Author's response to reviews

Title: Clinical presentation and predictors of outcome in patients with severe acute exacerbation of chronic obstructive pulmonary disease requiring admission to intensive care unit

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Author's response to reviews:

The manuscript has been revised as per the valuable suggestions of the Reviewers and the revised manuscript is being submitted for re-consideration for publication. There is a change in my designation from "Associate Professor" to "Additional Professor' as I have been promoted to the cadre of Additional Professor between the time of initial submission and now.

In the revised manuscript, the changes made are indicated with 'red font'.

POINT-WISE REPLY TO REVIEWERS' QUERIES

Reviewer: Surinder K. Jindal

Comment

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct) Why do the authors consider that the reliable data on COPD-epidemiology from India is lacking? The recent multicentric study from India quoted by the authors was fairly large and reliable.

Reply

We agree with the reviewer that the recent multicentric study on COPD epidemiology in India provides valuable, reliable epidemiological information. We intended to convey that reliable epidemiological data on the burden of “acute exacerbation of chronic obstructive pulmonary disease (AE-COPD) in the emergency room” are lacking from India. As per the Reviewer's suggestion, we have redrafted the sentence and have deleted the words "Reliable epidemiological data about COPD are lacking from India".

Comment

3. Discretionary Revisions (which the author can choose to ignore) Since the enrollement was done at admission, the authors should have data on 198 patients who presented to the Emergency but were not admitted in the ICU? A comparative assessment is important to assign significance to predictors. For example, the presence of comorbid conditions or metabolic abnormalities considered as important predictors of outcome in patients with AE-COPD might be similar in other group of patients who were not included in this analysis.

It is not clear how was the outcome (besides death) defined?

Reply

The suggestion made by the Reviewer is indeed a good one. However, in addition to identifying the predictors of mortality in patients who were admitted to the medical ICU, which we have reported in the present study, we are prospectively following-up all the patients who presented to the ER with AE-COPD between January 2000 and December 2005 for a further period of five years in order to understand the natural history of the disease, to study the quality of life and understand the long-term consequences of AE-COPD. As this study is ongoing, we would like to compare the data of patients with AE-COPD who required medical ICU admission with that of patients who did not at a later stage and not at this stage.
Therefore, these data are not being presented. For the reasons described, in the present study, the only outcome studied was in-hospital mortality in patients with AE-COPD presenting to the ER who required admission to the medical ICU.

Reviewer: Angshu Bhowmik

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

Comment
1. Abstract:
   a. Hypercapnia has been mentioned as a predictor of death, but the p value for this parameter in the multiple regression is only 0.083 whereas a cut-off of 0.05 has been selected.

Reply
We apologise for the typographical error. The p-value should have read 0.033. The correction (p<0.05) has been incorporated in the abstract as well as in the text and tables. This and other typographical errors in the manuscript have also been corrected.

Comment
b. In the Conclusions, it has been stated that metabolic abnormalities render the diagnosis of AE-COPD difficult and contribute to mortality, but it is unclear which metabolic abnormalities are referred to here. Table 4a suggests that they are hypoalbuminaemia and elevated transaminases.

Reply
We wish to clarify to the Reviewer as to what we meant by "metabolic abnormalities" in the abstract. When patients present with acute exacerbation of chronic obstructive pulmonary disease (AE-COPD), presence of metabolic abnormalities such as dyselectrolytemia, uremia, and hepatic function derangement (listed in Table 3) not only render the diagnosis of AE-COPD difficult but, if undetected and not corrected, can contribute to the mortality. We wish to state here that all the 15 of the 116 (12.9%) patients with altered sensorium manifested one or more metabolic abnormalities [hyponatremia (n=9); hypokalemia (n=7); hyperbilirubinemia (n =3); elevated transaminases (n=12) elevated blood urea (n=31); and elevated serum creatinine (n = 11)] or type II respiratory failure and carbon dioxide retention (n=11). These details have been incorporated in the text in the revised manuscript under the "Results" section. Some of them emerged as predictors of outcome and these have been listed in Tables 4a and 4b.

This is important in the Indian scenario because, majority of the patients with AE-COPD seek emergency care at primary health centres, district hospitals and general hospitals where facilities for round-the-clock laboratory monitoring are seldom available. Unless these factors (that are often correctable) are specifically sought and checked, they may be missed. We wish to caution the discerning practitioner to specifically look for these metabolic abnormalities so that proper corrective therapy can be administered. Therefore we wish to retain this sentence as it is.

