PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Community-acquired pneumonia – Use of clinical characteristics of acutely admitted patients for the development of a diagnostic model: A cross-sectional multicentre study
AUTHORS	Cartuliares, Mariana; Mogensen, Christian Backer; Rosenvinge, Flemming; Skovsted, Thor; Lorentzen, Morten; Heltborg, Anne; Hertz, Mathias; Kaldan, Frida; Specht, Jens; Skjøt-Arkil, Helene

VERSION 1 – REVIEW

REVIEWER	Luchsinger, Vivian Universidad de Chile
REVIEW RETURNED	23-Feb-2024

GENERAL COMMENTS	The article is very interesting, it addresses a prevalent topic (CAP) and includes the analysis of numerous variables. The article is appropriately written, although it requires standardizing the grammatical use of the term leukocyte. The authors sometimes write leucocytes (e.g. line 47 page 3), other times leukocytes (e.g. line 55 page 8), and another leucocyttes ((e.g. line 4 page 15). I recommend starting the sentence in line 9 page 8 : Seventy candidate predictors and not placing the number in parentheses because it is confusing.

REVIEWER	Garin, Nicolas HUG), Department of Medicine
REVIEW RETURNED	26-Mar-2024

GENERAL COMMENTS	This multicentric study based on prospectively collected data aims to identify characteristics present at admission and predictive of CAP in patients consulting for infectious symptoms ; to derive a clinical prediction model for the presence of CAP ; and to compare the accuracy of the clinical prediction model with that of the « clinical gestalt » of emergency department physicians. They included a total of 954 patients ; 229 had a final diagnosis of CAP according to the reference standard used in the study, expert panel adjudication. The research question is important and points to an unmet clinical need. The authors should be commended for their huge effort. The overall quality of the study is good, with few missing data ; the reference diagnosis is probably the most appropriate for this disease ; common errors (verification bias for example) seem to be avoided. The negative conclusion (a clinical prediction model is not better than clinical gestalt) is somehow disappointing, but is coherent with previous works.

	I have however one major and some minor comments that could improve the reporting of this study. General comments : English language should be thoroughly revised, as there are still many minor language errors (verbs omissions ; plurals…) Major comment The patient population may be a non-representative sample of the overall population of CAP presenting to the ED (exclusion of severe patients ; inclusion only during day-time and week days). This issue is partially commented in the Discussion section ; authors could additionnally provide an estimation of the number of patients leaving the four hospitals with a final diagnosis of CAP during the study to help appreciate this point. Minor comments Abstract Line 17. "Suspected CAP" instead of "CAP" Line 24. "cross sectional" and "prospective" are self-contradictory; please clarify or rename Line 47: "neutrophils" instead of "neutrophilocytes" Line 54: Area under ROC is usually presented as 0.85 instead of 85%; consider formatting all AUROC as a number btw 0 and 1. Also please introduce 95% CI before the figures of sensitivity and specificity in the brackets. I would also cleave the sentence after the AUROC. "Sensitivity and specificity were ... at a 35% probability cut-off" Line 7, page 3: You (appropriately) conclude that the clinical value of the model is questionable but don't tell why (it is implicit in the results paragraph that the model does not add to clinical gestalt, but it deserves clear formulation in the Conclusion. Introduction Page 3 Line 34 : Please delete « Traditionally » Line 43 : Please add « be » (might not be the optimal…) Page 4 Line 9 : Please replace « outcome diagnosis » by « reference diagnosis » Line 43. Consider replacing « to investigate » with « to compare » Methods Page 5 Line 40 : please state that you did not include consecutive patients (as we understand in the « recruitment section », patients presenting at night and on week-ends were excluded) Why were patients in need for urgent treatment or transferred to the ICU not included ? they may as well have a pneumonia, and their exclusion means that you included a selected population. Page 6 Line 30 I would include the information about the expert panel in a paragraph on« Reference diagnosis ». The outcome in your study is actually the accuracy of your predictive model compared with your reference diagnosis Please add the following details concerning your expert panel : how many pairs of experts ; was there a minimum number of years of clinical experience for the experts ; was a third expert involved when there was no consensus ; for radiology, did experts had access both to images and to the interpretation by a radiologist ; did you measure intra-observer and inter-observer agreement Results

