PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	LOw-dose CT cOmPared to Lung UltraSonography vs standard of care based-strategies for the diagnosis of pneumonia in the elderly: a multicentre randomised controlled trial (OCTOPLUS)
AUTHORS	Prendki, Virginie; Garin, Nicolas; Stirnemann, Jerome; Christophe, Combescure; Platon, Alexandra; Bernasconi, Enos; Sauter, Thomas; Hautz, Wolf

VERSION 1 – REVIEW

REVIEWER	Ticinesi, Andrea Università degli studi di Parma, Department of Medicine and Surgery
REVIEW RETURNED	09-Sep-2021

GENERAL COMMENTS	I have read with great interest the protocol of the OCTOPLUS study, addessing very important questions on the optimal diagnostic strategy for pneumonia in older patients presenting to Emergency departments. The study has a great potential of modifying the standard clinical practice in this field, and the authors must be commended for their work. There are however several issues needing clarification before the present manuscript can be considered for publication. 1) The study protocol is mainly centered on the comparison between the LDCT and CXR arms, while the LUS arm is considered only in secondary objectives and secondary analyses. The use of bedside LUS in emergency situations has considerable advantages in terms of diagnostic power, rapidity of diagnosis, patient safety and confort. These advantages are emphasized in older frail patients, that may represent the ideal candidates for this diagnostic approach for many reasons. However, rigorous studies on the diagnostic accuracy of LUS in older patients evaluated in Emergency Departments are still lacking, and I think that the OCTOPLUS study could give a fundamental contribution to fill this gap. Thus, I would suggest to include a deeper discussion on the use of LUS for diagnosing pneumonia in elderly patients in the Introduction/Study Rationale section. I also suggest to emphasize LUS-centered objectives and outcomes in the study methodology. 2) In the last sentence of the Introduction, the authors affirm that their hypothesis is "based on the results of our previous study". However, no reference or explanation is given on this study. I suggest to rephrase this sentence to improve comprehension by readers, including more details on this "previous study". 3) The planned dates of study conduction are not included in the manuscript. Furthermore, in the "Recruitment" section on page 9, the authors affirm that if the enrolment goals are not met, the study duration will be extended after the planned two years. How long do the authors plan to extend the study duration in this case? 4) The timing and order of the three diagnostic tests (CXR, LUS and

	LDCT) should be included in the manuscript because this is an important methodological detail. Will the tests be performed always in the same order or not? Is there a prespecified timing of execution of these tests. Long intervals between one test and another could affect the results and diagnostic accuracy. 5) More details should be included on the methods used to assure blinding of the diagnostic tests not pertaining to the randomization arm to managing physicians. I guess they will be obscured on electronic health records, is this correct? Who is responsible for this process and for the unblinding on the fifth day? 6) Will patients with viral pneumonia be included in the study? The authors have listed known RT-PCR tests positive for SARS-CoV-2 as an exclusion criterion. However, what about patients who are admitted to ED and have not been previously tested for SARS-CoV-2? What about patients with other causes of viral pneumonia? If they will be excluded, than the authors must underline that the focus of their research is bacterial pneumonia. 7) Will patients with suspect or confirmed aspiration pneumonia be considered in the study, or will they be excluded? 8) The authors should include a plan for modulation of the study procedures in case of a novel surge of COVID-19 cases. How will the study proceed in the case of a novel pandemic wave? 9) Which standardized report will be used for LUS examinations? How will LUS procedures be standardized among sonographers of the different participating centers? These issues should be more detailed in the manuscript. 10) The reference diagnosis will be based on the rating of the probability of pneumonia assigned a posteriori by a panel of experts. This procedure should be better justified and detailed. Is the procedure of rating the probability of pneumonia validated in the scientific literature? Is it based just on the clinical judgement of experts or on objective data? Why won't ICD-10 codes be used for establishing a reference diagnosis? Will the panel of experts review the images of CXR, LDCT and LUS or will they be blind to images? If the experts will be aware of the results of the three examinations, the possibility of bias should be considered. 11) More details on how the cost per patient will be measured should be included in the manuscript. 12) Objectives paragraph, last sentence. What does "characteristics of clinicians" mean? 13) The number of emergency unblindings and the number of unexpected diagnoses (for example, detection of a lung cancer or other silent pulmonary diseases) should be considered in safety analyses. 14) The consent procedures for patients unable to plead (those with cognitive impairment, delirium or dementia) should be better detailed. If I understood well, these patients will be evaluated also by a physician not belonging to the study team, who will sign the provisional consent for the patient. Then the patient or her/his legal representative will be asked to sign the consent form at a later stage, when it will be possible. How will the participation will be managed if the patient or the legal representative will deny consent? Will she or he be removed from the study? 15) A balanced discussion of study strengths and limitations should be included in the final part of the manuscript.

