PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Association of hypercapnia on admission with increased length of hospital stay and severity in patients admitted with community acquired pneumonia: a prospective observational study from Pakistan
AUTHORS	Iqbal, Nousheen; Irfan, Muhammad; Zubairi, Ali; awan, safia; A.Khan, Javaid

VERSION 1 - REVIEW

REVIEWER	Thomas J Marrie Dalhousie University, Canada
REVIEW RETURNED	28-Aug-2016

GENERAL COMMENTS	The question posed is a good one. However this study does not answer it because the statistical analysis is not well enough described to know if the multivariable analysis was able to show that elevated pCO2 was an independent risk factor for increased los etc . COPD and decreased pH were significantly different in the high pC02 group as one would expect and given this sample size I would be surprised if increased pC02 was an independent risk factor. Note lots of capitalization where it shouldn't be. The method for measuring pC02 should be described.

REVIEWER	Giulio DiDiodato Royal Victoria Regional Health Centre Intensivist, Department of Critical Care Medicine Canada
REVIEW RETURNED	30-Aug-2016

GENERAL COMMENTS	To summarize, this is a prospective observational study exploring the relationship between admission PaC02 levels and outcomes in consecutive adult patients admitted to hospital with CAP in a single hospital in Pakistan over a 12 month period. I would recommend accepting this study, but there are many major revisions that need to be completed prior to doing so. Major Revisions recommended include: 1) I would recommend that the authors review and ensure that their study report conforms to the STROBE checklist (http://www.strobe-statement.org/index.php?id=strobe-singel-news-view&tx_ttnews%5Btt_news%5D=1467&cHash=d32ea2d69f02b2f940b412133e537268) and submit the completed checklist to the journal. 2) The research question needs to be explicitly stated in PICO

	format, for example, it might read as follows: 'For adult patients admitted to a university-based hospital in Karachi, Pakistan with a diagnosis of community-acquired pneumonia, is the presence of hypercarbia on admission, defined as a PaC02>45 mm Hg on an arterial blood gas measurement, associated with an increased length of stay in hospital compared to patients with no hypercarbia on admission?' 2) The abstract should be rewritten to include an explicit research question. In addition, the primary and secondary outcomes should be explicitly stated. Also, in the 'Results' section, it appears to suggest that both NIMV and intubations are more often needed in hypercapneic patients, but this is clearly not the case given the OR intubation is 0.45. The conclusion is not consistent with the results, again suggesting that hypercapneic patients require more ICU care. 3) In your introduction, no mention is made of the importance of time to clinical stability in CAP and its relevance to important outcomes such as LOS, mortality, and ICU admission. In addition, the impact of systemic steroids on length of stay in CAP is not mentioned, and this is highly relevant to patients with more severe CAP and patients with acute exacerbations of COPD, a population that is over-represented in your study in the hypercapneic group. 4) For LOS outcome, you make a significant assumption of a normally distributed outcome which is almost never the case for LOS. Rather, most LOS is right-skewed and your analysis should either include evidence that your LOS is normally distributed to justify your analysis, or your statistical test should be appropriate for the distribution of this outcome. In addition, there is no indication whether your LOS incorporates the LOS of those who died, or if it only is based on LOS of survivors to hospital discharge? If LOS is composed of both survivors and deceased, then you should conduct a sensitivity analysis comparing LOS for only those who survived compared to LOS for both those who died and survived. In addition, time to clinical stability is one of the most important predictors of LOS, and this has not been provided in your study which raises serious questions about the validity of your results. 5) You need to explicitly state which variables were included in your multivariable analysis and why you included these variables. Did you only include those variables that were not well balanced in your univariate analysis in the final multivariate model or did you pre-specify which variables you would include according to previous studies? As it stands, your analysis cannot be repeated because your final model is not explicitly specified. 6) For your baseline data, you did not include information on systemic steroid use or seasonality, both of which may have contributed to differences in length of stay 7) In your baseline data, in the hypercapneic group, a significant proportion of your patients have a pH>7.35 suggesting a chronic hypercapneic group - how did you account for what may be a very different population of patients compared to acute hypercapneic patients? 8) You mention that NIMV care may be initiated in the ER, Special care or ICU areas, but you don't document where the patient receives the majority of their NIMV care? If some receive the majority of their in special care areas and others in the ICU, then this should be included in your baseline characteristics table as this may have implications on LOS 9) Your discussion needs to examine the limitations of your study. As an observational study, there may have been many other unobserved confounders that could have biased your results, for example, day and time of admission, seasonality, steroid use, time to

	clinical stability, etc.. You need to spend more time explaining your final covariate model, specifically, the variables included.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

1) The question posed is a good one. However this study does not answer it because the statistical analysis is not well enough described to know if the multivariable analysis was able to show that elevated pCO2 was an independent risk factor for increased los etc . COPD and decreased pH were significantly different in the high pC02 group as one would expect and given this sample size I would be surprised if increased pC02 was an independent risk factor.

