

Use of Pulmonary Computed Tomography for Evaluating Suspected Stroke-Associated Pneumonia

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Objectives: Accurate and timely diagnosis of pneumonia complicating stroke remains challenging and the diagnostic accuracy of chest X-ray (CXR) in the setting of stroke-associated pneumonia (SAP) is uncertain. The overall objective of this study was to evaluate the use of pulmonary computed tomography (CT) in diagnosis of suspected SAP. *Materials and Methods:* Patients with acute ischemic stroke (IS) or intracerebral hemorrhage (ICH) were recruited within 24h of clinically suspected SAP and underwent non-contrast pulmonary CT within 48h of antibiotic initiation. CXR and pulmonary CT were reported by two radiologists. Pulmonary CT was used as the reference standard for final diagnosis of SAP. Sensitivity, specificity, positive and negative predictive values (PPV and NPV), and diagnostic odds ratio (OR) for CXR were calculated. *Results:* 40 patients (36 IS, 4 ICH) with a median age of 78y (range 44y-90y) and a median National Institute of Health Stroke Scale score of 13 (range 3-31) were included. All patients had at least one CXR and 35/40 patients (88%) underwent pulmonary CT. Changes consistent with pneumonia were present in 15/40 CXRs (38%) and 12/35 pulmonary CTs (34%). 9/35 pulmonary CTs (26%) were reported normal. CXR had a sensitivity of 58.3%, specificity of 73.9%, PPV of 53.8 %, NPV of 77.2 %, diagnostic OR of 3.7 (95% CI 0.7 - 22) and an accuracy of 68.5% (95% CI 50.7% -83.1%). *Discussion:* CXR has limited diagnostic accuracy in SAP. The majority of patients started on antibiotics had no evidence of pneumonia on pulmonary CT with potential implications for antibiotic stewardship. *Conclusions:* Pulmonary CT could be applied as a reference standard for evaluation of clinical and biomarker diagnostic SAP algorithms in multi-center studies.

Key Words: Acute stroke—Ischemic stroke—Pneumonia—Stroke associated pneumonia—Pulmonary computed tomography—Chest X-ray

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Introduction

Pneumonia frequently complicates stroke, occurring in around 14% of hospitalized patients,¹ but may develop in 30% of those at greatest risk (e.g. advancing age, severe stroke, dysphagia).^{2,3} Pneumonia frequently occurs in the first week of stroke and has substantial impact on mortality, length of hospital stay and hospitalization costs.^{4,5} The pathophysiology of post-stroke pneumonia remains incompletely understood although emerging paradigms recognise the complex interplay between infectious challenge (e.g. changes in oral bacterial flora), impaired cough and swallowing facilitating oro-pharyngeal aspiration and transient stroke-induced immune suppression.^{6,7}

Accurate and timely diagnosis of pneumonia remains challenging. The clinical presentation of early pneumonia in patients with stroke may be non-specific, sputum microbiological samples have limited availability and practical value, and altered consciousness might be caused by stroke, as well as pneumonia.^{1,8} Stroke induces an acute phase response and thus fever, leukocytosis, and elevated C-reactive protein (CRP) concentrations frequently occur without infection.⁹ These issues are of major importance in the present era of antibiotic stewardship as once pneumonia is clinically diagnosed, antibiotic treatment is immediately commenced based on available recommendations.¹⁰ Therefore accurate diagnosis is crucial to avoid inappropriate use of antibiotics.^{11,12}

Operational criteria have been developed by the Pneumonia In Stroke ConsEnsuS (PISCES) group for definition and diagnosis of Stroke Associated Pneumonia (SAP)¹³ which encompasses the spectrum of lower respiratory tract infections (LRTIs) within one week of stroke symptom onset. This was based on the Centers for Disease Control and Prevention (CDC) criteria with the main modification being designation of probable or definite SAP dependent on presence or absence of chest X-ray (CXR) changes (Online Only Table I). Pneumonia beyond one week is classified as hospital acquired pneumonia. However, these criteria are yet to be tested in prospective studies and their validity and utility remains uncertain. The diagnostic accuracy of CXR, the 'standard of care' radiological investigation when pneumonia is suspected, is uncertain and may have limited utility in the early stages of SAP. Advanced chest imaging modalities such as pulmonary Computed Tomography (CT) could be of considerable value in evaluating the diagnostic performance of CXR or clinical criteria and inform clinical decision making. While pulmonary CT has previously been used as a reference standard for diagnosis of community and hospital acquired pneumonia^{14–16} it remains underutilized in stroke unit care. The overall aim of this pilot study was to investigate the role of pulmonary CT for evaluating suspected SAP, and to evaluate the diagnostic value of CXR.