REVIEWER	Jensen, Martin Bach Center for General Practice at Aalborg University
REVIEW RETURNED	03-Oct-2021

GENERAL COMMENTS	This is an important and well-designed study comparing low dose CT scan, point-of-care ultrasound, and X-ray for diagnosing pneumonia in elderly seen in the emergency room. The rationale and overall aim of the study are clearly described, the methodology and choice of outcomes are sound. Still, there are some aspects of the manuscript that could be improved. Firstly, there is a lack of detail in the description of some important outcomes. E.g. for cost, please specify the perspective of the cost evaluation. What is the timeframe for cost evaluation? Are only in-hospital costs included and will all costs be included (e.g. if a patient is re-hospitalized during the study period for other reasons)? Is there a reference to the different costs (more than stating 'Hospital financial database'). For antibiotics. Will use of any type and dose of antibiotic be regarded as treatment days (e.g. also the use of antibiotics typically given for cystitis, skin infections, etc)? Consider describing how you handle patients having had antibiotics prescribed prior to admission. There is no mention of study dates. When is the study planned to begin? In the ClinicalTrials registration the start date is set to 7th of July 2021. Please report the dates for planned beginning and end of this study. People not familiar with the Swiss health-care system may need a little more information regarding the setting. Please describe how patients are triaged to the emergency room. I.e. do they have free access to the emergency room or will they have to be seen by a general practitioner beforehand and referred on? For overview of the study, please provide a time-event diagram (Gantt diagram) including intervention, outcome assessment etc. On page 12 it is stated that the analysis follows the intention to treat principle. On page 14 the ‘Handling of missing data and drop-outs’ is described and it is stated that Missing data that cannot be avoided will be excluded from the primary analysis (complete case analysis) and signaled as such. To avoid uncertainty about the intention-to-treat approach please specify that all available data from all included patients will be included in the intention-to-treat analysis whereas patients with missing data will be excluded from the complete case analysis. The discussion is rather limited. Please discuss the limitations regarding reference diagnosis (e.g. perspectives on agreement/disagreement amongst the panel etc). Also, please discuss the choice of outcomes and their limitations. If possible, please provide names and versions of all diagnostic equipment used. Please report what language versions of questionnaires (e.g. EQ5D-3L) that will be used. The planned sample size is reported as 495 in the manuscript, in the trial registration as 500. Please be consistent.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1 Dr. Andrea Ticinesi
Comments to the Author:
I have read with great interest the protocol of the OCTOPLUS study, addressing very important questions on the optimal diagnostic strategy for pneumonia in older patients presenting to Emergency departments. The study has a great potential of modifying the standard clinical practice in this field, and the authors must be commended for their work.
We thank the reviewer for his supporting comment.