Comment
c. The relationship between past or active PTB, AE-COPD (acute exacerbations of COPD) and smoking has been highlighted, but the data presented in this paper do not seem to justify this conclusion. The authors have not shown that the prevalence of PTB in this population of patients with COPD admitted with AE is any higher than that in the general population. Nor have they shown data to suggest that it is COPD patients with PTB who are more likely to suffer AE than COPD patients who do not have PTB. While it has been shown that smoking is related to PTB and smoking is related to COPD, it is purely speculative to infer that there is a complex interplay between the three. This may merely be an epiphenomenon rather than the PTB somehow leading to worsening of COPD. If the latter is, in fact, the case, the data presented here is not adequate to show this. Perhaps the analysis has not been described in sufficient detail to make the relationship apparent.

Reply
We thank the reviewer for this valuable comment. When we conceived this study, we were unaware of this intriguing relationship between smoking, AE-COPD and past/active pulmonary tuberculosis (TB). The association became gradually evident as the study progressed.
As per the Reviewer's valuable suggestion, we are providing additional details of analysis. On comparing the prevalence of past pulmonary TB among the 314 patients with AE-COPD (116 patients with AE-COPD who were admitted to the ICU, the 198 patients who presented to the emergency room, but who did not require admission into the ICU) and the remaining 600 patients who were on follow-up but who did not develop AE-COPD, it was found that COPD patients with past pulmonary TB were more likely to suffer from AE-COPD than those who did not have pulmonary TB (61 of 314 vs. 24 of 600; chi-square = 56.343, p<0.001). These data have been added to the "Results" section in the revised manuscript and also under "Discussion".

Comparison of the prevalence of pulmonary TB in patients with AE-COPD with the prevalence of PTB in the general population of this area could not be undertaken as there are no reliable epidemiological data on the prevalence of pulmonary TB in the general population in this area.

Treated PTB is a poorly recognised but important cause of COPD. Smoking seems to increase the incidence of TB; and where smoking is highly prevalent, prevalence of COPD is high. Thus, in areas such as India where pulmonary TB is highly endemic and smoking is on the rise, the prevalence of COPD is expected to increase and severe AE-COPD would become a significant cause of morbidity and mortality in the ER. Given that smoking is entirely avoidable and the prevalence of pulmonary TB can be controlled by effectively run control programmes, we feel that, by controlling these two modifiable factors, morbidity and mortality from AE-COPD can be considerably reduced. We agree that while the association between pulmonary TB, COPD and smoking may appear speculative it is sufficiently intriguing to be documented. This should stimulate further studies with a larger sample size to corroborate these findings.

Comment
2. Introduction: The introduction states that all the patients included in the study were managed on an intensive care unit. However, in the "Materials and Methods" paragraph 6, it is stated that after initial stabilisation in the ER, the patients were managed in the ICU, Acute Medical Care Unit and Medical Wards. This needs clarification.

Reply
As per the Reviewer’s suggestion, we have clarified these details and have incorporated them under the Material and Methods section of the revised manuscript. Briefly, In our setup, after initial stabilisation and management in the ER, of the 314 patients who presented to the ER with AE-COPD, 116 were admitted to the medical ICU; 18 were discharged from the ER; and the remaining 180 were admitted to the acute medical care unit and the medical wards of the hospital. The predictors for mortality were studied in the 116 patients who were admitted to the medical ICU.

Comment
3. Materials and Methods: Some additional detail about the statistical analysis should be provided. "To determine the various predictors of death..." was a correlation performed? Was a correction used to allow for the use of multiple correlations?

Reply
We wish to clarify that statistical analysis was performed as described under the "Material and Methods" section. We chose to perform multivariate logistic regression to identify the predictors of outcome in patients with AE-COPD. We did not perform correlation analysis.

In addition to identifying the predictors of mortality which we have reported in the present study, we are prospectively following-up all the patients who presented to the ER with AE-COPD between January 2000 and December 2005 for a further period of five years in order to understand the natural history of the disease, to study the quality of life and understand the long-term consequences of AE-COPD. We would like to perform other analyses such as the one suggested by the Reviewer at a later stage. Therefore, these data are not being presented. For the reasons described, in the present study, the only outcome studied was in-hospital mortality in patients with AE-COPD presenting to the ER who required admission to the medical ICU.

Comments
4. Results:
a. The first paragraph of the results seems to largely duplicate the data presented in table 1.
Reply
We agree with the Reviewer's suggestion and have substantially revised and redrafted the first paragraph under the "Results" section in the revised manuscript.

Comments
b. I note that the definition of AE-COPD requires the presence of increased sputum purulence as well as increased sputum quantity, but the two features seem to have been combined into one in Table 2 without further clarification.