Materials and methods

This was a multi-center prospective observational cohort study designed and conducted in accordance with current Standards for Reporting Diagnostic Accuracy (STARD) guidelines.¹⁷ Ethical approval was given by local research ethics committees and informed consent provided by patients prior to recruitment. For patients judged to lack capacity, consent was sought from a personal consultee or professional consultee (when there was no available personal consultee). The data that support the findings of this study are available from the corresponding author upon reasonable request.

Data source

Two tertiary neurosciences centres (Manchester Centre for Clinical Neurosciences and Royal Stoke University Hospital) were involved in recruitment between April 2017 and May 2018. Patients with acute ischemic stroke (IS) or intracerebral hemorrhage (ICH) (diagnosed by the clinical stroke teams with brain imaging confirmation), aged ≥ 18 y, within 24h of clinically suspected pneumonia (first episode since admission only) and able to undergo pulmonary CT within 48h following diagnosis of pneumonia were eligible. Patients requiring mechanical ventilation, end of life care or those treated with antibiotics for a lower respiratory tract infection (LRTI) in the preceding month at the time of recruitment were excluded.

Data collection

Participating patient demographics, pre-morbid modified Rankin Scale (mRS) score, stroke subtype (IS or ICH), time interval from admission, National Institutes of Health Stroke Scale (NIHSS) score, swallow status, feeding status, concurrent medical history and co-morbidities were recorded. In addition, clinical variables such as maximal temperature ($^{\circ}$ C), maximal respiratory rate (RR), maximal heart rate (HR), chest signs on auscultation, new confusion, lowest oxygen saturations, initiation of oxygen therapy or increased oxygen requirements, sputum expectorated or suction required, positive sputum or blood culture result were recorded at baseline (in the last 24h) and at 48h following recruitment. The most recent clinical white blood cell (WBC) counts and differential, CRP and CXR findings were also collected.

Clinical suspicion and diagnosis of pneumonia

Neither of the participating sites routinely use standardised algorithms or societal criteria for diagnosis of SAP or to guide antibiotic initiation. Any documented diagnosis of clinically suspected or diagnosed first episode of SAP made by the treating clinical teams was considered for inclusion in the study.

Chest imaging acquisition and review

All participating patients had a baseline CXR at the time of recruitment or within 24h of clinical suspicion of pneumonia. If the baseline clinical CXR (Antero-Posterior; AP or Postero-Anterior; PA, depending on clinical status of the patient) at study entry did not definitively support a diagnosis of pneumonia according to interpretation by the clinical team, then the CXR was repeated 48h later. Pulmonary CT was undertaken as soon as possible and within 48h after consent following the clinical suspicion and/or diagnosis of pneumonia. Pulmonary CT was performed in inspiratory breath-hold, where possible, as volumetric thin-section acquisitions without intravenous contrast, unless there was a clinical indication, with the following acquisition parameters: 120 kV, mAs for slim (<50Kg), medium (50-90Kg) and large (>90 Kg) patients, to achieve dose constraints of 4.5mGy, 6.0mGy and 7.5 mGy respectively were performed. Reconstruction parameters were 1mm width, 1mm increment, medium soft tissue kernel, lung window settings. CXRs were interpreted in the first instance by the treating clinical teams. Both CXR and pulmonary CT were also reported by local radiologists with the accompanying clinical information. All CXRs were also anonymised and reviewed independently by four stroke physicians. In addition, all anonymized CXRs and pulmonary CT studies were also transferred electronically to a secure imaging archive platform at Royal Brompton Hospital for independent thoracic radiology review by an experienced, independent thoracic radiologist (AD) blinded to the clinical information. CXRs were categorised as possible SAP by the independent thoracic radiologist based on the presence or absence of findings compatible with pneumonia (specifically consolidation or air space shadowing). Pulmonary CTs were reviewed and categorized as normal, abnormal (pneumonia) and abnormal (other diagnosis). Pulmonary CT diagnosis of pneumonia by the independent thoracic radiologist was based on the presence of tree-in-bud nodules, ground glass opacity and consolidation as well as extent based on the number of pulmonary segments involved and classified as bronchiolitis, segmental pneumonia and lobar pneumonia (Online Only Table II).¹⁸ Pulmonary CTs with minimal abnormalities such as minor tree in bud nodularity or ground glass opacity in less than approximately one third or one pulmonary segment were categorised as normal.

