

Elevated C-reactive protein increases diagnostic accuracy of algorithm-defined stroke-associated pneumonia in afebrile patients

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Abstract

Background and aim: Pyrexia-dependent clinical algorithms may under or overdiagnose stroke-associated pneumonia. This study investigates whether inclusion of elevated C-reactive protein as a criterion improves diagnosis.

Methods: The contribution of C-reactive protein ≥ 30 mg/l as an additional criterion to a Centers for Disease Control and Prevention-based algorithm incorporating pyrexia with chest signs and leukocytosis and/or chest infiltrates to diagnose stroke-associated pneumonia was assessed in 1088 acute stroke patients from 37 UK stroke units. The sensitivity, specificity, and positive predictive value of different approaches were assessed using adjudicated stroke-associated pneumonia as the reference standard.

Results: Adding elevated C-reactive protein to all algorithm criteria did not increase diagnostic accuracy compared with the algorithm alone against adjudicated stroke-associated pneumonia (sensitivity 0.74 (95% CI 0.65–0.81) versus 0.72 (95% CI 0.64–0.80), specificity 0.97 (95% CI 0.96–0.98) for both; kappa 0.70 (95% CI 0.63–0.77) for both). In afebrile patients ($n = 965$), elevated C-reactive protein with chest and laboratory findings had sensitivity of 0.84 (95% CI 0.67–0.93), specificity of 0.99 (95% CI 0.98–1.00), and kappa 0.80 (95% CI 0.70–0.90). The modified algorithm of pyrexia or elevated C-reactive protein and chest signs with infiltrates or leukocytosis had sensitivity of 0.94 (95% CI 0.87–0.97), specificity of 0.96 (95% CI 0.94–0.97), and kappa of 0.88 (95% CI 0.84–0.93) against adjudicated stroke-associated pneumonia.

Conclusions: An algorithm consisting of pyrexia or C-reactive protein ≥ 30 mg/l, positive chest signs, leukocytosis, and/or chest infiltrates has high accuracy and can be used to standardize stroke-associated pneumonia diagnosis in clinical or research settings.

Trial Registration: <http://www.isrctn.com/ISRCTN37118456>

Keywords

Acute stroke, poststroke pneumonia, diagnostic accuracy, C-reactive protein

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Introduction

Stroke-associated pneumonia (SAP) has a significant effect on stroke outcome, being independently associated with nearly one-third of all deaths and increasing the likelihood of dependence at discharge.^{1,2} Many studies have shown the difficulties in diagnosing SAP because of the heterogeneity in the criteria used and lack of prospective studies validating diagnostic criteria.³ To confound matters, SAP is often used as a convenient diagnosis in severely ill or terminal stroke patients, many of whom do not fulfill the criteria for diagnosis.⁴ The consequences of the lack of a consistent approach for diagnosing SAP include inappropriate use of antibiotics in practice and inconclusive research findings.³ In order to reduce the variations in the diagnosis of SAP, the international multidisciplinary Pneumonia In Stroke ConsEnsuS Group proposed consistent use of algorithmic criteria, because of their objectivity and applicability to both clinical and research settings.⁵

A recent study of the diagnostic utility of a modified version of the Centers for Disease Control and Prevention (CDC) criteria for hospital-acquired pneumonia⁶ showed that although algorithmic approaches were very good at excluding patients who do not have SAP (high specificity), they were limited in predicting those with SAP (low sensitivity).⁷ This is because pyrexia is a component of the modified CDC algorithm criteria,⁶ and it is well known that many elderly stroke patients do not develop fever despite having pneumonia.⁸ In the study, 25% of patients adjudicated to have SAP were missed by the algorithm despite many having new chest signs, infiltrates on radiography, and/or leukocytosis because they were afebrile.⁷ Furthermore, the thresholds for fever used in diagnostic algorithms are arbitrary and have not been validated.⁵