There are however several issues needing clarification before the present manuscript can be considered for publication.
1) The study protocol is mainly centered on the comparison between the LDCT and CXR arms, while the LUS arm is considered only in secondary objectives and secondary analyses. The use of bedside LUS in emergency situations has considerable advantages in terms of diagnostic power, rapidity of diagnosis, patient safety and comfort. These advantages are emphasized in older frail patients, who may represent the ideal candidates for this diagnostic approach for many reasons. However, rigorous studies on the diagnostic accuracy of LUS in older patients evaluated in Emergency Departments are still lacking, and I think that the OCTOPLUS study could give a fundamental contribution to fill this gap. Thus, I would suggest to include a deeper discussion on the use of LUS for diagnosing pneumonia in elderly patients in the Introduction/Study Rationale section. I also suggest to emphasize LUS-centered objectives and outcomes in the study methodology.
We thank the reviewer for this valuable remark. Actually, the primary objective of the OCTOPLUS trial was to compare LDCT accuracy with CXR accuracy because our previous work provided numeric data on which to base our sample calculation (doi:10.1183/13993003.02375-2017). In this study, we did not assess LUS.
However, comparative accuracy of LUS is also of major interest in the OCTOPLUS trial and is a main secondary outcome.
We have added a deeper discussion on the use of LUS for diagnosing pneumonia in elderly patients in the introduction, as follows:
“In a non randomized monocentric study including patients hospitalized in an acute geriatric ward for a pneumonia, Ticinesi and colleagues showed that LUS was more accurate than CXR CXR (AUC of 0.90, 95% confidence interval [CI] 0.83–0.96 vs 0.67, 95%CI 0.60–0.74, P<0.001), particularly in frail patients (doi: 10.1097/md.0000000000004153). A recent review emphasized the advantages of chest US in geriatric settings, including US being unaffected by age-related changes of lower respiratory tract, nor by mobility limitations. The authors further emphazised the urgent need to perform studies focused on elderly patients. (doi:10.1016/j.jamda.2019.06.018).
In the same line, we have emphasized LUS-centered objectives and outcomes in the study methodology:
We have highlighted in bold in the paragraph Objectives:”The same objectives for the comparison between CXR- and LUS-based diagnostic strategies and between LDCT- and LUS based diagnostic strategies”.
We have also added “CXR, LDCT and LUS after imaging-based strategies” to keep the reader’s attention.
2) In the last sentence of the Introduction, the authors affirm that their hypothesis is "based on the results of our previous study". However, no reference or explanation is given on this study. I suggest to rephrase this sentence to improve comprehension by readers, including more details on this "previous study".
We have added the name and the reference of the study, that we explained better as follows in the paragraph Thoracic computed tomography scan:

“Similar results were obtained with elderly patients in the monocentric PneumO-LD-CT cohort, in which patients aged over 65 years with suspected pneumonia treated with antibiotics were included. All of them had both a CXR and low-dose CT-scan and the clinician in charge of the patients assessed his probability of pneumonia before and after the LDCT; the main outcome was the difference of probability of pneumonia according to the clinician in charge before and after LDCT.”
3) The planned dates of study conduction are not included in the manuscript. Furthermore, in the "Recruitment" section on page 9, the authors affirm that if the enrolment goals are not met, the study duration will be extended after the planned two years. How long do the authors plan to extend the study duration in this case?
The inclusions began on September 2021 and should end in August 2023. However, recruitment could be prolonged if necessary, in particular in view of the COVID-19 pandemic interfering with inclusions in times of high demands on emergency departments.
4) The timing and order of the three diagnostic tests (CXR, LUS and LDCT) should be included in the manuscript because this is an important methodological detail. Will the tests be performed always in the same order or not? Is there a prespecified timing of execution of these tests. Long intervals between one test and another could affect the results and diagnostic accuracy.
The tests will not always be performed in the same order as it depends on the availability of the clinician practicing US. But we agree with the reviewer that long intervals between the tests could affect the results and diagnostic accuracy and the 3 tests will be performed in the shortest delay possible, not to impact too much on the patient's care. The protocol specifies a maximum delay of 4/6 hours for completion of the diagnostic tests.
This has been added as follows in the paragraph
-Study design: “This study is carried out in an emergency setting. Pneumonia is a major cause of morbidity and mortality. Both diagnosing and treating the patient with suspected pneumonia must be performed within the first hours. Indeed international guidelines recommend treating the patient for a suspicion of pneumonia while he/she is still in the ED.
-Interventions: « The 3 tests won’t have to be performed in the same order as it will depend on the availability of the clinician practicing US but they will be done in the shortest delay possible and in no more than 4 hours to avoid any significant impact on patient's care.”
5) More details should be included on the methods used to assure blinding of the diagnostic tests not pertaining to the randomization arm to managing physicians. I guess they will be obscured on electronic health records, is this correct? Who is responsible for this process and for the unblinding on the fifth day?
The reviewer is right. When the images are taken, they won’t be sent on the electronic health records but on a research PACS with the help of the IT team. The radiologists or sonographist who perform/interpret the tests will be asked to keep secret on their diagnosis. The research staff will be present throughout the process to oversee the smooth running of the study. Moreover the research staff will perform the unblinding at day 5, by calling the IT team to send back the images on the electronic health records, and to upload the reports.
We added it in the text: “As soon the randomization has been done, the research staff will know which tests have to be blinded. Those will be kept in a research PACS with the help of the IT team instead of in the electronic health records.
Furthermore the radiologists or the sonographist who perform/interpret the tests will be asked not to communicate with each other and to keep secret on their diagnosis. The research staff will be present throughout the process to oversee the smooth running of the study.
At day 5, the research staff will ensure that the two blinded radiological examinations along with the standardized reports are made accessible again on the patient’s medical record.”
6) Will patients with viral pneumonia be included in the study? The authors have listed known RT-PCR tests positive for SARS-CoV-2 as an exclusion criterion. However, what about patients who are admitted to ED and have not been previously tested for SARS-CoV-2? What about patients with other causes of viral pneumonia? If they will be excluded, than the authors must underline that the focus of their research is bacterial pneumonia.