	A diagnosis of CAP should include the demonstration of an acute infiltrate on an radiological imaging. Could you please provide in the Result section the numbers and percentage of patients with CXR, CT-scan, and lung ultrasonography ? Patients were followed up to one week after ED admission ; what proportion of patients were admitted in the hospital wards ; and how were followed patients discharged from the hospital directly from the ED or before one week ? Discussion Page 15 Line 11-13 : The sentence is incomplete (27 characteristics associated with CAP in univariate…) Line 36-39 : « The model could be tested externally… » : not sure what this sentence means ; all the more so as you appropriately report in the following sentence that the model results are surpassed by the ED physician appreciation Page 16 Line 47 : « cardiac heart failure » ; please suppress cardiac

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Vivian Luchsinger, Universidad de Chile
Comments to the Author:
The article is very interesting, it addresses a prevalent topic (CAP) and includes the analysis of numerous variables.
Comment: We are grateful for your time and interest in reviewing our manuscript.
The article is appropriately written, although it requires standardizing the grammatical use of the term leukocyte. The authors sometimes write leucocytes (e.g. line 47 page 3), other times leukocytes (e.g. line 55 page 8), and another leucocyttes ((e.g. line 4 page 15).
Answer: Thank you very much for pointing that. We have streamlined the text in British English and kept it as leukocyte throughout the manuscript and the supplementary material.
I recommend starting the sentence in line 9 page 8 : Seventy candidate predictors and not placing the number in parentheses because it is confusing.
Answer: Thank you very much. We have followed your recommendation for better clarity.

Reviewer: 2
Prof. Nicolas Garin, HUG)
Comments to the Author:
This multicentric study based on prospectively collected data aims to identify characteristics present at admission and predictive of CAP in patients consulting for infectious symptoms ; to derive a clinical prediction model for the presence of CAP ; and to compare the accuracy of the clinical prediction model with that of the « clinical gestalt » of emergency department physicians. They included a total of 954 patients ; 229 had a final diagnosis of CAP according to the reference standard used in the study, expert panel adjudication.
The research question is important and points to an unmet clinical need. The authors should be commended for their huge effort. The overall quality of the study is good, with few missing data ; the reference diagnosis is probably the most appropriate for this disease ; common errors (verification bias for example) seem to be avoided. The negative conclusion (a clinical prediction model is not better than clinical gestalt) is somehow disappointing, but is coherent with previous works.
I have however one major and some minor comments that could improve the reporting of this study.
Comment: Thank you very much for your comments and we are grateful for the thorough review which has improved our manuscript.

General comments : English language should be thoroughly revised, as there are still many minor language errors (verbs omissions ; plurals…)
Answer: Thank you very much for your observation. The manuscript was reviewed by our research support specialist with English as a native language, with many small errors identified and changed.
Major comment
The patient population may be a non-representative sample of the overall population of CAP presenting to the ED (exclusion of severe patients; inclusion only during daytime and week days). This issue is partially commented in the Discussion section ; authors could additionally provide an estimation of the number of patients leaving the four hospitals with a final diagnosis of CAP during the study to help appreciate this point.
Answer: Thank you very much for this very relevant comment. We acknowledge the limitations in generalizing our study findings to all CAP populations, particularly as our sample mainly consisted of patients seen on weekdays with predominantly mild-to-moderate cases. In our discussion section, we have tried to address this limitation more transparently and in more depth.
“Patients with severe conditions or acute cognitive impairment who could not consent were excluded. Furthermore, the inclusion of patients took place during work hours and weekdays, which may have reduced the number of severe cases as admission during out-of-hours and weekends are associated with increased mortality and ICU admissions [58].Therefore, our results can only be generalised to patients suspected of CAP and admitted on weekdays during the daytime”.
Though our population predominantly included mild-to-moderate CAP, it is notable that we have still included severe patients, as Table 1 shows that 25% of the patients had a triage colour red/orange. The severe cases not included in this study were those where life-saving treatment or consent would be interrupted by the inclusion process. Furthermore, this study used prospectively collected data, and clock-around data collection was not possible due to logistic and resource issues.
We can estimate of the number of patients leaving the four hospitals with a final diagnosis of CAP during the study. However, it wouldn’t be comparable to our results because our population is only those admitted with suspected infection by the ED physician (we cannot estimate this number due to the prospective design). So patients who the physician did not suspected CAP and those not allocated to the internal medicine speciality but ended with the diagnosis CAP would be included in the estimation. This issue is discussed in the discussion section: “Another limitation is the selected population of the patients allocated to the internal medicine speciality that may have masked atypical predictors from patients assigned to other specialities. Furthermore, some patients with atypical clinical presentation might have an infection that the ED physician had not suspected upon admission and, therefore, was not included in our study. Patients with severe conditions or acute cognitive impairment who could not consent were excluded”.
Therefore, we cannot compare the number of our CAP diagnosis with the number of patients leaving the four hospitals.