Statistical analysis

The primary outcome measure was pulmonary CT confirmed pneumonia as reported blinded to clinical status by the independent thoracic radiologist. The main secondary outcome measure was pneumonia meeting the PISCES clinical criteria (Online Only Table 1) AND with changes of pneumonia on pulmonary CT, agreed by an adjudication panel (CJS, AK, AD). Baseline characteristics and the main

Table 1. Participating patient characteristics (n=40).

Male, n (%)	25 (61)
Median age (Range), y	78 (44-90)
Right Hemisphere, n (%)	19 (48)
Median NIHSS (Range)	13 (3-31)
ICH, n (%)	4 (10)
Thrombolysis, n (%)	10 (28)
Pre-morbid mRS, n (%)	
0-1	29 (72)
≥2	11 (28)
Nil Orally, n (%)	19 (48)
Nasogastric tube feeding, n (%)	7 (17.5)
Modified Diet/fluids, n (%)	9 (22)
Stroke onset to antibiotic initiation, hrs (range)	45 (5-111)
Co-morbidities, n (%)	
Hypertension	20 (51)
Diabetes Mellitus	15 (36.5)
Dyslipidemia	11 (27)
Atrial fibrillation	16 (41)
Ischemic Heart Disease	4 (10)
Previous Stroke/TIA	15 (39)
Heart Failure	6 (15)
Chronic Lung Disease	17 (42)
Malignancy	6 (15)
Smoking History	8 (20)

ICH=Intracerebral hemorrhage; NIHSS=National Institute of Health stroke scale; mRS=modified Rankin Scale; TIA=Transient ischemic attack

outcome measures were described using appropriate summary statistics. Inter-rater reliability of the clinician interpretation of CXRs was evaluated using Kappa statistics, independently by four stroke physicians (NJ, DS, KW and PT) blinded to clinical information using independent thoracic radiologist reporting as standard. Inter-rater reliability of reported CXRs and pulmonary CTs between the local radiologists with that of the independent thoracic radiologist (AD) was also assessed using Kappa statistics. Pulmonary CT reporting was also analyzed descriptively. The primary analyses incorporated standard assessments of diagnostic accuracy, including sensitivity, specificity, positive and negative predictive value (PPV and NPV), and diagnostic odds ratio (OR) for CXR singly and with repeat CXR when undertaken with independent radiologist reporting pulmonary CT as reference standard. In secondary analyses, logistic regression analysis was used to investigate the associations between discrete categorical variables (temperature, RR, HR, WBC, and CRP) and independent radiologist reporting pulmonary CT diagnosis of pneumonia, to obtain an OR and 95% confidence interval (CI). Stats Direct software for Windows (version X) was used for statistical analysis. For all analyses, statistical significance was set at 0.05. We estimated that a sample size of up to 50 participants would enable assessment of feasibility and reliability whilst providing meaningful preliminary data for hypothesis generation in the secondary analyses.

Results

Study population

40 patients were considered eligible and included in the study (Fig. 1). Demographic and stroke characteristics are detailed in Table 1. The median age was 78y (range 44y-90y) and the median NIHSS was 13 (range 3-31). The median duration from stroke symptom onset to clinical suspicion of pneumonia and/or initiation of antibiotics was 2d (range 1d-8d). Monotherapy with β -lactam antibiotics (20%) or in combination with β -lactamase inhibitors (30%) or macrolides (20%) were most commonly used, and given for up to seven days after clinical diagnosis of SAP. Other antibiotics used included tetracyclines as monotherapy (10%) or in combination with β -lactam antibiotics (7.5%), fluoroquinolones (7.5%), and nitroimidazole in combination with β -lactamase inhibitors (2.5%) or macrolides (2.5%).