C-reactive protein (CRP) is a widely used acute-phase biomarker in clinical practice, and elevated levels have been shown to be predictive of infections in stroke patients.^{9,10} A study in older people showed that elevated CRP values were highly sensitive for the diagnosis of a bacterial infection, even in the absence of pyrexia.¹¹ However, mild elevations of CRP are common in acute stroke patients, even in the absence of infections, because of inflammation associated with infarction or hemorrhage.¹² Indeed, the precise role of CRP in the diagnostic approach to SAP is uncertain based on a recent systematic review and consensus statement,⁵ and analysis of the Intravascular Cooling Treatment in Acute Stroke-2 Trial.¹³ A more recent study using receiver operating characteristics analysis showed that CRP concentration >25.60 mg/l was the optimal diagnostic threshold for the diagnosis of SAP, with high sensitivity (0.85) but low specificity (0.67).⁸

As the pyrexia-based CDC algorithm has high specificity but low sensitivity⁷ and the CRP threshold has high sensitivity but low specificity for diagnosis of SAP,⁸ we hypothesized that combining a CRP threshold criterion with the pyrexia-based algorithm would have high specificity and high sensitivity for SAP diagnosis. The objective of this study was therefore to determine if incorporating CRP ≥ 30 mg/l as an additional criterion to the existing CDC-based algorithm^{7,14} would improve accuracy of SAP diagnosis using adjudicated SAP as the reference standard.

Methods

The STROKE-INF study was a prospective, multicenter, cluster randomized, open-label controlled trial with blinded end-point assessment, undertaken in 1217 stroke patients with dysphagia (nil by mouth) recruited from 37 UK stroke units.¹⁴ Patients were eligible for inclusion if they were aged over 18 years, had a confirmed diagnosis of new stroke, onset of symptoms ≤ 48 h at recruitment, and were considered unsafe to swallow because of impaired consciousness or failed bedside swallowing assessment.¹⁵ Patients with preexisting dysphagia, pyrexia or known infection at admission, antibiotics within last seven days, or expected survival <14 days were excluded. The primary outcome was SAP in the first 14 days, assessed using a CDC criteria-based hierarchical algorithm masked to allocation. Written informed consent/assent was provided by patients or the next of kin. The study (ISRCTN 37118456) was approved by the National Research Ethics Committee (08/H0803/1).

Patient characteristics were recorded on enrolment. Data on respiratory rate, temperature, chest symptoms and signs, white cell counts, and CRP were collected prospectively at baseline, two, four, seven, 10, and 14 days. Local guidelines for radiological and microbiological investigations were followed for suspected SAP. The algorithmic SAP diagnosis was based on CDC criteria for pneumonia⁶ and performed at the end of trial by the study statistician (JH) who was masked to physician diagnosis, treatment details, or outcomes and independent of treating physicians at trial centers or the central trial team. Eight clinical/laboratory observations at six time points were interrogated using Stata software (StataCorp. 2009. Stata Statistical Software: Release 11. College Station, TX) as yes/no responses for:

1. Temperature $\geq 37.5^{\circ}\text{C}$ on two consecutive measurements or a single measurement of $\geq 38.0^{\circ}\text{C}$ (C1) AND
2. Respiratory rate $\geq 20/\text{min}$ OR cough and breathlessness OR purulent sputum (C2) AND

3. White cell count $>11.0 \times 10^9/l$ OR new chest infiltrates on X-ray OR positive sputum culture/microbiology OR positive blood culture (C3).

A diagnosis of SAP or no SAP on the algorithm could not be established in 129 (10%) patients because of missing data (Figure 1). Analyses of diagnostic accuracy were undertaken in 1088 patients; there were no differences in the baseline characteristics or outcomes between the 1217 patients in the STROKE-INF trial and the 1088 patients in the analysis, which could result in selection bias (Table 1).

