

Peer Review File

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Reviewer A:

Comment 1: The authors concluded that "T0-Ph was significantly higher in patients requiring invasive MV." However, could it be interpreted differently, such as patients requiring intubation having acidosis and significant changes over 24 hours?

Response: We don't conclude that there is a causality link between high phosphatemia level and the need for invasive mechanical ventilation, but it is a fact that in our univariate analysis, T0-Ph was significantly higher in patients requiring invasive MV as compared to others. We changed the end of the conclusion to clarify this issue. (line 322-323)

Comment 2-3: Could it be reflecting the severity of COPD and osteoporosis, rather than a direct link to the outcomes?

Could it be reflecting the severity of pneumonia rather than being a direct marker for the specified outcomes?

Response: The questions raised by the reviewer are very interesting and meaningful. We completely agreed that, the clinical meaning of phosphatemia remained undetermined as it is addressed in the limitation section. A lot of intricated factors could affect phosphatemia and it is difficult to confirm our hypothesis. However, we sought it raised some questions for future studies. In the limitation section we addressed our concern regarding the value of T0-Ph: "but clinical meaning of T0-Ph remained undetermined. It could reflect the severity of the exacerbation, the consequences of respiratory acidosis, a compensatory mechanism triggered by the intracellular acidosis, or all at the same time". (Line 308-3011)

Comment 4: The authors' conclusions may not be directly applicable to clinical practice. How can these findings be applied in clinical settings? It would be beneficial if there were suggestions on how to apply these findings clinically, such as identifying patients with significant 24-hour phosphorus fluctuations who might be at higher risk for intubation and considering preventative measures through supplementation.

Response: We agreed again, but we sought that is phosphatemia is measured in such kind of patient it could be a warning signal if phosphatemia is increased. We add a sentence is this in that way in the discussion/limitations (line 314-316)

Reviewer B:

Major comments:

Comment 1: a patient who has a contraindication to NIV treatment should be excluded from the study as these patients are more likely to be invasively ventilated disregarding their phosphate level.

Response: After verification, in our cohort we don't identified any patient in which NIV couldn't be performed due to a specific contraindication (i.e. anatomical). We add a sentence in the method section to clarify this point. (Line 101-102)

Comment 2: Phosphate measurements taken at 24 hours of admission are reported to decrease compared to admission phosphate in the ventilated patients. However, as median time of NIV in the ventilation group is 2 days, it is likely that some of the patients in the groups of the ventilated patients were not ventilated at 24 hours (as more than half of them were ventilated after 48 hours of NIV). In order to examine any effect of ventilation on phosphate level, it must be clarified that the phosphate level examined is taken after ventilation onset. That it not the case as explained in the manuscript. Therefore, the explanation in lines 264-265 regarding phosphate decrease after ventilation initiation seems inaccurate (another alternative is that the methods and results sections regarding phosphate level in 24hours is inaccurate. If that it the case, these sections should be clarified).

Line 255-265 – the authors suggest a physiological explanation for the result of higher phosphate levels at admission in the patients that would be ventilated. The main assumption is that the greater work of breathing causes accelerated use of ATP which is degraded to ADP and phosphate, and hence phosphate level increases. Another mechanism contributing to phosphate level increment is the baseline respiratory acidosis of COPD exacerbation, causing a physiological increase in phosphate level to enhance phosphaturia, for enhanced titratable acid excretion. This is supported by the decrement of phosphate level after Invasive ventilation. Without experimental physiological evidence, this theory can neither be proved nor disputed. However, there are reports that show opposite results¹. This should be addressed in the discussion. Moreover, bearing in mind that one of the mechanisms suggested is overwhelming ATP degradation, it seems logical that anaerobic metabolism will increase in the very same tissues, leading to hyperlactatemia. However, lactate levels are not different between the groups. This should also be addressed in the discussion.

Response:

1) Regarding this point, our results are expressed in a confusing way. The duration of NIV correspond to the total duration of NIV meaning before invasive MV and after invasive MV in the group of patients intubated. So, the totality of the patient (except one) in the intubated group was intubated before 24H after admission. We modify the **table 2**, to clarify this issue and we add a sentence in the results (**line 195-196**)

2) We agreed with the reviewer regarding its comment on our physiological hypothesis, we notify in several occasion that it is a hypothesis and because of its design (retrospective study) some elements are missing to prove our hypothesis as it is addressed in the limitation section: “important data such as phosphaturia was not monitored, it would have been helpful to

determine in which proportion acid load was eliminated through the phosphate buffer between the two groups of patients”. (Line 301-303)

We also say that we cannot link hyperphosphatemia to a specific cause and it can be due to intricate factors: “but clinical meaning of T0-Ph remained undetermined. It could reflect the severity of the exacerbation, the consequences of respiratory acidosis, a compensatory mechanism triggered by the intracellular acidosis, or all at the same time”. Other study designed to investigate these issues are de facto needed. (Line 303-306)

Regarding the reports that show different results (1), the full text of the study is not available, whereas it is stated that the paper is free. The abstract raised some question. First there is a lot of typographic fault, second in the results section there are no results. The authors stated that hypophosphatemia and other electrolytes deficiency is associated with less mechanical ventilation etc.....without any number and statistical analysis. Based on that we have serious doubt on the pertinence of this study.