Statistical analysis are explained in details and mentioned in statistical analysis from lines 229 to 244. We are agree with the comment that 38% of our patients in hypercapnic group had ph>7.35 .As Copd patients were significantly present in this group this could be due to underlying copd however these patients reported first time in ER so we couldn't differentiate between these patients. This is now mentioned in discussion from line 299 to 302.
2) Note lots of capitalization where it shouldn't be.

We have tried to minimize capitalization and changes are made.

3) The method for measuring pC02 should be described.

Method of measuring PCo2 is mentioned from lines 189 to 191.
Reviewer: 2

1) I would recommend that the authors review and ensure that their study report conforms to the STROBE checklist (http://www.strobe-statement.org/index.php?id=strobe-singel-news-view&tx_ttnews%5Btt_news%5D=1467&cHash=d32ea2d69f02b2f940b412133e537268) and submit the completed checklist to the journal.
STROBE list is attached

2) The research question needs to be explicitly stated in PICO format, for example, it might read as follows: 'For adult patients admitted to a university-based hospital in Karachi, Pakistan with a diagnosis of community-acquired pneumonia, is the presence of hypercarbia on admission, defined as a PaC02>45 mm Hg on an arterial blood gas measurement, associated with an increased length of stay in hospital compared to patients with no hypercarbia on admission?'

The research question is now stated in PICO format as you suggested and included in abstract.

3) The abstract should be rewritten to include an explicit research question. In addition, the primary and secondary outcomes should be explicitly stated. Also, in the 'Results' section, it appears to suggest that both NIMV and intubations are more often needed in hypercapneic patients, but this is clearly not the case given the OR intubation is 0.45. The conclusion is not consistent with the results, again suggesting that hypercapneic patients require more ICU care.

Yes we have noted these important points and made changes accordingly. The abstract now include research question in PICO format, primary and secondary outcomes are explicitly stated and conclusion is changed according to the results.

4) In your introduction, no mention is made of the importance of time to clinical stability in CAP and its

relevance to important outcomes such as LOS, mortality, and ICU admission. In addition, the impact of systemic steroids on length of stay in CAP is not mentioned, and this is highly relevant to patients with more severe CAP and patients with acute exacerbations of COPD, a population that is over-represented in your study in the hypercapneic group.

In introduction we have now mentioned about time required to Clinical stability and impact of steroids on Los in CAP patients mentioned in introduction from line 145 to 158.
5) For LOS outcome, you make a significant assumption of a normally distributed outcome which is almost never the case for LOS. Rather, most LOS is right-skewed and your analysis should either include evidence that your LOS is normally distributed to justify your analysis, or your statistical test should be appropriate for the distribution of this outcome. In addition, there is no indication whether your LOS incorporates the LOS of those who died, or if it only is based on LOS of survivors to hospital discharge? If LOS is composed of both survivors and deceased, then you should conduct a sensitivity analysis comparing LOS for only those who survived compared to LOS for both those who died and survived. In addition, time to clinical stability is one of the most important predictors of LOS, and this has not been provided in your study which raises serious questions about the validity of your results.

We compared LOS of both survivors and deceased and now analysis of survivor and both of diseased and survivor along with time required for clinical stability TCS is added in table 2.

6) You need to explicitly state which variables were included in your multivariable analysis and why you included these variables. Did you only include those variables that were not well balanced in your univariate analysis in the final multivariate model or did you pre-specify which variables you would include according to previous studies? As it stands, your analysis cannot be repeated because your final model is not explicitly specified.
Statistical Analysis are explained in detail in section from line 228 to 243.

7) For your baseline data, you did not include information on systemic steroid use or seasonality, both of which may have contributed to differences in length of stay

In baseline data we have added information regarding systemic steroids and seasonality mentioned inTable 1.

8) In your baseline data, in the hypercapneic group, a significant proportion of your patients have a pH>7.35 suggesting a chronic hypercapneic group - how did you account for what may be a very different population of patients compared to acute hypercapneic patients?

We are agree with the comment that 38% of our patients in hypercapnic group had ph>7.35 .As Copd patients were significantly present in this group this could be due to underlying copd however these patients reported first time in ER so we couldn’t differentiate between these patients. This is now mentioned in discussion from line 299 to 302.