Components of the algorithmic criteria, clinical findings, and all laboratory investigations for the whole episode of hospitalization of patients (including detailed chest radiology reports and free-text clinical narrative) were reviewed by two independent expert adjudicators (a chest physician and a general physician not involved with the study). The adjudicators worked separately for reassignment as SAP or no SAP, and were unaware of diagnoses made by treating physicians in trial centers or of algorithm diagnosis made by the statistician. In the event of disagreement, clinical data were reviewed jointly by the two experts and consensus

Figure 1. STARD diagram of participant flow for the criteria pyrexia or \uparrow CRP + chest signs + leukocytosis or chest infiltrates.

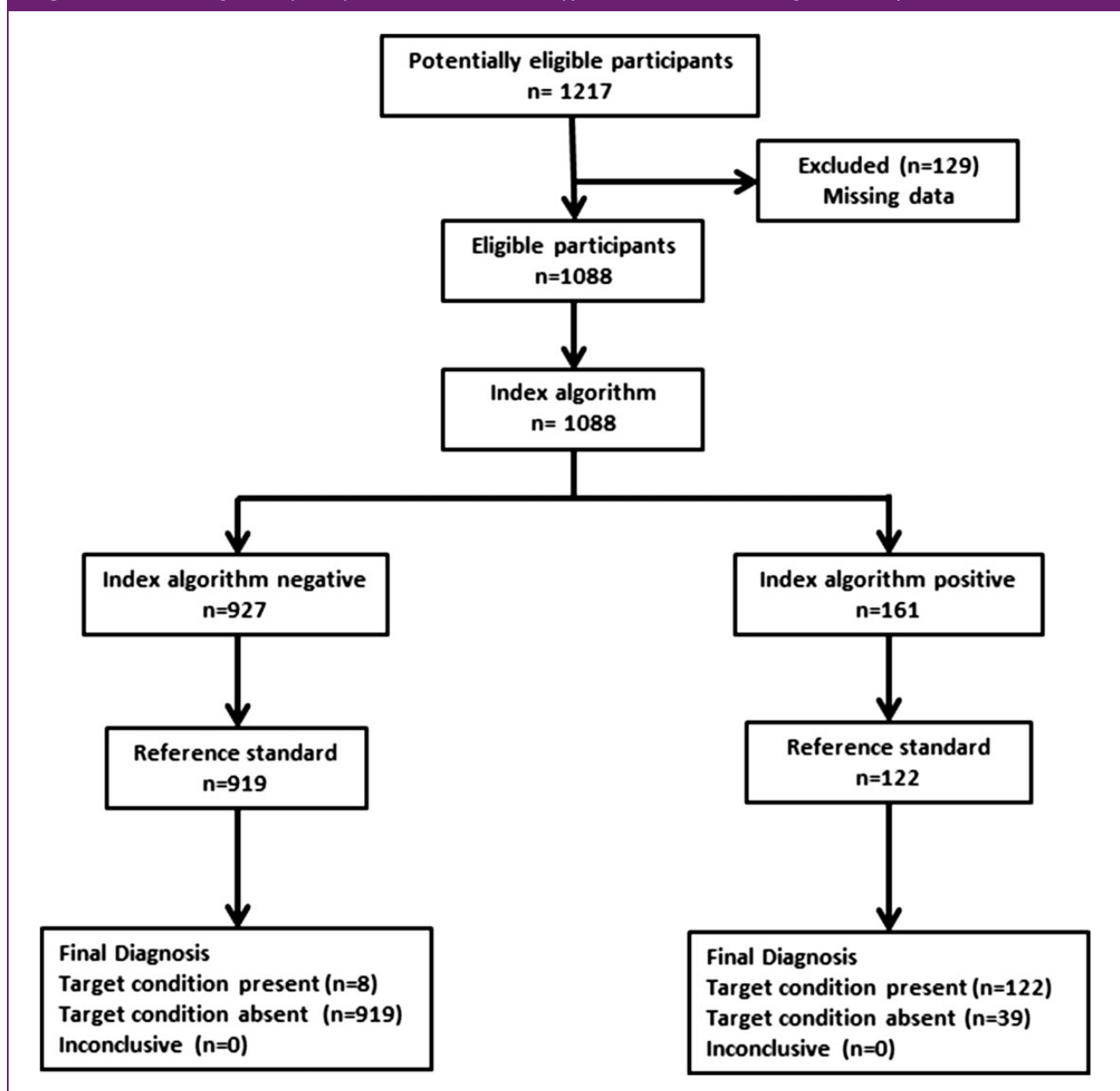


Table 1. Baseline patient demographics

	All patients in the STROKE-INF Trial	Patients with algorithm SAP diagnosis	Afebrile patients
No. of patients	1217	1088 (89.4%)	965 (79.3%)
Age: mean (SD)	77.9 (12.1)	77.10 (12.25)	77.13 (12.44)
(missing)	1	0	0
Male: n(%)	523 (43.0%)	466 (42.8%)	398 (41.2%)
(missing)	4	4	3
Stroke type: n(%)			
Ischemic	1091 (89.7%)	973 (89.5%)	874 (90.1%)
Hemorrhagic	125 (10.2%)	114 (10.5%)	91 (9.9%)
(missing)	1	1	0
Thrombolysis: n(%)	397 (32.7%)	347 (31.9%)	304 (31.5%)
(missing)	3	0	0
NIHSS: median (IQR)	15 (9–20)	15 (9–20)	15 (8–20)
(missing)	4	4	0
Comorbidities: n(%)			
Hypertension	837 (68.9%)	751 (69.1%)	660 (68.4%)
Diabetes	202 (16.6%)	179 (16.5%)	158 (16.4%)
Atrial fibrillation	448 (36.9%)	393 (36.1%)	339 (35.1%)
Previous strokes	352 (29.0%)	316 (29.0%)	282 (29.2%)
(missing)	1	0	0
Premorbid mRS (0–2): n(%)	988 (81.3%)	939 (86.3%)	799 (82.8%)
(missing)	18 (1.5%)	9 (0.8%)	6 (0.6%)
Mortality at 90 days: n(%)	342 (28.1%)	231 (21.2%)	256 (26.5%)
(missing)	36 (3.0%)	0	0
mRS 0–2 at 90 days: n(%)	230 (18.9%)	274 (25.9%)	201 (20.8%)