This is a very good question.
Our aims are to include elderly patients presenting at the ER for suspected community or nursing-home acquired pneumonia, regardless of the underlying pathogen or mechanism (see question 7)). Hence we will also include patients with viral pneumonia. All patients will have a nasopharyngeal swab to perform a panel of PCR for classical respiratory virus.
In our previous PneumO-LD-CT (https://doi.org/10.1016/j.cmi.2018.12.037) on which we based our sample size calculation, 1/3 of the patients had positive PCR for virus on naso-pharyngeal swabs (62 out of 200).
We decided to exclude patients diagnosed with known acute COVID-19 infection before the inclusion in order to reduce the possible biases related to the SARS-CoV-2 pandemic; however patients diagnosed with SARS-CoV-2 detected after inclusion will not be excluded.
We added this sentence in the paragraph Eligibility criteria: “Patients with suspicion of bacterial, viral or aspiration pneumonia will be included on a non-preferential basis. Patients with a current diagnosis of pneumonia or a chest imaging obtained during the recent episode will be excluded, as well as those with a recent diagnosis of COVID-19 -to minimize the overrepresentation of COVID cases in the cohort-. Patients with hospital-acquired pneumonia will be excluded.”
Following the questions of the reviewer, we will perform a comparison of sensitivity of each test according to the type of pneumonia, viral or non viral (which will be determined by the panel of experts).This comparison will be exploratory and may be useful to generate hypotheses.
This has been added in the Statistical Analysis:
“Additional analyses:
The sensitivity of each diagnostic strategy will be assessed in patients with a viral pneumonia as determined by the panel of experts and in patients with a bacterial pneumonia or patients without a detected pathogen. A comparison will be conducted with Fisher’s exact test. This comparison will be exploratory.”
7) Will patients with suspect or confirmed aspiration pneumonia be considered in the study, or will they be excluded?
Yes, we include these patients unless they have an exclusion criteria such as a hospital-acquired pneumonia. We will describe viral, aspiration and microbiologically documented bacterial pneumonia for all included patients.
These outcomes have been added in Table 3.
We also added this last mention in the paragraph Eligibility criteria: “Patients with suspicion of bacterial, viral or aspiration pneumonia will be included on a non-preferential basis”.
8) The authors should include a plan for modulation of the study procedures in case of a novel surge of COVID-19 cases. How will the study proceed in the case of a novel pandemic wave?
As explained in point 6), in order to reduce the possible consequences and biases related to the SARS-CoV-2 pandemic, we decided to exclude patients diagnosed with COVID-19 before the inclusion.
9) Which standardized report will be used for LUS examinations?
We have standardized reports for each test and also to collect the clinician’s diagnosis before the patient is discharged from the emergency room. We added the report of LUS at the end of this document and we can add it to the appendix of the manuscript if required by the editor.
How will LUS procedures be standardized among sonographers of the different participating centers? These issues should be more detailed in the manuscript.
This is a good point.
To minimize heterogeneity between the clinicians and centres, standardization of LUS practice has been performed before the beginning of the study. To minimize the impact of the examiner on the results, we ensure that: 1) all examiners have an US certificate -the Swiss standard for emergency LUS-, 2) the practice of LUS has been standardized between the centres and a common protocol has been agreed upon, 3) all examiners have participated in a joint POCUS workshop to standardize the use of the study protocol and practice.
Moreover their years of practice of ultrasonography will be collected.