9) You mention that NIMV care may be initiated in the ER, Special care or ICU areas, but you don't document where the patient receives the majority of their NIMV care? If some receive the majority of their in special care areas and others in the ICU, then this should be included in your baseline characteristics table as this may have implications on LOS

In majority of our patients NIMV initiated in ER and then they shifted to scu where it was continued usually in ICU we have intubated patients this statement is more clear now and mentioned from line 201 to 203.

10) Your discussion needs to examine the limitations of your study. As an observational study, there may have been many other unobserved confounders that could have biased your results, for example, day and time of admission, seasonality, steroid use, time to clinical stability, etc.. You need to spend more time explaining your final covariate model, specifically, the variables included.

Limitations of study are mentioned now in details in the end of discussion.

Thank you

VERSION 2 – REVIEW

REVIEWER	Thomas J Marrie Dalhousie university , NS, Canada
REVIEW RETURNED	14-Nov-2016

GENERAL COMMENTS	While the authors have addressed many of the concerns raised by the reviewers a number of items remain. 1. manuscript is poorly written. 2. abstract - methods - primary outcome etc does not belong in methods section. 3. strengths of the study are wrong - these are not strengths of the student. 4. same comment applies to limitations.

REVIEWER	Giulio DiDiodato Royal Victoria Regional Health Centre Canada
REVIEW RETURNED	09-Nov-2016

GENERAL COMMENTS	In the data analysis section lines 219-220, this statement "Odds Ratios (OR) and their 95% Confidence Intervals (CI) were estimated using Logistic Regression, with variable hypocapnia and hypercapnia as an outcome" seems to conflict with primary outcome of LOS - is this supposed to read that a multiple linear regression was performed with LOS as an outcome measure and PaC02 included as a categorical covariate in the model? the entire paragraph from 219-227 discusses logistic regression and using hypercapnia as an outcome which has never been previously identified as an outcome variable - I have to assume this must be an error by the authors. I think the authors need to explain that the LOS is composed of two components - the time to clinical stability and the time from clinical stability to discharge - their results clearly show that hypercapnia leads to a longer time to clinical stability, but once this achieved, the time to discharge is actually shorter than in the other groups compared to the hypercapnia group - this is a potentially interesting finding since this helps us understand that differences in LOS in this group may not be modifiable.

REVIEWER	Are Hugo Pripp Oslo Centre of Biostatistics and Epidemiology Research Support Services Oslo University Hospital Norway
REVIEW RETURNED	11-Dec-2016

GENERAL COMMENTS	Comments on statistical analysis: * As I understand it, the authors assess relationship between the exposure paCO2 level divided into the groups hypocapnic, hypercapnic and normocapnic on primary outcome length of hospital stay and the secondary outcomes mechanical ventilation, ICU admission and in-hospital mortality. * I find it not appropriate to use logistic regression to assess relationship between paCO2 level groups as exposure and length of hospital stay as outcome (sentence 219 – 227). Length of hospital stay is a continuous outcome. They should use for example linear regression analysis or cox regression (survival analysis) * I think the sample size calculations are not appropriate for this study design. It seems that the authors have used methods for surveys – please revise. * Table 1: Effect of season should be analyzed with a chi-square test to give an overall p-value (not p-values for each season). *Table 1: “paO2 Level” is given in two rows. It is not clear what the difference between them is. * Table 2: Results from analysis with multivariable regression models on the selected outcomes could be provided. * Table 2: Length of hospital stay can be highly skewed and affect statistical analysis. Please comment on that in the manuscript. * Table 3: I recommend that it is revised. The authors should after my opinion use statistical models with LOS, NIMV use, ICU/Intubations or mortality as outcome (i.e. dependent variable) and paCO2 levels in three groups and other relevant exposures as predictor variables (i.e. independent variable). In table 3 it is turned opposite to the objective of the study. They have now assessed hypercapnia as an outcome and LOS, NIMV, ICU or mortality as exposures. * I recommend that the authors collaborate with a medical statistician.