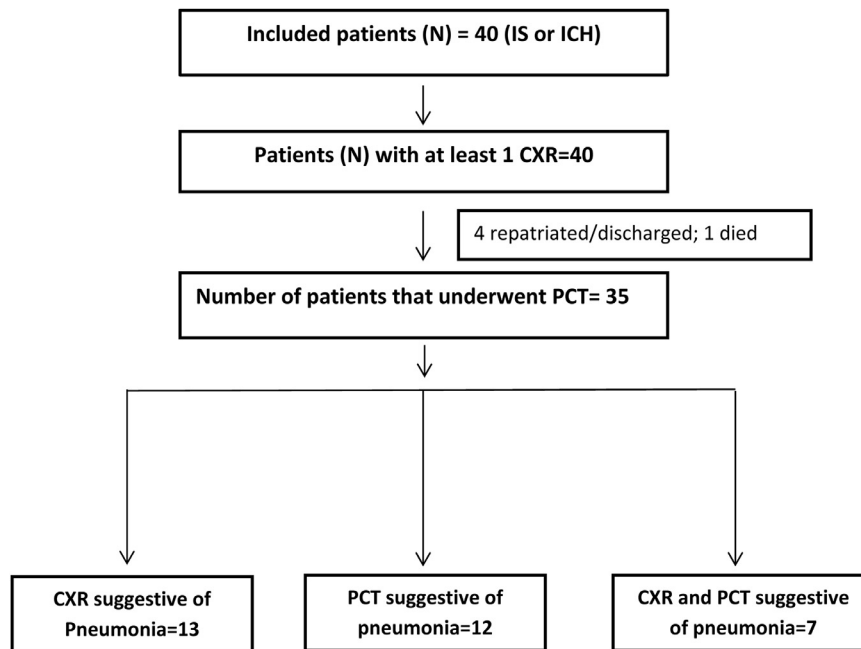
Clinical and radiological interpretation of CXR

First CXR was reported as suggestive of pneumonia in 15/40 patients (38%) by the local radiologists, of which only 4/15 (27%) had pneumonia on the CXR interpreted by the clinical teams. 17 patients (43%) with a normal CXR underwent a second CXR within 48h of recruitment; 2/17 (12%) of these further CXRs were reported as suggestive of pneumonia by the local radiologist. Overall, 13 CXRs (32.5%; 11 first CXR, 2 second CXR) were reported

as suggestive of pneumonia by the independent thoracic radiologist. The inter-rater reliability of reported CXR interpretation of pneumonia between the local radiologists and independent thoracic radiologist was moderate ($\kappa=0.42$; 95% CI 0 to 0.84). The inter-rater reliability for CXR diagnosis of pneumonia between the 4 stroke physicians (independent thoracic radiologist as standard) was weak ($\kappa=0.35$, 95% CI 0.13-0.36).

CXR and pulmonary CT concordance

35/40 patients (88%) underwent pulmonary CT within 48h of suspicion of pneumonia. Of the remaining 5, one patient died and four were repatriated to their local hospitals for ongoing stroke care prior to pulmonary CT. Examples of representative CXRs and pulmonary CTs are shown in Fig. 2. Pulmonary CT confirmed pneumonia in only 12/35 patients (34%). Where pulmonary CT confirmed SAP, it revealed segmental or sub-lobar pneumonia in 6/12 (50%), lobar pneumonia in 3/12 (25%) and bronchiolitis in 3/12 (25%) of cases. Only 5/12 (42%) of patients with pulmonary CT confirmed pneumonia had features suggestive of pneumonia on the first CXR report, and a further two when a second CXR was undertaken (Table 2). Compared to the pulmonary CT reported by the independent thoracic radiologist as the reference standard for diagnosis of SAP, CXR had a sensitivity of 58.3% (95% CI 27.6%-84.8%), a specificity of 73.9% (95% CI 0.51-0.89), a PPV of 53.8% (95% CI 33.5%-72.9%), a NPV of 77.2%



IS=ischemic stroke; ICH=Intracerebral hemorrhage; CXR= Chest X-ray, PCT=Pulmonary CT

Fig. 1. Study flowsheet.



Fig. 2. Representative CXR and pulmonary CT appearances for patients with suspected pneumonia. (2a): Patient 1 with AP semi-erect CXR reported as normal allowing for rotation. NG tube is coiled projected over the oesophagus; (2b): Patient 1 with pulmonary CT showing left lung ground glass opacities suggestive of pneumonia. There are also small bilateral pleural effusions; (2c): Patient 2 with CXR reported as showing right mid-zone consolidation suggestive of pneumonia; (2d): Patient 2 with pulmonary CT shows that opacity on CXR corresponds with chronic appearing middle lobe atelectasis, with no evidence of pneumonia.