Regarding anaerobic metabolism and lactate production it is difficult to determinate the part of the anaerobic metabolism in respiratory muscle of patient with acute respiratory failure. The lactate is similar between the two group of patients but in our hypothesis, we only suggest that in the most severe patients ATP hydrolysis is higher and could participate to the increase of phosphatemia in patient who need invasive MV in ICU. We add a sentence in the discussion to address this issue. (Line 283-287)

Comment 3: given the physiological theory for the high phosphate level in the ventilated group, the authors should address why it was not found significant in the multivariate analysis.

Response: We add a sentence in the discussion section. (Line 288-292)

Minor comments:

Comment 1: Line 66 – better rephrasing of the end of the line (perhaps “consist of” instead of “consist in”). Line 78 – should be “until now”, (instead of “since now”)

Response: Correction have been made in the text. (Line 66 and 76)

Comment 2: Line 92-93 & line 97 – The inclusion criteria are not clear. Lines 92-93 state that patients with COPD comorbidity were included. Line 97 states that patients with reasons other than COPD exacerbation were excluded. I think it would be clearer to state that COPD exacerbation in a patient over 40 is the inclusion criterion.

Response: The sentence stating the patients with reasons other than COPD exacerbation were excluded was deleted. (Line 99)

Comment 3: Line 99 – To those who are not familiar with French law (like me), the informed consent in a retrospective study is odd. Perhaps a general clarification, stating that French law mandates obtaining patients’ informed consent for future retrospective studies. If it is not the situation, then it is not clear how can a patient refuse to participate in a retrospective study.

Response: All patient must be informed of the use of their medical data in a retrospective way. The ethics section has been clarified (Line 86-89). We also removed the sentence: “patient refusal to participate” in the patient’s section as it is not clear.

Comment 4: Line 112 – I think neither Dysphosphatemia nor phosphatemia fits. Maybe just mention phosphate reference values. Also, adding in barracks the reference values in mg/Dl might assist readers who are used to it (2.5-3.5mg/Dl).

Response: Reference values in mg/dl have been added. (Line 116-117)

Comment 5:

Line 135 – correct the , in the number to a “.” (0,66 □ 0.66)

Line 137 – Length of ventilation should be added the data collected section.

Response:

Line 135 Correction has been made (Line 137)

Line 137 It is already stated in this section: “type and duration of ventilatory assistance (oxygen administration, NIV, invasive MV” (Line 146-147)

Comment 6: Lines 158-160 – Pease explain why including only variables with $p < 0.001$ in the multivariate analysis, and not all the significant variables in univariate analysis.

Response: we included variables with $p < 0.001$ and those that were clinically relevant. As the group of intubated patients included 33 patients we used four variables in the model.

Comment 7: Line 174-175 – too much “and” in the sentence. “... Of whom 132 were men; median age was 70...; median SAPS 2 was 38...”.

Response: Corrections have been made. (line 178-180)

Comment 8: Line 187 – “plasmatic bicarbonate” (remove the “S”).

Response: Correction have been made.(Line 192)

Comment 9: Please add to the results section data regarding adherence to ward protocol: How many were actually corrected with phosphate supplementation; corresponds to line 133-135).

Response: We add sentences about phosphate supplementation in the results sections (Table 2 and Line 220-223)

Comment 10: Line 239 – The sentence syntax is not clear. Should add “phosphate level of” before the phosphate levels mentioned (0.93 and 1.1)

Response: Correction has been made (line 251-252)

Comment 11: Line 240 – the data is cited incorrectly. Patients who were ventilated for less than 5 days had higher levels of phosphate.

Response: Correction has been made (line 251-253)

Comment 12: Lines 229-244 – at all the studies mentioned, but the one of Talakoub, it is not clear when the phosphate level was taken (upon ICU admission? How many days after ventilation? etc.). this is relevant for comparison for current study.

Response: It has been clarified. (Line 242 and line 245-247).

Reviewer C

Comment 1: P 4 line 97: It reads, that patients without T0-Ph dosage available are excluded. I believe it is patients without T0-Ph plasma measurement that are excluded.