This has been added in the manuscript in the paragraph Interventions as follows:
“To enhance homogeneity of sonographists reporting, they will be trained to use the standardized report form before the beginning of the inclusions, using a common protocol agreed upon at meetings. All examiners will have participated in a joint POCUS workshop to standardize the use of the study protocol and practice and their years of practice will be collected.”
10) The reference diagnosis will be based on the rating of the probability of pneumonia assigned a posteriori by a panel of experts. This procedure should be better justified and detailed. Is the procedure of rating the probability of pneumonia validated in the scientific literature? Is it based just on the clinical judgement of experts or on objective data? Why won't ICD-10 codes be used for establishing a reference diagnosis? Will the panel of experts review the images of CXR, LDCT and LUS or will they be blind to images? If the experts will be aware of the results of the three examinations, the possibility of bias should be considered.
We already used the same method of adjudication in PneumO-LD-CT study (10.1183/13993003.02375-2017), as well as Claessens et al (doi:10.1164/rccm.201501-0017OC). Such a methodology is recommended in the absence of a gold standard, which is the case in the diagnosis of pneumonia in elderly patients in whom it seems not ethical to perform a broncho-alveolar lavage (doi:10.1016/j.jclinepi.2009.02.005). (see point 15)).
The experts will have access to all three imaging modalities obtained for all patients irrespective of randomization arm in order to minimize information bias. However this might induce an incorporation bias as the tests under evaluation will be known when interpreting the reference standard but is still better than showing only one or two among the 3 tests, according to us.
As asked, we added more information on the process of the panel of experts:
“A panel of experts composed of senior clinicians and board-certified specialists, including internists, geriatricians, infectious diseases specialists and radiologists, blinded to the allocation arm and the probability of pneumonia estimated by the clinician in charge, will rate prospectively and a posteriori the probability of pneumonia. They will be trained before the adjudication process and asked to follow international guidelines for the diagnosis of pneumonia. They will have access to all available but de-identified patient data present in the medical records, including clinical data, biological, microbiological data –as results of PCR viral detection on naso-pharyngeal swabs- and images of CXR, LDCT, LUS and corresponding reports, hospital notes, and the final medical report. Each patient’s diagnosis of pneumonia will be analysed using a Delphi method as follows: each expert will give an individual opinion on the probability of pneumonia on a 3-point Likert scale (low, intermediate, high). Next, each expert will re-examine the cases where there was a disagreement between expert ratings, in full knowledge of the other experts’ first decisions. Finally, the adjudication committee will make consensus decisions in a plenary session and in the presence of a radiologist. The adjudication committee’s final decision will be considered as the reference diagnosis. “
The ICD-10 code in our hospital is used for billing purposes and based on one clinician’s diagnosis and hence is also biased. Therefore we do not propose to use it as a gold standard.
11) More details on how the cost per patient will be measured should be included in the manuscript.
Cost outcomes are defined as costs within the hospital calculated using a Swiss standard called REKOLE (https://rekole.hplus.ch/fr/produkt/rekole-comptabilite-analytique-a-lhopital/).
The manual strictly defines how all the hospital costs must be attributed to the hospital stays based on a minimal set of keys that are linked to the actual resource consumptions.
They include: direct cost items recorded directly at the case level (e.g. medication, material); costs that are calculated based on direct consumption e.g. unit’s nursing costs are distributed on hospital stays using minutes of care recorded in the patient’s file as key, imagery’s costs that are distributed based on each exam’s relative consumption points. And at last, indirect costs which are mostly overhead costs are added.
This has been added in the manuscript as follows:
“Cost outcomes are defined as costs within the hospital calculated using a Swiss standard called REKOLE (https://rekole.hplus.ch/fr/produkt/rekole-comptabilite-analytique-a-lhopital/).
The main costs components of are: nursing care, physician, imaging, laboratory, treatment (including

antibiotic therapy) and others per patient during hospitalization, health related quality of life at 3 months; unit of work consumption per hospital (number of minutes of care, physician, laboratory and imaging points) up to 3 months."