(missing)	36 (3.0%)	29 (2.7%)	28 (2.9%)

IQR: interquartile range; mRS: modified Rankin scale; NIHSS: National Institutes of Health Stroke Scale; SAP: stroke-associated pneumonia.

reached on assignment. Adjudicated SAP was used as the reference standard for diagnosis of SAP using the post hoc algorithm approaches applied blindly to trial data.

All analyses were prespecified and undertaken by researchers masked to the findings of the original STROKE-INF study. In the first analysis, performance of the algorithm (C1+C2+C3) to diagnose SAP was

compared with approaches that used: (1) the algorithm (C1+C2+C3) AND elevated CRP ≥ 30 mg/l at any of the six time points (to reduce false-positive rate of the algorithm), and (2) the algorithm (C1+C2+C3) OR C2+C3 with elevated CRP ≥ 30 mg/l at any of the six time points (to reduce false-negative rate) as additional criteria for diagnosis. In the second analysis, the CDC criterion of temperature (C1) was excluded as a criteria

and substituted by elevated CRP at any one of the six measurement time points, and SAP diagnosed if this and C2+C3 criteria were met for the whole patient group and for the subset of afebrile patients ($n=965$). Diagnostic accuracy was assessed by calculating the sensitivity, specificity, positive predictive value, negative predictive value, false-positive and false-negative rates and compared using McNemar's test. Agreement of these approaches using CRP to diagnose SAP with adjudicated SAP was assessed using Cohen's kappa statistic.

Results

The baseline characteristics of the patients included in this study are given in Table 1.

The age, sex, vascular risk factors, premorbid function, or stroke severity characteristics of afebrile patients ($n=965$) were comparable to the whole patient group in whom algorithm diagnosis of SAP was possible (1088) and not different from all patients participating in the STROKE-INF study.

