PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Diagnostic utility of appetite loss in addition to existing prediction models for community-acquired pneumonia in the elderly: a prospective diagnostic study in acute care hospitals in Japan
AUTHORS	Takada, Toshihiko; Yamamoto, Yosuke; Terada, Kazuhiko; Ohta, Mitsuyasu; Mikami, Wakako; Yokota, Hajime; Hayashi, Michio; Miyashita, Jun; Azuma, Teruhisa; Fukuma, Shingo; Fukuhara, Shunichi

VERSION 1 – REVIEW

REVIEWER	Antonella Francesca Simonetti Hospital Universitari de Bellvitge Barcelona, Spain
REVIEW RETURNED	11-Sep-2017

GENERAL COMMENTS	The manuscript: “Appetite loss in addition to existing prediction models for the diagnosis of community-acquired pneumonia in the elderly: external validation and extension of diagnostic models” is a well written article, with a clear clinical question, well addressed and answered. Nevertheless, there are some important limitation that should be addressed with more deepness: Major comment: The precedent predicting models for diagnostic of CAP that are assessed in this study, except the study by Heckerling PS et al., were all tested and validated in an outpatients setting, a complete different clinical setting from that of the current study, the general medicine departments of three Japanese teaching hospitals. Although the authors acknowledge this limitation, the differences between populations are so relevant that I wonder about the opportunity of this study. As a matter of fact, a diagnostic model based on clinical rule could be very useful in an outpatients setting, where often there are not other tools available and where the physician should take the decision to derive or not the patient to the hospital for further tests (such as Chest X-ray) and eventually hospitalization based only on clinical signs and symptoms. However, once in the hospital, I do not see the usefulness of a diagnostic model with a relative poor power of discrimination, to decide to which patient perform a Chest X-ray, that, we know, it is cheep, easy available and could address not only the diagnosis of pneumonia, but also a large list of differential diagnostics in patients with cough.

	Moreover, due to the different setting, it is very hasty to consider that these findings should apply to the outpatients setting. I would like more details by the authors of the utility, applicability and generalization of the findings of the current study. Finally, I consider that the number of patients included is quite low and can not lead to any firm conclusion. Minor comments: Methods: - why do the authors exclude patients coming form nursing homes? - what happened to patients that could not answer to the question of appetite loss, that is based on self assessment (i.e.: loss of consciousness, impossibility to answer for demencia or other pathology, etc)? They were excluded from the study? Results: It would be useful a list of the final diagnosis for all the patients Page 9: I consider not necessary to include the formula for the prediction models in the text; it would be better placed in a table or appendix material.

REVIEWER	Lorenzo Malatino Department of Clinical and Experimental Medicine, University of Catania, Catania, Italy Heart Failure, Natriuretic Peptides, Hypertension, Thromboembolic diseases, pulmonary diseases.
REVIEW RETURNED	13-Sep-2017

GENERAL COMMENTS	This paper by Takada et al. assessed the value of appetite loss to predict CAP in the elderly.An extremely complex method for external validation of existing models was also applied prior to compared this models to appetite loss. Unfortunately, Authors do not refer to limitations of Pneumonia Severity Index (PSI) and Confusion, Urea, Respiratory rate, Blood pressure, aged 65 and older (CURB-65). This has been recently published, and a comparison between these above mentioned scores with neutrophil to lymphocyte ratio (NLR) performed (E. Cataudella et al. JAGS 2017). Specific Comments 1. Sample size looks rather small. Did Authors estimate the power? 2. Appetite loss is a very common symptom in the elderly. Its discriminant value for CAP diagnosis in comparison with existing models is evident in some, but not all, cases (Table 3). 3. Did Authors assess the value of NLR to predict CAP?

VERSION 1 – AUTHOR RESPONSE

Reply to the reviewer 1:
Thank you for your thoughtful comments for improving the content and quality of our manuscript.

Comment 1:
The precedent predicting models for diagnostic of CAP that are assessed in this study, except the study by Heckerling PS et al., were all tested and validated in an outpatients setting, a complete different clinical setting from that of the current study, the general medicine departments of three Japanese teaching hospitals.
Although the authors acknowledge this limitation, the differences between populations are so relevant that I wonder about the opportunity of this study.
As a matter of fact, a diagnostic model based on clinical rule could be very useful in an outpatients setting, where often there are not other tools available and where the physician should take the decision to derive or not the patient to the hospital for further tests (such as Chest X-ray) and eventually hospitalization based only on clinical signs and symptoms.
However, once in the hospital, I do not see the usefulness of a diagnostic model with a relative poor power of discrimination, to decide to which patient perform a Chest X-ray, that, we know, it is cheep, easy available and could address not only the diagnosis of pneumonia, but also a large list of differential diagnostics in patients with cough.
Moreover, due to the different setting, it is very hasty to consider that these findings should apply to the outpatients setting. I would like more details by the authors of the utility, applicability and generalization of the findings of the current study.

Reply: We appreciate the opportunity to clarify this point. The setting of the current study was the outpatient services of the general medicine departments of three teaching hospitals in Japan. As you pointed out, chest X-ray is easily available in hospitals, but its routine use in all elderly patients with respiratory symptoms is time-consuming and might not be cost-effective. Because 3 of the 6 existing prediction models were derived in the hospital setting (1–3), we believe that there is a need for prediction models to estimate the diagnostic probability of CAP in both hospital and primary care settings. Furthermore, healthcare in Japan is a free-access system that allows people to be examined and treated at the medical institutions of their choice (4). Therefore, the differences in patient characteristics between the hospital and primary care settings might be less prominent in Japan than those in other countries where patients have to see their primary care physicians first. Therefore, we believe that there was a need to correctly estimate the diagnostic probability of CAP in both hospital and primary care settings. Nevertheless, the external validity of our findings should be further explored. We have added these points in the Discussion section. (page 12, first paragraph, line 6 and second paragraph, line 9)

Comment 2:
Finally, I consider that the number of patients included is quite low and can not lead to any firm conclusion.