Response 1: The suggested correction has been made. (Line 100).

Comment 2: P5 line 135: Intravenous infusion would be the correct word instead of perfusion.

Response 2: Correction has been made. (Line 136).

Comment 3: I would recommend to re-group the phosphate variable into three group of low, normal, and high and redo the regression analyses. Or as an alternative, I hope the authors will do a secondary analysis comparing patients with low plasma levels to those with normal plasma levels.

Response 3: We agreed with the reviewer's comment which is very interesting. We add a statistical analysis to compare the proportion of patient with a T0-Ph below < 0.80 mmol/l in each group (table 3) and a sentence in the results section and discussion. (Line 205-206 and 227-228).

Reviewer D

Comment 1: Title. I suggest replacing “an observational cohort study” for “an retrospective cohort study” because it better explains the study design.

Response 1: We did the change suggested. (Title).

Comment 2: Abstract – Results section. I suggest adding the p value for this sentence: “Median T0-Ph was significantly higher 48 among patients requiring invasive MV as compared to non-intubated patients (1.23 [1.07-1.41] 49 mmol/l and 1.09 [0.91-1.27] mmol/l)”.

Response 2: We add the p value. (Line 49).

Comment 3: I suggest excluding affirmation about NIV, lines 68-69.

Response 3: We exclude the sentence as suggested. (Line 68)

Comment 4: I suggest adjusting the text, line 76, because reference 9 don't associate hypophosphatemia and weaning failure.

Response 4: Change has been done. (Line 74).

Comment 5: Please, describe the prespecified hypothesis of the researchers.

Response 5: We add the hypothesis in the introduction. (Line 78-79).

Comment 6: How did you define strongly suspected COPD? Please, describe it.

Response 6: We add a sentence to specify how we defined suspected COPD in inclusion criteria (Line 94-97).

Comment 7: It was not clear the sample calculation. Please, inform it, even though it's a convenience sample.

Response 7: A sentence has been added in the statistical analysis in this respect. (Line 153-155).

Comment 8: Data collection subsection. Did you have the time between emergency department (or other) and ICU admission.

Response 8: Unfortunately, we don't have the time between admission to emergency department and to ICU. Indeed, it could affect the results. We added a sentence in the limitation section. (Line 306-307)

Comment 9: Statistical analysis subsection. Why did you use pH with a cut-off value of 7.33 and phosphatemia with a cut-off value of 1.13 mmol/l, if 7.35 and 1.15 mmol/l are the real expected normal values?

Response 9: We did a mistake in the statistical section and table 4 regarding the value of T0-Ph, we used the value of 1.11 mmol/l (instead of 1.13 mmol/l, it is a typographical mistake)

because it is the median of T0-Ph value in the overall population. For the same reason we used a pH value of 7.33. Correction have been made regarding the mistake on the T0-Ph value in the statistical analysis section and in table 4. (Line 163)

Comment 10: I believe that the explanation for phosphorus levels > 1.13 in patients requiring invasive mechanical ventilation has biological plausibility. However, it is necessary to describe in the article potential confounding factors for this case.

Response 10: We discuss it in the limitation section. (Line 303-305 and 308-311).

Comment 11: According the results and table 1, I suggest discussing about the found of hyperphosphatemia in the patients with worse kidney function, which may have reduced phosphorus excretion and have caused hyperphosphatemia. The table 1, 2 and 3 describe more prevalent chronic kidney failure and increased creatinine values in CODP patients requiring invasive mechanical ventilation.

Response 11: The prevalence of medical history of chronic kidney failure was similar in our two groups of patients (table 1). Although plasmatic creatinine level was superior in the patient requiring invasive MV it was in the normal range (median of 72 [61-105] $\mu\text{mol/L}$) and we can hardly conclude that kidney failure was superior in the invasive MV group.

Comment 12: I also suggest discussing about the phosphorus reduction that commonly occurs in ICU patients and cite numerous confounding factors that interfere with its value.

Response 12: We already discuss this aspect in the limitation section (Line 303-305). We don't talk about refeeding syndrome as we studied plasmatic phosphate at admission and at 24H.

Comment 13: I suggest adding details about limitations, mainly selection bias.

Response 13: We added some sentences in this respect. (Line 299-301 and 306-307)

Comment 14: Please, adding N/A legend to all tables.

Response 14: After the changes made in the table, there is no N/A acronym.

Comment 15: Give a cautious overall interpretation of results. I suggest correcting the information and clarify that it is a hypothesis-generating study. Write that this finding was not significant in the multivariate analysis and that further studies are needed.

Response 15: We corrected the quick look section according to reviewer's comment. (Line 548-552)