Minor comments
Abstract
Line 17. “Suspected CAP” instead of “CAP”
Answer: Thank you for this comment. We have added “suspected”.
Line 24. “cross sectional” and “prospective” are self-contradictory; please clarify or rename
Answer: Thank you for mentioning this. We have clarified the sentence in the abstract: “Design: Cross-sectional, multicentre study”, and in the method section describing the study design: “This study had an analytical, cross-sectional, multicentre design. The data was collected prospectively and originates from the INfectious DisEases in Emergency Departments (INDEED) study”.
Line 47: “neutrophils” instead of “neutrophilocytes”
Answer: Thank you, we have reworded “neutrophilocytes” to “neutrophils” in the manuscript and the supplementary.

Line 54: Area under ROC is usually presented as 0.85 instead of 85%; consider formatting all AUROC as a number btw 0 and 1. Also please introduce 95% CI before the figures of sensitivity and specificity in the brackets.
Answer: Thank you for this comment. We have checked all AUROC results and ensure they are now all between 0 and 1. We have also introduced 95% CI in brackets in the abstract and changed parentheses for brackets along the manuscript.
I would also cleave the sentence after the AUROC. “Sensitivity and specificity were ... at a 35% probability cut-off”
Answer: Thank you for your recommendation, we have deleted the sentence “Sensitivity and specificity were ... at a 35% probability cut-off” as well the sentence “sensitivity and 75% (72%-78%) specificity” to streamline the presentation of the results.
Line 7, page 3: You (appropriately) conclude that the clinical value of the model is questionable but don’t tell why (it is implicit in the results paragraph that the model does not add to clinical gestalt, but it deserves clear formulation in the Conclusion.
Answer: Thank you very much for this comment. We have enhanced the conclusion to ensure a more comprehensive understanding: “The clinical value of the prediction model is questionable in our setting as it does not outperform the clinician’s assessment”

Introduction
Page 3
Line 34 : Please delete « Traditionally »
Answer: Thank you, we have deleted « Traditionally »
Line 43 : Please add « be » (might not be the optimal…)
Answer: Thank you for pointing this, we have added « be »

Page 4
Line 9 : Please replace « outcome diagnosis » by « reference diagnosis »
Answer: Thank you, we have replaced « outcome diagnosis » by « reference diagnosis »

Line 43. Consider replacing « to investigate » with « to compare »
Answer: Thank you for this recommendation we have replaced « to investigate » with « to compare »

Methods
Page 5
Line 40 : please state that you did not include consecutive patients (as we understand in the « recruitment section », patients presenting at night and on weekends were excluded)
Answer: Thank you for mentioning this. We have been more precise that the sample was a convenience sample: “The population was a convenient sample of eligible patients consecutively identified from the patient management system by a project assistant.”
Why were patients in need for urgent treatment or transferred to the ICU not included ? they may as well have a pneumonia, and their exclusion means that you included a selected population.
Answer: Thank you for this very relevant comment. We recognize that patients requiring urgent treatment or ICU transfer may also have pneumonia, and their exclusion could lead to a selected study population. The urgency of their conditions necessitates immediate attention, and the process of obtaining written consent might interfere with their emergency care. Moreover, the severity of their illness may preclude them from giving consent, as they could be too unstable. However, our study did include a subset of severely ill patients, as indicated in Table 1, comprising 24.4% of cases, with only 2% excluded due to urgent treatment needs (Figure 1). We aimed to capture the majority of patients presenting at the ED and not the most severely ill. Therefore our population is appropriated selected to present the patients with the greatest challenges at the ED. For participation in research, Danish legal and ethical standards require mental competence. Since ICU admission in Denmark typically requires mental incapacity, inclusion in our study would not align with Danish law. Additionally, we

were unable to gather data once the patient's acute condition stabilized, as our study design focused on information available upon arrival.

