.

9. Definitions Paragraph 2: Clarify ‘Acute GVHD... occurring before day 100’. Minor essential revision

Response:
On the page 8, Definitions section, 2nd paragraph, 1st sentence:
Acute GVHD was defined as occurring two to four weeks after myeloablative chemotherapy and generally occurring before day 100 [11].
Revised as:
Acute GVHD was defined as GVHD occurring before day 100 after myeloablative chemotherapy [11].

10. Results Paragraph 1: Replicates data already presented in table 1. Minor essential
Mean age at transplantation was 34.5 years old, and 37 patients (61.6%) were male. The main underlying diseases of these patients were acute leukemia (n = 23, 38%) and chronic myeloid leukemia (n = 12, 20%). Most patients received an allogenic stem cell transplantation (n = 36, 60%) either from non-identical siblings with matched human leukocyte antigens (HLA) (n = 29) or from HLA-matched unrelated donors (n = 7). A total of 31 of the 46 (67%) allogenic transplantation patients (36 patients with peripheral blood and 10 patients with bone marrow) had GVHD. The mean APACHE II score and SOFA score were 24.5 and 12 at ICU admission.

Some of the data in paragraph 2, such as the non-significant difference in CMV infection or neutropenia, may also be omitted (they are included in table 2). Also data on ORs from multiple logistic regression (they are also presented in table 3).

Response:
On the page 10 and 11, Result section, 2nd paragraph, we omitted the below sentences:

(1) 7th line to 10th line: The CMV infection rate was higher but not significantly different in patients with IFI compared to those without IFI (33% vs. 25%, \(p = 0.1\)). The two groups of patients had the same ratio of neutropenia (80%) on the first day of ICU admission.

(2) 16th line to 20th line: The odds ratios of duration to ICU admission after HSCT (>40 days) were 1.001 (95% confidence interval, 1.001-1.006, \(p = 0.008\)); odds ratio of GVHD were 8.291 (95% confidence interval, 1.687-40.476, \(p = 0.009\)); odds ratio of high-dose corticosteroid use were 9.459 (95% confidence interval, 2.040-43.867, \(p = 0.004\)) for IFI.

12. Paragraph 2: instead of ‘duration of ICU admission’, late ICU admission. The same correction should be applied in the abstract, discussion section and in table 3. Also rephrase ‘Table 3 reveals ... corticosteroid use’ Minor essential revision

Response:
We revised as “late ICU admission” instead of “longer duration of ICU admission” in the abstract, discussion section and table 3.

Abstract:
On the page 2, Result section, 4th line
On the page 2, Conclusion section, 2nd line

Discussion section:
On the page 13, 1st paragraph, 3rd line
On the page 17, 1st paragraph, 3rd line

Table 3:
In table 3, Variable column, 3rd item:
“Duration to ICU after HSCT>40 days” revised as “Late ICU admission (>40 days after HSCT)”

On the page 11, 9th line:
Rephrased as: Table 3 reveals multivariate analysis to identify the following variables to be independent of statistic significance: duration of late ICU admission after HSCT (>40 days after HSCT), GVHD and high dose corticosteroid use.

On the page 18, Key message 2:
The risk factors for IFI in HSCT patients with mechanical ventilation were longer duration of late ICU admission after HSCT, GVHD and high dose corticosteroid use.

13. Paragraph 5: ‘Aspergillus was the most infection fungal’? Rephrase. Minor essential revision

Response:
On the page 12, Result section, 5th paragraph, 4th line:
Aspergillus was the most infection fungal, affecting 12 of these 20 patients.
Revised as: Aspergillus species were the most common isolated fungi, affecting 12 of these 20 patients.

14. Table 2 Duration to ICU after HSCT: the authors probably refer to early vs late ICU admission and not ‘duration’ Minor essential revision

Response:
In table 2, 3rd item:
“Duration to ICU after HSCT (day)” revised as “Early vs late ICU admission after HSCT (day)”

Table 2 can be made more concise. Simply state the presence of factors such as GVHD, CMV infection, mortality (or survival) etc and not both presence and absence of these entities. Minor essential revision
Response:
In table 2, we revised the presentations of the items of GVHD, CMV infection, Neutropenia, Concurrent bacteremia, High dose corticosteroid and ICU mortality.
Table 2. Characteristics of HSCT patients with and without invasive fungal infection