Adjudicated SAP was present in 129/1088 (11.8%) patients. Of these, 97 (75%) had pyrexia (C1), 48 (37%)

had new infiltrates on a chest radiograph (C3), and 39 (30%) had productive cough (C2). SAP was diagnosed by the algorithm in 123 (11.3%) patients. The algorithm had high specificity (0.97), low sensitivity (0.72), and moderate agreement (kappa 0.70) against adjudicated SAP (Table 2). The algorithm missed SAP in 37 patients because the fever criterion was not met (false negative). On the other hand, 30 patients without focal chest findings met algorithm criteria for SAP (false positive) because of fever, leukocytosis, and tachypnea.

The inclusion of elevated CRP as an additional criterion to the full algorithm did not increase its overall diagnostic accuracy or agreement with adjudicated SAP (Table 2). However, if the requirements for SAP diagnosis included patients who fulfilled algorithmic criteria or had elevated CRP with definitive chest findings regardless of pyrexia, diagnostic accuracy improved significantly to reach sensitivity of 0.94, specificity of 0.96, and agreement with adjudicated SAP of nearly 0.90 (Table 2).

It was possible that both pyrexia and CRP, being components of the acute phase response were

Table 2. Accuracy of algorithm AND/OR elevated CRP in the diagnosis of stroke-associated pneumonia (SAP) using adjudicated SAP as the reference standard in 1088 stroke patients

	Algorithm (C1+C2+C3)		Algorithm (C1+C2+C3) AND CRP		Algorithm (C1+C2+C3) OR CRP+C2+C3	
		95% confidence interval		95% confidence interval		95% confidence interval
SAP prevalence	11.9%	10.0–13.9%	11.6%	10.0–14.0%	11.9%	10.1–14.1%
Sensitivity	0.72	0.64–0.80	0.74	0.65–0.81	0.94	0.88–0.97
Specificity	0.97	0.96–0.98	0.97	0.95–0.98	0.96	0.94–0.97
False-positive rate	24.4%		25.8%		14.8%	
False-negative rate	3.7%		3.5%		0.9%	
Positive predictive value	0.76	0.67–0.83	0.75	0.66–0.81	0.75	0.68–0.82
Negative predictive value	0.96	0.95–0.98	0.96	0.95–0.98	0.99	0.98–1.00
Positive likelihood ratio	23.05	15.95–33.30	21.4	15.07–30.39	23.05	16.9–31.44
Negative likelihood ratio	0.29	0.22–0.38	0.27	0.20–0.36	0.06	0.03–0.12
Agreement						
Algorithm (C1+C2+C3) versus adjudicated SAP: kappa 0.70 (95% CI 0.63–0.78)						
Algorithm (C1+C2+C3) AND CRP versus adjudicated SAP: kappa 0.70 (95% CI 0.63–0.77)						
Algorithm (C2+C3) OR CRP + C2+C3 versus adjudicated SAP: kappa 0.88 (95% CI 0.84–0.93)						

CRP: C-reactive protein.

measuring the same phenomenon related to infection, and elevated CRP may be a better biomarker of infection compared with temperature. In the second analysis, the temperature criterion of the CDC-based algorithm was substituted by $\text{CRP} \geq 30 \text{ mg/l}$ in the presence of other chest and laboratory criteria, and applied to the whole dataset and the subset of afebrile patients. The second analysis showed that this improved the diagnostic accuracy of the algorithm with sensitivity of 0.80, specificity of 0.98, positive predictive value of 0.78, and agreement with adjudicated SAP of 0.80, especially in afebrile patients (Supplementary Table). Elevated CRP also appeared to be associated with higher mortality in afebrile patients with adjudicated SAP. CRP levels were elevated in 30/36 (83.3%) apyrexial SAP patients, 19 (63.3%) of whom died.