Reply
The Reviewer has raised a valid point and we thank the Reviewer for pointing to this issue. Accordingly, we have split "increased sputum purulence and increased sputum quantity" as two separate entities in the Table 2.

Comment
c. "Chest radiographs revealed infiltrates...." Does this mean pneumonia was present? In this case, should these patients have been analysed as "pneumonia" rather than exacerbations of COPD? This should be clarified.

Reply
We wish to clarify that patients with bacterial pneumonia were not included in the 116 patients with AE-COPD who were studied. Overall, of the 116 patients with AE-COPD, 33 had evidence of past pulmonary TB; and 5 patients were diagnosed to have sputum smear-positive pulmonary TB. In the remaining 10 patients, focal parenchymal infiltrates without air-bronchogram, suggestive of lower respiratory tract infection and all these patients had negative sputum and blood culture. These details have been provided under the "Results" section in the revised manuscript.

Comment
d. Tuberculosis: I am confused about the inclusion of patients with active tuberculosis in this study. Several diseases such as bronchiectasis and interstitial lung disease have been excluded, as has been the case in other published work on the subject, so it is unclear why tuberculosis has been left in. The authors should justify this inclusion rigorously as it is unjustifiable in the manuscript as it stands. As mentioned in my comments about the abstract, the data has not been analysed in sufficient detail with adequate numbers of control subjects in order to reach the conclusion that the co-existence of PTB and COPD is anything other than an epiphenomenon in a locality where both diseases are highly prevalent.

Reply
It is well documented that past pulmonary TB is an independent etiological factor in the causation of COPD irrespective of smoking status. This is particularly true in areas where TB is highly endemic (Hassan IS, Al-Jahdali HH. Obstructive airways disease in patients with significant post tuberculous lung scarring. Saudi Med J 2005;26:1155-7; Hnizdo E, Singh T, Churchyard G. Chronic pulmonary function impairment caused by initial and recurrent pulmonary tuberculosis following treatment. Thorax 2000;55:32-8; Wilcox PA, Ferguson AD. Chronic obstructive airways disease following treated pulmonary tuberculosis. Respir Med 1989;83:195-8; Snider GL, Doctor L, Demas TA, Shaw AR. Obstructive airway disease in patients with treated pulmonary tuberculosis. Am Rev Respir Dis 1971;103:625-40). If this issue is not widely recognised, we feel it is because of under reporting and lack of documentation on this topic in recent times. We also feel that because of the sequelae of treated pulmonary TB would exacerbate/ have additive effect on smoking related lung damage resulting in COPD. Therefore, we feel justified in including patients with AE-COPD with past pulmonary TB. Given the recent evidence linking tobacco smoking and the occurrence of pulmonary TB (Gajalakshmi V, Peto R, Kanaka TS, Jha P. Smoking and mortality from tuberculosis and other diseases in India: retrospective study of 43000 adult male deaths and 35000 controls. Lancet 2003;362:507-15; Davies PD, Yew WW, Ganguly D, Davidow AL, Reichman LB, Dheda K, Rook GA. Smoking and tuberculosis: the epidemiological association and immunopathogenesis. Trans R Soc Trop Med Hyg 2006;100:291-8. Epub 2005 Dec 1), the spectre of rising tobacco smoking in developing countries, and evidence that sequelae of pulmonary TB can result in COPD, we believe that our observations are worth documenting.

Comment
5. Discussion:
a. Paragraph 1: it is "traditional" to emphasise the important results, or the contribution made by the paper to what is known on this subject, in the first paragraph of the discussion.
As per the Reviewer’s suggestion, we have modified the first paragraph of the “Discussion” section in the revised manuscript.

Comment
b. paragraph 2 lines 5 - 8: “...dyselectrolytemia, uremia and hepatic function derangements” - I presume the authors mean Table 3 rather than Table 2. But there is no data/analysis showing if there is a relationship between these metabolic abnormalities and altered sensorium.

Comment
As rightly pointed out by the reviewer, we were referring to Table 3. This has been corrected in the revised manuscript. As mentioned in the reply to an earlier comment, we have provided details regarding the occurrence of metabolic abnormalities in patients with altered consciousness in the revised manuscript. All the 15 of the 116 (12.9%) patients manifested one or more metabolic abnormalities [hyponatremia (n=9); hypokalemia (n=7); hyperbilirubinemia (n=3); elevated transaminases (n=12) elevated blood urea (n=31); and elevated serum creatinine (n = 11)] or type II respiratory failure and carbon dioxide retention (n=11).