12) Objectives paragraph, last sentence. What does "characteristics of clinicians" mean?
In a substudy of OCTOPLUS, called CIRCUS for Calibration of reasoning confidence in uncertain situations, factors affecting physician confidence in their diagnosis will be collected. A secondary aim is to describe the calibration of physician confidence with their actual diagnostic accuracy, which is measured as part of the OCTOPLUS trial by comparing a physician's diagnosis against that of an expert panel.
These objectives have been added in the paragraph Other secondary objectives as follows:
- Association between characteristics of clinicians and accuracy of imaging-based strategies
- Factors of the physician such as experience or gender, of the patient such as urgency or presenting complaint and of the context such as daytime affecting physician confidence in their diagnosis (CIRCUS substudy for Calibration of reasoning confidence in uncertain situations).
- Calibration of physician confidence with their actual diagnostic accuracy (CIRCUS)
13) The number of emergency unblindings and the number of unexpected diagnoses (for example, detection of a lung cancer or other silent pulmonary diseases) should be considered in safety analyses.
This is a good point but we have chosen to consider the number of emergency unblindings as a secondary outcome and not as a safety one. At this point it is difficult to make a major modification of the protocol, especially since we believe that these cases will be very rare in the population of interest (as we have excluded patients with severity criteria).
The number of unexpected diagnoses will be considered as an exploratory analysis.
14) The consent procedures for patients unable to plead (those with cognitive impairment, delirium or dementia) should be better detailed. If I understood well, these patients will be evaluated also by a physician not belonging to the study team, who will sign the provisional consent for the patient. Then the patient or her/his legal representative will be asked to sign the consent form at a later stage, when it will be possible. How will the participation will be managed if the patient or the legal representative will deny consent? Will she or he be removed from the study?
According to Swiss law on Human research (HRA, Art. 7, 16, and 18, 42; ClinO, Art. 7 - 9), it is possible to ask a consent to an independent physician for patients consulting at the emergency room and unable to plead. Moreover, it is possible to obtain consent from the legal representative who might be next of kin.
If the patient or the legal representative finally denies consent, all data collected until this point will be kept and used in the analysis as written in the letter of information and consent as follows:
"Withdrawal from the project:
You may withdraw from the study at any time and end your participation if you wish. However, the medical data and biological material collected up to that point may still be analyzed in coded form. In the event of withdrawal, your data and samples will continue to appear in coded form in the study documents, to ensure medical safety. You should verify that you agree with this before you give your consent."
All this has been modified in the manuscript in the part Ethics and dissemination as follows:
"Vulnerable participants will be included. Indeed, clinical studies in elderly patients are scarce, in part because informed consent is difficult to obtain due to acute confusion or permanent cognitive impairment. If the patient has his/her ability to consent in the ER, he/she will be invited to participate to the study and will be asked to read and sign the standard consent. If not, a physician independent of the study will give consent for the patient to participate in the study or not and will sign the dedicated written confirmation. When the patient recovers his capacity to consent during hospitalization, he will sign the standard consent for participant. Otherwise it will be signed by the legal representative. If the latter finally denies consent, all data collected until then will be kept and used in the analysis. Consents and written confirmation of the physician independent of the study are

found in appendix."
15) A balanced discussion of study strengths and limitations should be included in the final part of the manuscript.
Thanks for this remark. We added the discussion as follows:
"To our knowledge, no randomized trial has ever compared the performance of CXR, CT scan and US in pneumonia. The OCTOPLUS trial will allow a head to head comparison in a randomized trial of CXR-, LDCT- and LUS-based strategies for the diagnosis of pneumonia.
The results will have an important impact for emergency medicine, general practice, and internal medicine, as the issue of the superiority of LDCT over CXR in diagnosing pneumonia in the elderly will be addressed. Confirmed superiority could profoundly affect recommendations for the diagnosis of pneumonia in elderly patients, and LDCT could become the preferred diagnostic option over CXR. This could also apply to superiority of LUS over CXR, with the added benefit of being more easily available and non-irradiating compared with LDCT. Other strengths of the study will be the blinding of two among the three imaging modalities to the patients and clinicians, and the LUS standardization among ultrasonographists. We will use an adjudication committee for the reference diagnosis using the Delphi method to obtain consensus as recommended in case of absence of gold standard (10.3389/fpubh.2020.00457; 10.1016/j.jclinepi.2009.02.005). The experts will have access to all three imaging modalities obtained for all patients irrespective of randomization arm in order to minimize information bias. However, this might induce an incorporation bias as the tests under evaluation will be known when interpreting the reference standard.
This might be considered as a limitation of the study but such a methodology is recommended in the absence of a gold standard, which is the case in the diagnosis of pneumonia in elderly patients in whom it seems not ethical to perform a broncho-alveolar lavage.
A limitation of the study is that the primary outcome (difference in accuracy) is not a clinical outcome but we have added clinical outcomes in the secondary objectives."

