PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	The long-term mortality after community-acquired pneumonia: Impacts of diabetes and newly discovered hyperglycaemia. A prospective, observational cohort study.
AUTHORS	Koskela, Heikki; Salonen, Paivi; Romppanen, Jarkko; Niskanen, Leo

VERSION 1 - REVIEW

REVIEWER	Anke HW Bruns UMC Utrecht The Netherlands
REVIEW RETURNED	07-Jul-2014

GENERAL COMMENTS	Major comments - My main concern is the low number of patients included in the study which strongly influcences the robustness of the data - A validated pneumonia severity score is missing; please calculate the CURB 65 score to document pneumonia severity. - the karnofsky score or frailty is a much stronger predictor for mortality than the post prandial glucose or diabetes in the cox model. Please emphasise more on this aspect in the discussion Minor comments - I would not include the analysis on the cut off value of fasting glucose and post-prandial glucose in pneumonia patients; this is not the major objective of the study and standardized cut off values for hyperglycaemia are clearly defined in literature. - page 4 line 8, I would avoid the word victim.

REVIEWER	Yana Vinogradova Nottingham University, UK
REVIEW RETURNED	13-Jul-2014

GENERAL COMMENTS	The study is well designed and the paper well written. There are some minor issues: The authors have used the Karnofski index - it would be useful, particularly for readers who are not physicians, to briefly describe it and to add reference where it could be found in details. It is not clear which level of glucose was used for defining postprandial hyperglycaemia, whether it was a pre-defined cut point or derived from the ROC analysis. This should be clarified in the definitions.

	Observations with missing values are supposed to be removed from the analysis. According to the legend for table 2, the analysis was based on all 153 patients. There were 11 observations with missing data for urea, however, which suggests that only 142 patients could have been included in this analysis. It would also be useful to know the number of diabetic and non-diabetic patients in the analysis.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name Anke HW Bruns
Institution and Country UMC Utrecht
The Netherlands
Please state any competing interests or state 'None declared': None declared

My main concern is the robustness of conclusion and generalisibilty. Since present study is a single centre study with a low number of patients included and very low numbers of endpoint (16 deaths). I cannot excluded that post prandial hyperglycaemia is an surrogate marker for frailty because the karnofsky score is a much stronger predictor for long term mortality but the cox model does not correct completely for it, because the low numbers.

Reply: The total number of deaths was 36, the number of deaths in the group "no diabetes, with postprandial hyperglycaemia" was 16 (Table 4). We must admit that the relatively small number of patients and deaths may degrease the generalisibity of the results. This has now been mentioned in the revised version of the manuscript, see page 14, first paragraph. We have also softened the conclusion, see page 14, second paragraph.

The small number of patients may cause type II statistical error. This is a major concern in negative studies. However, the present study is not negative: Even with the present population we could show that both the presence of diabetes and new postprandial hyperglycaemia have independent, statistically significant impacts on late mortality after pneumonia.

Major comments
- My main concern is the low number of patients included in the study which strongly influcences the robustness of the data

Reply: See our reply above

- A validated pneumonia severity score is missing; please calculate the CURB 65 score to document pneumonia severity.

Reply: The management of the present patients was based on local guidelines. The Finnish pneumonia guideline suggested the use of a validated severity score not until autumn 2008, i.e., after the present patient population had been collected. The lack of systematic recording of respiratory rate precludes the calculation of CURB 65 or any other validated severity scores afterwards. This explanation has been added to the revised manuscript, see page 13, last paragraph. We are very sorry about this obvious weakness but cannot do much about it afterwards. However, many other, pneumonia severity-related features were presented. Furthermore, as patients with confusion or need for treatment in intensive care unit were excluded, it is clear that the present material consists of patients with mild to moderate pneumonia (page 14, first paragraph).

- the karnofsky score or frailty is a much stronger predictor for mortality than the post prandial glucose or diabetes in the cox model. Please emphasise more on this aspect in the discussion

Reply: We agree with the reviewer only partly. We were actually surprised that diabetes and postprandial hyperglycaemia were so strong predictors of late mortality, also when compared with the Karnofsky score (tables 2 and 3.) However, we see the reviewer's point and have modified the manuscript in this respect, see the first paragraph of Discussion, page 11.

Minor comments
- I would not include the analysis on the cut off value of fasting glucose and post-prandial glucose in pneumonia patients; this is not the major objective of the study and standardized cut off values for hyperglycaemia are clearly defined in literature.

Reply: Standardised cut-off values have been defined to diagnose diabetes but not to detect stress hyperglycaemia. They are two different phenomena, as we and others have shown. This is the reason why we still would like to use the ROC-defined cut-off values. The present study gives a rare opportunity towards validating the cut-off values for stress hyperglycaemia. Our cut-off values were surprisingly close to those adopted from diabetes diagnostics. Utilising the cut-off values for diabetes diagnostics would not have changed the results. This information has been added to the revised manuscript, see page 13, first paragraph.

- page 4 line 8, I would avoid the word victim.

Reply: We have changed that word to "casualties", see the first paragraph of the Introduction.

Reviewer: 2
Reviewer Name Yana Vinogradova
Institution and Country Nottingham University, UK
Please state any competing interests or state 'None declared': None declared

The study is well designed and the paper well written. There are some minor issues:

The authors have used the Karnofski index - it would be useful, particularly for readers who are not physicians, to briefly describe it and to add reference where it could be found in details.

Reply: The Karnofsky score was originally described in a book which was published in 1949. The score can be found in detail in a review article from 1980. Both publications have now been referred in the revised version of the manuscript, and a brief description of the score is presented. See page 5, second paragraph, and references 15 and 16.

It is not clear which level of glucose was used for defining postprandial hyperglycaemia, whether it was a pre-defined cut point or derived from the ROC analysis. This should be clarified in the definitions.

Reply: The cut-off values obtained from the ROC analysis were utilised. This information has now been added to the revised manuscript, definitions, see page 7, first paragraph.

Observations with missing values are supposed to be removed from the analysis. According to the legend for table 2, the analysis was based on all 153 patients. There were 11 observations with missing data for urea, however, which suggests that only 142 patients could have been included in this analysis. It would also be useful to know the number of diabetic and non-diabetic patients in the analysis.

Reply: True, only 142 patients were included in this analysis as 11 patients lacked the urea values. The urea measurement was missed in 1/22 (5 %) diabetic patients and 10/131 (8 %) non-diabetic patients. See the revised table 2.