Reply: As you pointed out, we agree that the number of patients was not enough to make firm conclusions. Our findings should be further investigated by studies with larger samples; nevertheless, we believe that our results could be useful, since this was the first study that suggested the value of appetite loss in the diagnosis of CAP in elderly patients. We have added this point in the Discussion section. (page 12, second paragraph, line 4)

Comment 3:
Why do the authors exclude patients coming from nursing homes?

Reply: Thank you for the comment. If we included patients coming from nursing homes, we could have recruited more patients. However, CAP and health-care-associated pneumonia (HCAP) have been reported to have different epidemiology (5). Therefore, in this study, we decided to focus solely on patients with CAP. We have clarified it in the Materials and Methods section. (page 6, third paragraph, line 3)

Comment 4:
What happened to patients that could not answer to the question of appetite loss, that is based on self assessment (i.e.: loss of consciousness, impossibility to answer for demencia or other pathology, etc)? They were excluded from the study?

Reply: We appreciate your helpful comment. When the patients themselves were unable to answer the questions, the physicians collected data from their caregivers. We have clarified it in the Methods and Materials section. (page 6, fourth paragraph, line 2)

Comment 5:
It would be useful a list of the final diagnosis for all the patients.
Reply: As suggested, we have added a list of the final diagnoses in Table 1 in order to help readers understand the characteristics of our setting.

Comment 6:
Page 9: I consider not necessary to include the formula for the prediction models in the text; it would be better placed in a table or appendix material.

Reply: According to your suggestion, we have placed it in a supplementary file.

Response to reviewer 2:
Thank you for your thoughtful comments for improving the content and quality of our manuscript.

Comment 1:
Unfortunately, Authors do not refer to limitations of Pneumonia Severity Index (PSI) and Confusion, Urea, Respiratory rate, Blood pressure, aged 65 and older (CURB-65). This has been recently published, and a comparison between these above mentioned scores with neutrophil to lymphocyte ratio (NLR) performed (E. Cataudella et al. JAGS 2017).

Reply: As you commented, we agree on the importance of predicting the prognosis of CAP in elderly patients. For that reason, a correct diagnosis CAP is required. We have added this point in the Introduction and cited the article you suggested. (page 5, first paragraph, line 2)

Comment 2:
Sample size looks rather small. Did Authors estimate the power?

Reply: As described above, we agree with you that the sample size was not enough. Unfortunately, we could not estimate the power because it was not feasible in the analyses, such as net reclassification index and decision curve analysis.

Comment 3:
Appetite loss is a very common symptom in the elderly. Its discriminant value for CAP diagnosis in comparison with existing models is evident in some, but not all, cases (Table 3).

Reply: We appreciate the opportunity to clarify this point. We evaluated the discrimination and calibration of appetite loss in this model, in comparison with those of existing models. As you pointed out, appetite loss was not always superior to existing models.

Comment 4:
Did Authors assess the value of NLR to predict CAP?
Reply: Unfortunately, we could not assess the value of NLR. As the purpose of the current study was to predict the diagnosis of CAP by history and physical examination, we did not include blood tests as predictors. However, your suggestion made us interested in pursuing future research on the performance of such blood markers for the diagnosis of CAP.
References
1. Diehr P, Wood RW, Bushyhead J, Krueger L, Wolcott B, Tompkins RK. Prediction of pneumonia in outpatients with acute cough--a statistical approach. J Chronic Dis 1984;37:215–25.
2. Singal BM, Hedges JR, Radack KL. Decision rules and clinical prediction of pneumonia: evaluation of low-yield criteria. Ann Emerg Med 1989;18:13–20.
3. Heckerling PS, Tape TG, Wigton RS, et al. Clinical prediction rule for pulmonary infiltrates. Ann Intern Med 1990;113:664–70.
4. Toyabe S. Non-specialized inpatient care provided by university hospitals in Japan. Risk Manag Healthc Policy 2008;1:23–9.
5. Kollef MH, Shorr A, Tabak YP, et al. Epidemiology and outcomes of health-care-associated pneumonia: results from a large US database of culture-positive pneumonia. Chest 2005;128:3854–62.

VERSION 2 – REVIEW

REVIEWER	Antonella Francesca Simonetti Hospital Universitari Bellvitge Barcelona, Spain
REVIEW RETURNED	26-Sep-2017

GENERAL COMMENTS	This reviewed version address better the strengths and limitations of the current study, placing it in the setting from the title, so that the reader can better understand the study population characteristics. I appreciate the clarification of the setting, and, also if I did not totally agree with the idea that chest X-ray should be discarded based on a test with a low discrimination power, it is possible that prediction models for CAP diagnosis could have some utility also in hospital settings. The other comments were correctly addressed in the new manuscript version. Thank to the authors for their effort to improve the manuscript.

REVIEWER	Prof. Lorenzo Malatino Department of Clinical and Experimental Medicine, University of Catania, Catania, Italy
REVIEW RETURNED	03-Oct-2017

GENERAL COMMENTS	This Reviewer has no further concern.