Reviewer: 2
Prof. Martin Bach Jensen, Center for General Practice at Aalborg University
Comments to the Author:
This is an important and well-designed study comparing low dose CT scan, point-of-care ultrasound, and X-ray for diagnosing pneumonia in elderly seen in the emergency room. The rationale and overall aim of the study are clearly described, the methodology and choice of outcomes are sound.
Again, we thank the reviewer for his supporting comment.
Still, there are some aspects of the manuscript that could be improved.

Firstly, there is a lack of detail in the description of some important outcomes. E.g. for cost, please specify the perspective of the cost evaluation. What is the timeframe for cost evaluation? Are only in-hospital costs included and will all costs be included (e.g. if a patient is re-hospitalized during the study period for other reasons)? Is there a reference to the different costs (more than stating 'Hospital financial database').
We thank the reviewer for pointing out this oversight.
Cost outcomes are defined as costs within the hospital calculated using a Swiss standard called REKOLE (https://rekole.hplus.ch/fr/produkt/rekole-comptabilite-analytique-a-lhopital/).
The manual strictly defines how all the hospital costs must be attributed to the hospital stays based on a minimal set of keys that are linked to the actual resource consumptions.
They include: direct cost items recorded directly at the case level (e.g. medication, material); costs that are calculated based on direct consumption e.g. unit's nursing costs are distributed on hospital stays using minutes of care recorded in the patient's file as key, imagery's costs that are distributed based on each exam's relative consumption points. And at last, indirect costs which are mostly overhead costs are added.
This has been added in the manuscript as follows:
"Cost outcomes are defined as costs within the hospital calculated using a Swiss standard called

REKOLE (https://rekole.hplus.ch/fr/produkt/rekole-comptabilite-analytique-a-lhopital/).
The main costs components of are: nursing care, physician, imaging, laboratory, treatment (including antibiotic therapy) and others per patient during hospitalization, health related quality of life at 3 months; unit of work consumption per hospital (number of minutes of care, physician, laboratory and imaging points) up to 3 months."
For antibiotics. Will use of any type and dose of antibiotic be regarded as treatment days (e.g. also the use of antibiotics typically given for cystitis, skin infections, etc)? Consider describing how you handle patients having had antibiotics prescribed prior to admission.
We planned to collect any type and dose of antibiotics prescribed during the 30 first days as we think that it will be very difficult to specify the indication of antibiotic therapy in this population. However we will collect data about readmission to hospital at 1 and 3 months and for which medical reason (for example a new pneumonia).
Patients who had antibiotics before admission will be included in the study and the name of the antibiotic will be recorded in the CRF.
There is no mention of study dates. When is the study planned to begin? In the ClinicalTrials registration the start date is set to 7th of July 2021. Please report the dates for planned beginning and end of this study.
The inclusions began on June 2021 and should run until August 2023 but it should be extended if necessary (particularly in these times of COVID-19 pandemic which may significantly slow down patient recruitment).
People not familiar with the Swiss health-care system may need a little more information regarding the setting. Please describe how patients are triaged to the emergency room. I.e. do they have free access to the emergency room or will they have to be seen by a general practitioner beforehand and referred on?
There is no gate-keeping in the Swiss healthcare system; any patient presenting to the emergency department is evaluated by a nurse and a doctor. This applies to patients referred by a general practitioner, by an ambulance, by relatives, or on their own initiative.
We may add this point has been detailed in the manuscript, in Patient population:
"Any patients admitted to the ER will be included in the study if eligible according pre-specified criteria. They may be referred by a doctor, an ambulance, a relative, or come on their own initiative."
For overview of the study, please provide a time-event diagram (Gantt diagram) including intervention, outcome assessment etc.
As asked by the reviewer, we have added a new table to better illustrate the interventions and assessments of the study:

Table 4. Timeline of patient enrolment/allocation, interventions, and assessments
Study periods Screening Randomization Discharge from ER Discharge from the acute setting Day 30 Day 90 Reference diagnosis
Visit 1 2 3 4 5
6 7
Time (hour, day) hr0 hr2 hr6 dx d30 d90
Demographics x
Medical history x
In-/exclusion criteria x
Physical examination x
Vital signs x
Laboratory tests x x
CXR, LDCT, LUS x
Main diagnosis before ER discharge x x
Other diagnosis outcomes x x x
No. of antibiotic free days x
Clinical, safety and cost outcomes x x