VERSION 2 – AUTHOR RESPONSE

Reviewers' Comments:
Reviewer: 2

In the data analysis section lines 219-220, this statement "Odds Ratios (OR) and their 95% Confidence Intervals (CI) were estimated using Logistic Regression, with variable hypocapnia and hypercapnia as an outcome" seems to conflict with primary outcome of LOS - is this supposed to read that a multiple linear regression was performed with LOS as an outcome measure and PaC02 included as a categorical covariate in the model? the entire paragraph from 219-227 discusses logistic regression and using hypercapnia as an outcome which has never been previously identified as an outcome variable - I have to assume this must be an error by the authors.
Answer: Changes have been made and discussed in statistical analysis section. Our statistician

suggested this," Due to the skewed distribution of length of hospital stay, it was categorized for the main analysis. Length of hospital stay was dichotomized around mean: <7 days and more than 7 days of hospital stay. Odds Ratios (OR) and their 95% Confidence Intervals (CI) were estimated using Logistic Regression, with length of stay as outcome variable". (lines 220 -223)
I think the authors need to explain that the LOS is composed of two components - the time to clinical stability and the time from clinical stability to discharge - their results clearly show that hypercapnia leads to a longer time to clinical stability, but once this achieved, the time to discharge is actually shorter than in the other groups compared to the hypercapnia group - this is a potentially interesting finding since this helps us understand that differences in LOS in this group may not be modifiable.
Answer: Length of stay is discussed in detail in discussion and this point is highlighted as suggested (Lines 264-273)

Reviewer: 1

1. manuscript is poorly written.
Answer: We have tried to improve the quality of the manuscript.
2. abstract - methods - primary outcome etc does not belong in methods section.
Answer : It is corrected, it is now mentioned in abstract under the subheading of outcomes.
3. strengths of the study are wrong - these are not strengths of the student.
Answer: Strength of the study is written again
4. same comment applies to limitations.
Answer : Limitations are written again in details
Reviewer: 3
Comments on statistical analysis:

* I find it not appropriate to use logistic regression to assess relationship between paCO2 level groups as exposure and length of hospital stay as outcome (sentence 219 – 227). Length of hospital stay is a continuous outcome. They should use for example linear regression analysis or cox regression (survival analysis)
Answer: Changes have been made and discussed in statistical analysis section. Our statistician suggested this," Due to the skewed distribution of length of hospital stay, it was categorized for the main analysis. Length of hospital stay was dichotomized around mean: <7 days and more than 7 days of hospital stay. Odds Ratios (OR) and their 95% Confidence Intervals (CI) were estimated using Logistic Regression, with length of stay as outcome variable ".(lines 220 -223)

* I think the sample size calculations are not appropriate for this study design. It seems that the authors have used methods for surveys – please revise.
Answer: sample size is revised (Lines 203-205)

* Table 1: Effect of season should be analyzed with a chi-square test to give an overall p-value (not p-values for each season).
Answer : overall p value is mentioned now
*Table 1: "paO2 Level" is given in two rows. It is not clear what the difference between them is.
Answer : In first row PaO2 level is mentioned while in another PaCo2 level is mentioned.
* Table 2: Results from analysis with multivariable regression models on the selected outcomes could be provided.
Answer : In results multivariable and univariate analysis are mentioned.
* Table 2: Length of hospital stay can be highly skewed and affect statistical analysis. Please comment on that in the manuscript.
Answer: This is mentioned in statistical analysis
* Table 3: I recommend that it is revised. The authors should after my opinion use statistical models with LOS, NIMV use, ICU/Intubations or mortality as outcome (i.e. dependent variable) and paCO2

levels in three groups and other relevant exposures as predictor variables (i.e. independent variable). In table 3 it is turned opposite to the objective of the study. They have now assessed hypercapnia as an outcome and LOS, NIMV, ICU or mortality as exposures.
Answer : Table 3 is revised now.

VERSION 3 – REVIEW

REVIEWER	Are Hugo Pripp Oslo Centre of Biostatistics and Epidemiology Research Support Services Oslo University Hospital Norway
REVIEW RETURNED	15-Feb-2017

GENERAL COMMENTS	I think the paper could be of interest for readers of BMJ open. Length of hospital stay can also be assessed with survival analysis / time to event statistics as e.g. Kaplan-Meier plots, log-rank tests and/or Cox regression. A Kaplan Meier plot could be very illustrative and is quickly made using SPSS or other appropriate software. A suggestion is a plot showing the hospital stay for the three PaCO2 groups.

VERSION 3 – AUTHOR RESPONSE

Reviewer: 3
2)Please state any competing interests or state 'None declared':
None declared
Answer: This statement is mentioned clearly from Line # 342-343

3)I think the paper could be of interest for readers of BMJ open. Length of hospital stay can also be assessed with survival analysis / time to event statistics as e.g. Kaplan-Meier plots, log-rank tests and/or Cox regression. A Kaplan Meier plot could be very illustrative and is quickly made using SPSS or other appropriate software. A suggestion is a plot showing the hospital stay for the three PaCO2 groups.
Answer: Kaplan-Meier plots is mentioned as Figure 1 and mentioned in data analysis lines 226-227 and in outcomes line # 256.