<table>
<thead>
<tr>
<th></th>
<th>Invasive fungal infection (n = 20)</th>
<th>Without invasive fungal infection (n = 40)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age at ICU admission</td>
<td>30 ± 7.9</td>
<td>37 ± 11.0</td>
<td>0.024 *</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>12 (60%)</td>
<td>15 (37.5%)</td>
<td>0.099</td>
</tr>
<tr>
<td>Female</td>
<td>8 (40%)</td>
<td>25 (62.5%)</td>
<td></td>
</tr>
<tr>
<td>Early vs. late ICU admission after HSCT (day)</td>
<td>209 ± 158.2</td>
<td>73 ± 56.6</td>
<td>0.068</td>
</tr>
<tr>
<td>ICU length of stay (day)</td>
<td>10.7 ± 7.6</td>
<td>12.8 ± 14.5</td>
<td>0.533</td>
</tr>
<tr>
<td>Underlying disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALL</td>
<td>4 (20%)</td>
<td>5 (12.5%)</td>
<td></td>
</tr>
<tr>
<td>AML</td>
<td>8 (40%)</td>
<td>7 (17.5%)</td>
<td></td>
</tr>
<tr>
<td>CML</td>
<td>3 (15%)</td>
<td>9 (22.5%)</td>
<td></td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>1 (5%)</td>
<td>3 (7.5%)</td>
<td></td>
</tr>
<tr>
<td>Hodgkin’s disease</td>
<td>2 (10%)</td>
<td>2 (5%)</td>
<td></td>
</tr>
<tr>
<td>Other hematological disease</td>
<td>2 (10%)</td>
<td>14 (34.5%)</td>
<td></td>
</tr>
<tr>
<td>Type of transplantation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allo-PBSCT / Allo-BMT</td>
<td>13 (65%) / 4 (20%)</td>
<td>24 (60%) / 5 (12.5%)</td>
<td></td>
</tr>
<tr>
<td>Auto-PBSCT/Auto-BMT</td>
<td>3 (15%) / 0</td>
<td>10 (25%) / 1 (2.5%)</td>
<td></td>
</tr>
<tr>
<td>GVHD</td>
<td>16 (80%)</td>
<td>15 (37.5%)</td>
<td>0.003 **</td>
</tr>
<tr>
<td>CMV infection</td>
<td>7 (35%)</td>
<td>6 (15%)</td>
<td>0.101</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>16(80%)</td>
<td>32 (80%)</td>
<td>0.099</td>
</tr>
<tr>
<td>Concurrent bacteremia</td>
<td>12 (60%)</td>
<td>26 (65%)</td>
<td>0.705</td>
</tr>
<tr>
<td>High dose corticosteroid</td>
<td>13 (65%)</td>
<td>10 (25%)</td>
<td>0.003 *</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>22 ± 5.7</td>
<td>27 ± 9.8</td>
<td>0.014 *</td>
</tr>
<tr>
<td>SOFA score</td>
<td>10.45 ± 2.7</td>
<td>13 ± 4.0</td>
<td>0.020 *</td>
</tr>
<tr>
<td>ICU mortality</td>
<td>17 (85%)</td>
<td>36 (90%)</td>
<td>0.676</td>
</tr>
</tbody>
</table>

*: P-value ≤ 0.05; **: P-value ≤ 0.01.
Data represent as mean ± S.D or number (ratio)
Abbreviations: HSCT: hematopoietic stem cell transplantation; ALL: acute lymphoid leukemia; AML: acute myeloid leukemia; CML: chronic myeloid leukemia; MDS: myelodysplastic syndrome; PBSCT: peripheral blood stem cell transplantation; BMT: bone marrow transplantation; GVHD: graft versus host disease; APACHE II: acute physiology and chronic health evaluation II; SOFA score: sequential organ failure assessment score; and ICU: intensive care unit.
15. Tables 4 and 5 are probably redundant.

Response:
1. We deleted Table 4 and Table 5.
2. On the page 12, Results section, 4th paragraph, 3rd line: delete below sentence
   Table 4 reveals the outcomes of the different diagnostic categories in these IFI patients.
   On the page 12, Results section, 4th paragraph, 8th line: delete below sentence
   Table 5 shows the outcomes of different fungal species in the IFI patients.

16. Discussion The major finding of the study is high prevalence of IFI in mechanically ventilated HSCT patients, whereas the dismal prognosis of mechanically ventilated HSCT patients has long been known. Given the already very high mortality in this subgroup, presence of IFI does not seem to affect outcome. It would be interesting to have data on the prevalence and influence on outcome of IFI in non-ventilated critically ill patients. Major compulsory revision

Response:
On the page 14, Discussion section: We added one paragraph after 4th paragraph.
   During the study period, there were 7 HSCT patients were admitted to ICU without mechanical ventilation. Among these 7 non-ventilated critically ill patients, four patients had IFI (57%). All of these 4 IFI patients were diagnosed possible IFI and were infected by Aspergillus species at late ICU admission after HSCT (>40 days). The ICU mortality rate was 50% in these 4 IFI non-ventilated critically ill patients. Because of the small sample size (n=4), large scale study is warranted to clarify the influence of IFI on the outcome of non-ventilated critically ill HSCT patients.

17. 7th paragraph: in fact the finding of the paper is not that prognosis of IFI in HSCT patients is poor, but that IFI has no further impact on the already dismal prognosis of mechanically ventilated HSCT patients. The rest of the paragraph (discussion Candida score, Candida infection as predictor in the general ICU patients), is irrelevant. Minor essential revision

Response:
On the page 15 and 16, Discussion section, 7th paragraph: Revised as below
   The prognosis for HSCT patients with IFI is poor. We had the same disappointing outcomes with an 88% ICU mortality rate in HSCT patients with mechanical ventilation. Leon had reported an easy-to-use Candida score to predict likelihood of Candidiasis [25].
In one retrospective study, Chen reported that nosocomial Candida infection was an independent predictor of ICU mortality in critically ill patients [26]. Our present study had the same ICU mortality rate and reflected these unique groups of patients with host variables and severe comorbidities. IFI has no further impact on the already dismal prognosis of mechanically ventilated HSCT patients.

18. Discussion should be more concise. Major compulsory revision

   **Response**:
   Thanks the reviewer comment and we had carefully check again and revised my discussion to be more concise.

19. **Level of interest**: An article of importance in its field

20. **Quality of written English**: Needs some language corrections before being published

   **Response**:
   Thanks the reviewer comment and we had carefully check again for typographical and grammatical error in our manuscript.

21. **Statistical review**: No, the manuscript does not need to be seen by a statistician.