(95% CI 62.5 %-87.3%), a diagnostic OR of 3.7 (95% CI 0.7 - 22.3) and an accuracy of 68.5% (95% CI 50.7% -83.1%).

Pulmonary CT was normal in 9/35 (26%) participants, while other abnormalities were demonstrated in 14/35 (40%) participants; most commonly as unilateral or bilateral pleural effusions (23%), followed by interstitial lung disease (9%), radiotherapy fibrosis (4%), and bronchiectasis (4%). Co-existent effusion was found in just over a third of patients with pneumonia. A comparison of the pulmonary CT reports between the independent thoracic radiologist and local radiologists is detailed in Online table III. The inter-rater reliability for pulmonary CT reporting between the independent thoracic radiologist and study radiologists was moderate ($\kappa = 0.53$; 95% CI 0.22-0.82).

Association between clinical or laboratory variables and pulmonary CT confirmed pneumonia

At the time of initiating antibiotics 5/40 patients (13%) had a productive cough and/or purulent sputum that needed suctioning, 4/40 patients (10%) needed oxygen support, 10/40 patients (25%) had altered awareness or confusion and 29/40 patients (78%) had rales or crackles unilaterally or bilaterally on examination. When the PISCES clinical criteria (Online only Table I) were applied retrospectively using CXR findings reported by the independent thoracic radiologist (AD), there were only 3 probable SAPs and 1 definite SAP (Table 3). The maximum (range) HR, temperature, RR, WBC count, and CRP concentrations recorded at time of recruitment are shown in Online only Table IV. None of the clinical or laboratory variables was associated with SAP using pulmonary CT as the reference standard (Online only Table IV).

Discussion

We found that CXR had limited diagnostic value in clinically suspected SAP when using pulmonary CT as a diagnostic reference standard. We also found that the majority of patients with clinically suspected SAP did not have corresponding changes on pulmonary CT consistent with pneumonia, and that pulmonary CT confirmed pneumonia in only around 1 in 3 patients with suspected SAP. Further, inter-rater reliability of CXR interpretation between stroke physicians as well as reporting radiologists was weak to moderate at best. The low sensitivity and specificity of CXR in the present study is in keeping with previous diagnostic accuracy studies of community acquired pneumonia (CAP).¹⁴ The poor inter-rater reliability in CXR interpretation among clinicians and radiologists is also not surprising and is also recognized in CAP.^{14,20,21}

A contributing factor to the poor diagnostic performance of CXRs in SAP, is the challenge associated with obtaining optimally acquired CXRs in this group of patients. Limited patient mobility may result in rotated

Table 2. CXR & Pulmonary CT concordance.

	PCT Positive	PCT negative	
CXR Positive	7 (TP)	6 (FP)	PPV: 7/13=53.8%
CXR Negative	5 (FN)	17 (TN)	NPV: 17/22=77.2 %
	Sensitivity: 7/12=58.3%	Specificity: 17/23=73.9%	

CT=Computed Tomography; TP= True positive; FP=False positive; PPV=Positive predictive value; NPV=Negative predictive value; CXR=Chest X-ray.

Table 3. Pulmonary CT& PISCES criteria concordance.

	PISCES Criteria		
	No Pneumonia	Probable Pneumonia	Definite Pneumonia (CXR positive)
Pulmonary CT positive	10	1	1
Pulmonary CT negative	21	2	0

CT= Computed Tomography; PISCES=Pneumonia In Stroke ConsEnsuS Criteria; CXR=Chest X-Ray.

CXRs acquired semi-erect as in Fig. 2b, which may impede image interpretation. Unlike chest radiography, pulmonary CT provides cross-sectional images and differences in tissue attenuation and parenchymal changes caused by an acute inflammatory process can be readily seen making it a valuable tool in diagnosing pneumonia. It is not widely used in clinical settings to evaluate for pneumonia due to greater cost, increased time required to obtain images, and higher radiation exposure.^{19,22} However, even on pulmonary CT, pneumonia can often be difficult to differentiate from atelectasis, pulmonary edema, lung cancer, or lung infarct,²³ which may be one of the reasons why only a moderate inter-rater reliability of pulmonary CT reporting was seen in this study. We found alternative pathologies to pneumonia on pulmonary CT (such as pleural effusions, bronchiectasis and fibrosis) which may have explained the clinical and radiological suspicion of pneumonia in some of the patients.