Discussion

Our study shows that adding CRP to the full algorithm in all patients did not increase diagnostic performance. However, $\text{CRP} \geq 30 \text{ mg/l}$, in the presence of chest findings and leukocytosis or new radiological chest infiltrates, is highly suggestive of SAP in afebrile stroke patients and has very good agreement (kappa 0.80) with adjudicated diagnosis of SAP. The greatest diagnostic accuracy (sensitivity 0.94, specificity 0.96, kappa 0.88), for the whole patient cohort (regardless of pyrexia) was achieved using the criteria:

1. Temperature $\geq 37.5^\circ\text{C}$ on two consecutive measurements or a single measurement of $\geq 38.0^\circ\text{C}$, OR, a single measurement $\text{CRP} \geq 30 \text{ mg/l}$, AND
2. Respiratory rate $\geq 20/\text{min}$, OR, cough and breathlessness, OR, purulent sputum, AND
3. White cell count $> 11.0 \times 10^9/\text{l}$, OR, new chest infiltrates on X-ray, OR, positive sputum culture/microbiology OR positive blood culture.

Pyrexia, a hallmark of infection, may be absent in 25–66% of patients with SAP.^{7,8} Diagnosis may be facilitated by referring to blood biomarkers of inflammation, of which CRP is one of the most easily available and widely used investigations. A recent meta-analysis of 699 patients from seven studies showed higher CRP levels within 24 h were independently associated with poststroke infection.¹⁶ Further, in a study of community-acquired pneumonia, CRP, but not temperature, was independently associated with extent of infiltrates on chest radiography.¹⁷ However, CRP levels in stroke patients can be elevated due to noninfective inflammatory processes or infections elsewhere.¹² This was seen in both the STROKE-INF and the MAPS (metoclopramide to prevent pneumonia in stroke patients fed via nasogastric tubes) studies, in

which 44 and 91% patients had elevated CRP levels but only 12 and 73% had SAP, respectively.^{8,14} As most noninfective processes in stroke lead only to modest elevations in CRP, one approach would be to identify a CRP threshold above which SAP is most likely. ROC analysis of MAPS data showed that the optimal cutoff level for CRP to preserve the sensitivity required for a screening test was 25.60 mg/l but this was at the expense of lower specificity.⁸ The present study combines the high sensitivity of elevated CRP and/or pyrexia for infections with the high specificity of new chest findings (whether clinical or radiological) as seen with the algorithm to develop objective criteria for identifying SAP, which have both high sensitivity and high specificity.

This study has several strengths. First, it provides external validation of the diagnostic value of a CRP threshold, derived from a smaller sample, in a large, independent, prospective dataset of actual practice collected from 37 centers across the UK. A second strength was the application of adjudicated SAP, based on assessment by two independent adjudicators, as the diagnostic reference standard. The CRP inclusive algorithm is consistent with the core criteria used in previous incidence and prevalence studies,³ and was applied masked to adjudicated SAP, outcomes, or antibiotic use. The study also has some limitations. The CRP criterion was considered to be met if any one of the six measurements before the endpoint of SAP was met was $\geq 30 \text{ mg/l}$. It was not possible to correlate this with the date of onset of SAP because of timing of assessments and diagnostic rules prespecified in the STROKE-INF study. It is well known that onset of SAP can be insidious and the time of onset and that of diagnosis may not coincide. This bias was investigated by doing further analyses requiring at least two elevated CRP values or an increase in CRP value $> 10 \text{ mg/l}$ as alternative criteria but these did not show any significant changes in diagnostic accuracy. Further, while we were not able to use a standardized analytical approach to CRP measurement given the logistics of the trial, our findings reflect real-life practice with respect to measurement of CRP across a large number of UK stroke units.

Despite these limitations, this is the first large study to investigate the usefulness of CRP as a potential biomarker for the diagnosis of SAP. It describes a simple algorithm incorporating CRP for diagnosis of SAP, which has high sensitivity and specificity, and could be implemented in daily practice to inform clinical decisions in stroke patients with suspicion of SAP, even in the absence of fever. Further prospective studies are required to replicate our findings and to also evaluate the utility of the diagnostic algorithm in antibiotic decision making and on relevant clinical and health-economic outcomes in stroke unit care.

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