The point we were trying to convey is as follows. When a patient presents to the ER with severe AE-COPD, and is in altered sensorium; in addition to type II respiratory failure and carbon dioxide narcosis, metabolic derangements such as dyselectrolytemia, uremia and hepatic function derangement could also contribute to the altered sensorium. These have to be looked for and corrected. If the hospital setting where patients with AE-COPD are treated does not have the facilities for around the clock ABG analysis and serum biochemistry evaluation (which is by and large the situation in primary health centres, district hospitals and general hospitals in India), many of these otherwise correctable abnormalities would have been missed. Thus, these factors not only confuse the diagnosis but also contribute to mortality. In the analysis for predictors of death, some of these factors emerged as significant predictors of mortality. We feel that this information is relevant and useful. These details have been incorporated under the “Discussion” section of the revised manuscript.

Comment
c. Paragraph 6: The authors have not considered the updated 2004 ATS/ERS position paper on the diagnosis and treatment of patients with COPD nor the BTS-NICE guidelines of 2004. This paragraph is therefore completely out of date.

Reply
We thank the reviewer for this valuable suggestion. As indicated, the suggested current references have been incorporated and the mentioned paragraph has been completely rewritten in the revised manuscript.

Comment
d. Paragraph 8 (conclusions): I cannot see where the authors have shown that the presence of co-morbidities makes the diagnosis of AE-COPD difficult although I agree that the inclusion of PTB into the analysis has probably confounded the results. The data presented does not justify the conclusion that “Correction of metabolic abnormalities such as dyselectrolytemia and ...antimicrobial treatment...help in reducing the mortality”.

Reply
We submit that the issues concerning co-morbid conditions and the diagnosis of AE-COPD, reasons for inclusion of pulmonary TB into the analysis have been described in detail above in response to earlier comments. In scenario of developing world, for reasons already described in detail we feel justified in stating that “Co-morbid conditions render the diagnosis of AE-COPD difficult and contribute to morbidity and mortality. Correction of metabolic abnormalities such as dyselectrolytemia and judicious use of empirical antimicrobial treatment will also help in reducing the mortality” and wish to retain the same. However, we leave the final decision to the discretion of the Editor.

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

Comment
1. Reference 6 is quoted in support of the statement that there is an increasing tendency to abuse tobacco in India but this does not seem to be correct.
We thank the Reviewer for this comment. The list of references cited should read "3-5" instead of 3-6. The correction has been incorporated in the revised manuscript.

Comment
2. Materials and methods: paragraph 2, line 7: "...that is not fully reversible". I presume reversibility testing was done for all patients. However, data on baseline or exacerbation spirometry (accepting that spirometry might not always be possible at exacerbation) as well as reversibility data has not been presented and should be included so that the reader may obtain a definite impression about the severity of COPD in the patients described.

Reply
We thank the reviewer for this valuable suggestion. We have incorporated the baseline PFT data regarding patients who presented to the ER with AE-COPD in Table 1 in the revised manuscript.

Comment
3. The description of the investigation and management of the patients is too long and parts of it could easily be omitted (e.g. methods of ECG, arterial blood gas analysis, details of oxygen and bronchodilator therapy etc.) (Incidentally, the dose of nebulised ipratropium 0.5 mg every 15 minutes seems quite high).

Reply
We feel that the description of the investigations and management are required to give an idea regarding the setup in which the patients were managed. We leave the choice of retaining this portion to the discretion of the Editor.

Comment
4. SI units should be used for all quantities (e.g. PaO2, bilirubin, albumin, etc).

Reply
As suggested, SI units have been provided in parantheses where required in the revised manuscript.

Comment
5. Earlier in the methods, it is mentioned that the tobacco content of 4 bidis is equivalent to one cigarette when calculating pack-years of smoking. Apparently contradicting this, in the first paragraph of the discussion, it is stated that bidi smoking causes 2 - 3 times more tar and nicotine inhalation than conventional cigarettes. Has this been taken in to account in the methods?

Reply
We also noticed the point raised by the Reviewer. We used the well standardised accepted method for calculation of "pack-years" of bidi smoking. Here, a weight of 0.25 has been assigned for bidi based on grams of tobacco content. However, great variation exists regarding the "how long" and "how deeply" a subject inhales while smoking either a cigarette or a bidi. Because of the poor combustibility of the bidi and greater puff frequency needed to keep the bidi alight, it has been estimated that bidi smoking is considered to cause about two to three times greater nicotine and tar inhalation than do conventional cigarettes. Therefore we feel justified in mentioning both the facts.