Pulmonary CT was reported as normal in around 1 in 4 patients with clinically diagnosed SAP. A similar frequency of normal pulmonary CTs has also been reported in a study evaluating viral and bacterial LRTIs where viral LRTI's were more likely to have normal pulmonary CTs.²⁴ It is plausible that a viral etiology contributed to some of the clinically diagnosed pneumonia in our study. Another consideration is the timing of pulmonary CT relative to symptom onset (within 48h in this study) and evolution of changes on CT. Evaluation using serial pulmonary CTs e.g. at day 2 and day 7 might improve yield of confirmed SAP, although there are resource implications as well as additional risks of radiation exposure to consider. A further issue is the need to improve reliability of pulmonary CT reporting and agreement on standardized reporting methodology of pneumonia, suggested by the moderate

inter-rater reliability agreement in pulmonary CT reporting in our study.

Once SAP is diagnosed, immediate treatment with antibiotics is recommended.¹² However, inappropriate administration of antibiotics has serious implications for antimicrobial stewardship and evolving antibiotic resistance, adds to healthcare costs and may cause harm. Administering antibiotics in acute stroke in the absence of proven infection is of no benefit in prophylactic antibiotic studies to date.^{25,26} Two recent studies using pulmonary CT in other clinical settings suggested a re-classification of diagnosis of hospitalized pneumonia in 8%-18%.²⁷ Our data suggest that clinician diagnosis of pneumonia in stroke patients may over-diagnose pulmonary CT confirmed pneumonia, in line with previous prospective studies comparing clinician diagnosis with standardized, adjudicated diagnostic criteria for SAP.^{25,28} When we retrospectively applied the PISCES diagnostic criteria to those with a pulmonary CT diagnosis of pneumonia, only three patients met clinical criteria for SAP. Pulmonary CT could have possibly resulted in reclassification of diagnosis in over two-thirds of patients with clinically suspected SAP highlighting its potential use in antibiotic stewardship. In addition, there is also a potential role for pulmonary CT in validating risk scores for SAP as suggested in a previous study involving 45 patients at high risk of pneumonia.²⁹ Further, using pulmonary CT may improve the utility of blood inflammatory or stress biomarkers (e.g. CRP and procalcitonin) in diagnosing and managing SAP. Composite algorithms using clinical criteria and/or biomarkers in addition to pulmonary CT findings could also be evaluated in future studies.

Our study has several limitations. Although undertaken at two sites and prospectively conducted, the

sample size was relatively small, limiting interpretation and generalization of results. Moreover, recruitment was non-continuous which may have caused selection bias. We were also unable to recruit the projected target of 50 patients due to funding limitations, but this is unlikely to have materially affected our findings. It was unclear from the available data what factors prompted the clinical suspicion of pneumonia by the treating clinicians. Also unclear are the clinical implications of pulmonary CT diagnosed pneumonia as opposed to a clinically diagnosed pneumonia. As patients were not followed up once discharged or repatriated to their local stroke units, longer term outcomes including recurrence of pneumonia or influence of antibiotic treatment were not known. Statistical analysis in this study was based on CXR and pulmonary CT reporting performed at a later stage by an independent thoracic radiologist. Implications of having these investigations reported in real time were not assessed. In our opinion, there are likely to be significant regional variations in reporting times for CXR and pulmonary CTs in clinical practice that could have implications in clinical diagnosis of pneumonia. Further, standardized reporting of pulmonary CT was used only by the independent thoracic radiologist limiting the interpretation of Kappa statistic on pulmonary CT reporting. Moreover, pneumonia cannot be definitely excluded even on pulmonary CT particularly in the setting of tracheobronchial infection. It may also lead to numerous incidental findings, whose potential downstream impacts are not well appreciated.³⁰

In conclusion, CXR has limited diagnostic value in suspected SAP and the PISCES diagnostic criteria need to be urgently assessed in larger studies. Pulmonary CT can be considered as a reference standard while evaluating SAP. However, assessment of the timing, utility and cost-effectiveness of pulmonary CT in the diagnosis and management of SAP, including the impact on antibiotic clinical decision-making and longer-term clinical outcomes is also required. Further, improvement in reliability of pulmonary CT reporting for pneumonia using standardized criteria is needed prior to larger, multi-center studies.

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Supplementary materials

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