Page 6
Line 30 I would include the information about the expert panel in a paragraph on« Reference diagnosis ». The outcome in your study is actually the accuracy of your predictive model compared with your reference diagnosis
Please add the following details concerning your expert panel : how many pairs of experts ; was there a minimum number of years of clinical experience for the experts ; was a third expert involved when there was no consensus ; for radiology, did experts had access both to images and to the interpretation by a radiologist ; did you measure intra-observer and inter-observer agreement
Answer: Thank you very much for this comment that significantly improves this section in the manuscript. We have rewritten the section now and renamed the section « Reference diagnosis » instead of “outcome” and added more information concerning the expert panel (number of experts, level of experience and how they met a concensus). Furthermore, we added information relating to information from imaging. We did not measured intra-observer and inter-observer agreement.

Results
A diagnosis of CAP should include the demonstration of an acute infiltrate on an radiological imaging. Could you please provide in the Result section the numbers and percentage of patients with CXR, CT-scan, and lung ultrasonography ?
Answer: Thank you for this comment. One of the strengths of this study lies in the expert panel evaluating the presence of CAP or not. This approach is particularly valuable given the recognized limitations of CXR (Chest X-ray) in diagnosing CAP, owing to its imprecision and reduced sensitivity, especially when conducted upon admission, as lung infiltrates may evolve over time. However, we have now adjusted the results to include the number of chest CT-scans, but due to ethical reasons this investigation was only conducted on patients suspected of CAP. We chose to present the numbers of chest CTs as chest CT is the golden standard and the most reliable assessment compared to CXR and ultrasonography. We chose not to present the number of CT scans in the table as this variable was not included in the development of our clinical prediction model. We have written in the results: “The evaluation of 332 chest CT scans showed that 188 (57%) patients had verified pneumonia, and from those, 148 (76%) had CAP assessed by the expert panel and confirmed by a chest CT scan”. The diagnostic accuracy between chest CT, CXR, and ultrasonography will be presented in another publication.

Patients were followed up to one week after ED admission; what proportion of patients were admitted in the hospital wards ; and how were followed patients discharged from the hospital directly from the ED or before one week ?
Answer: Thank you for this comment. I have added the description of the results of discharge destination at the start of the result section: “ Most patients (65%) with CAP were discharged to an internal medicine ward, whilst 29% of the patients diagnosed with CAP by the expert panel were discharged directly home. There were 2.5% , 2.5% and 1.0% of the population with CAP that were discharged to the ICU, surgical, other wards respectively “.

Discussion
Page 15
Line 11-13 : The sentence is incomplete (27 characteristics associated with CAP in univariate…)
Answer: Sorry, but we could not identify this incomplete sentence.
Line 36-39 : « The model could be tested externally… » : not sure what this sentence means ; all the more so as you appropriately report in the following sentence that the model results are surpassed by the ED physician appreciation

Answer: We agree that this is confusing, therefore, we have added an example to clarify this sentence: “Therefore, the model could be tested externally at other sites, especially where clinicians are not always available due to the lack of resources, and contribute to the initial management of CAP, guiding clinical investigation”.

Page 16
Line 47 : « cardiac heart failure » ; please suppress cardiac
Answer: Thank you for pointing this, we have deleted cardiac.

VERSION 2 – REVIEW

REVIEWER	Garin, Nicolas HUG), Department of Medicine
REVIEW RETURNED	26-Apr-2024

GENERAL COMMENTS	Dear Author, You did an excellent job in answering all the points I have mentionned in my review. I have no additionnal comment and I think that the manuscript is now ready for publication