Readmission and mortality x x
QoL questionnaire x x x
Panel of experts x
CXR: chest x-ray, LDCT: low-dose computed tomography, LUS: lung ultrasonography, ER: emergency room, QoL: quality of life

On page 12 it is stated that the analysis follows the intention to treat principle. On page 14 the 'Handling of missing data and drop-outs' is described and it is stated that Missing data that cannot be avoided will be excluded from the primary analysis (complete case analysis) and signaled as such. To avoid uncertainty about the intention-to-treat approach please specify that all available data from all included patients will be included in the intention-to-treat analysis whereas patients with missing data will be excluded from the complete case analysis.
As proposed by the reviewer, we changed the sentence for:
"All available data from all included patients will be included in the intention-to-treat analysis whereas patients with missing data will be excluded from the complete case analysis".
The discussion is rather limited. Please discuss the limitations regarding reference diagnosis (e.g. perspectives on agreement/disagreement amongst the panel etc). Also, please discuss the choice of outcomes and their limitations.
We added this part to the discussion as follows:
"To our knowledge, no randomized trial has ever compared the performance of CXR, CT scan and US in pneumonia. The OCTOPLUS trial will allow a head to head comparison in a randomized trial of CXR-, LDCT- and LUS-based strategies for the diagnosis of pneumonia.
The results will have an important impact for emergency medicine, general practice, and internal medicine, as the issue of the superiority of LDCT over CXR in diagnosing pneumonia in the elderly will be addressed. Confirmed superiority could profoundly affect recommendations for the diagnosis of pneumonia in elderly patients, and LDCT could become the preferred diagnostic option over CXR. This could also apply to superiority of LUS over CXR, with the added benefit of being more easily available and non-irradiating compared with LDCT. Other strengths of the study will be the blinding of two among the three imaging modalities to the patients and clinicians, and the LUS standardization among ultrasonographists. We will use an adjudication committee for the reference diagnosis using the Delphi method to obtain consensus as recommended in case of absence of gold standard (10.3389/fpubh.2020.00457; 10.1016/j.jclinepi.2009.02.005). The experts will have access to all three imaging modalities obtained for all patients irrespective of randomization arm in order to minimize information bias. However, this might induce an incorporation bias as the tests under evaluation will be known when interpreting the reference standard.
This might be considered as a limitation of the study but such a methodology is recommended in the absence of a gold standard, which is the case in the diagnosis of pneumonia in elderly patients in whom it seems not ethical to perform a broncho-alveolar lavage.
A limitation of the study is that the primary outcome (difference in accuracy) is not a clinical outcome but we have added clinical outcomes in the secondary ones."
If possible, please provide names and versions of all diagnostic equipment used.
We have added this information in the table below. If the reviewer and editor thanks that this information should be added in the manuscript, we could add it as the following appendix.
Table 1bis. Name and version of the equipment in radiology and sonography
Center CXR LDCT US
Geneva Philips Eleva – Philips® CT Somatom Force - Siemens®
CT Somatom Definition Edge - Siemens®
Aquilion Prime CT - Canon® Philips Sparq-Philips®
Bern Philipps DigitalDiagnost, Philips® CT Somatom Siemens® Definition Edge Philips Affinity 70-Philips®
Lugano DigitalDiagnost C90 High Performance
Philips CT Siemens Somatom Definition Edge

CT Somatom Definition Flash GE Logiq e - GE®

Please report what language versions of questionnaires (e.g. EQ5D-3L) that will be used.
EQ5D-3L will be used in local language, meaning French, German and Italian according Swiss cantons recruiting.
The planned sample size is reported as 495 in the manuscript, in the trial registration as 500. Please be consistent.
Thank you for pointing out this error, which has been corrected.

VERSION 2 – REVIEW

REVIEWER	Ticinesi, Andrea Università degli studi di Parma, Department of Medicine and Surgery
REVIEW RETURNED	28-Feb-2022

GENERAL COMMENTS	The authors have provided detailed and convincing responses to all my previous comments. The quality of the manuscript has now improved and I'd be happy to endorse it for publication. I'm sure the OCTOPLUS Study, once completed, will represent a milestone of research on the diagnosis of pneumonia in older people.

REVIEWER	Jensen, Martin Bach Center for General Practice at Aalborg University
REVIEW RETURNED	07-Mar-2022

GENERAL COMMENTS	I think that the authors have adequately addressed the comments made by the reviewers in the revised version of the manuscript. Therefore, I have no further comments.