Author's response to reviews

Title: Ventilatory and ECMO treatment of H1N1-induced severe respiratory failure: results of an Italian referral ECMO center.

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Author's response to reviews:

Re: MS: 1608630004020891

Dear Editor,

I would like to thank You and the Referees for the constructive criticisms and comments to our manuscript.

The revised manuscript has been amended according to the points raised by the Referees, and language has been edited by an English native speaker. A point by point reply to the Referee’s comments is enclosed.

We hope that our paper can be now of interest for your Journal.

Yours sincerely,

Giovanni Zagli (corresponding author of behalf of all the authors)

Answer to Reviewers.

We thank all Reviewers for their time and effort in reading the manuscript. Modified parts have been written in blue for an easier verification.
Answer to Reviewer #1.

Major comments
1) Bleeding episodes occurred but were not critical, despite patients required special care and blood transfusion. In the context of an extracorporeal lung assistance with the need heparin infusion, we believe that it is not possible to eliminate these kind of adverse events, but the possibility to manage them, makes ECMO a safe and feasible therapeutico option.

2) We thank Reviewer #1 for the suggestion: algorithm has been added as table.

3) In Draeger Evita XL ventilator (as in many modern ventilators), a software to perform the inspiratory/expiratory curve and the analysis of inflection points is available. The level of PEEP, as bottom value of the curve, can be adjusted. In our protocol we set it at a value of 5 and the pressure limit was set at 40 mmHg.

4) You are right, we apologize for the badly written sentence: recruitment manoeuvres were performed (if needed) maximum twice per day. This has been stated in the revised version.

Minor comments
1) “rescue solution” was referred to all cases (usually from peripheral hospitals) for which ECMO is requested after prolonged ventilation treatment with high pressure. Our intention was to invite colleagues to consider ECMO in an early stage of disease and not in case of non-responding patients.

2) Table 1 has been corrected, we apologize for the trivial errors.

Answer to Reviewer #2.

Major comments
Introduction section
The comment of Reviewer is correct: the sentence has been changed.

Method section
• The study was retrospective, now specified.
• Pressure plateau limit was set at 30 cmH2O. Steroids were administered at low dosage (20 mg metilprednisolon twice per day) to prevent lung fibrosis. Diuretic were administered in different dosage, depending on patient’s renal function and clinical judgment.
• Correct, we thank: criteria have been added in a new table.
• All samples were daily collected: BAL was obtained with a mini-invasive system, not by bronchoscopy (specifications added in methods). Details has been now added in the revised version.

Result section
Overall
Tables have been modified and corrected.
Ventilatory and ECMO parameters have been and presented in Table 4.

LUS
We thank Reviewer #2 for this comment. The section has been changed and the role of LUS clarified.

ECMO section
Duration of ECMO and days on ventilation have been added and reported for any single patient, in Table 4.
In table 2 duration of ventilation of non-ECMO and ECMO patients is presentd.
Ventilatory parameters before and during ECMO are detailed in Table 4.

Discussion section
The key points were chosen to underline the features of the manuscript which were, in our opinion, more interesting, in consideration of the case series presented.

Minor comments
All corrections have been made, as suggested.

Answer to Reviewer #3

Lung Ultrasound
The more frequent ultrasound patterns are reported, and the impact in reducing conventional radiological investigation have now been added.
A thorough report of our LUS data are subject of another publication, actually under revision. Therefore we cannot provide a more detailed presentation of this aspect.

H1N1 diagnosis
We acknowledge that sensitivity of a test (i.e. PCR from bronchoalveolar lavage or from pharyngeal swab which we described in our work) should be calculated in relation to a "gold standard". Unfortunately assays for antibodies titres for H1N1 are not clinically available at our institution, therefore such a comparison could not be conducted.
Therefore, in order to accept your suggestion, we have amended the text, reporting the percentage of positive tests in our population and any reference to the term "sensitivity" has been deleted.
The criteria for starting ECMO are now reported in Table 1.

Mortality rate and bleeding complications
Thank you for your stimulating criticism about this subject. We think that a comparison of our mortality rate with larger series of patients is unfeasible and drawing any conclusion about mortality outcome is not an aim of our report. Nevertheless it is still possible that we adopted a more “liberal” use of ECMO. But we think that this is a natural occurrence as a technique become more available and previous studies encourage its utilization. We have added some comments about that in discussion chapter.

Some comments have been added to discussion for a more accurate appraisal of bleeding.

Answer to Reviewer #4
We really thank to Reviewer #4 for the appreciation of our article, and for the constructive criticisms and suggestions. The language has been edited by an English native speaker.
Details on cannulas type and size have been added to Methods section.
Blood transfusion requirements have been added in table.
Heparin infusion was adjusted for an aPTT level between 50 and 80 seconds (now stated in methods).
No antifibrinolytic drugs were commonly used.
More comments on bleeding adverse event have been added in discussion, and limitations have been highlighted.