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Original article

Community-acquired pneumonia in the emergency department: an algorithm to facilitate diagnosis and guide chest CT scan indication

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ABSTRACT

Objective: The aim was to create and validate a community-acquired pneumonia (CAP) diagnostic algorithm to facilitate diagnosis and guide chest computed tomography (CT) scan indication in patients with CAP suspicion in Emergency Departments (ED).
Methods: We performed an analysis of CAP suspected patients enrolled in the ESCAPED study who had undergone chest CT scan and detection of respiratory pathogens through nasopharyngeal PCRs. An adjudication committee assigned the final CAP probability (reference standard). Variables associated with confirmed CAP were used to create weighted CAP diagnostic scores. We estimated the score values for which CT scans helped correctly identify CAP, therefore creating a CAP diagnosis algorithm. Algorithms were externally validated in an independent cohort of 200 patients consecutively admitted in a Swiss hospital for CAP suspicion.
Results: Among the 319 patients included, 51% (163/319) were classified as confirmed CAP and 49% (156/319) as excluded CAP. Cough (weight = 1), chest pain (1), fever (1), positive PCR (except for rhinovirus) (1), C-reactive protein ≥50 mg/L (2) and chest X-ray parenchymal infiltrate (2) were associated with CAP. Patients with a score below 3 had a low probability of CAP (17%, 14/84), whereas those above 5 had a high probability (88%, 51/58). The algorithm (score calculation + CT scan in patients with score between 3 and 5) showed sensitivity 73% (95% CI 66–80), specificity 89% (95% CI 83–94), positive predictive value (PPV) 88% (95% CI 81–93), negative predictive value (NPV) 76% (95% CI 69–82) and area under the curve (AUC) 0.81 (95% CI 0.77–0.85). The algorithm displayed similar performance in the validation cohort (sensitivity 88% (95% CI 81–92), specificity 72% (95% CI 60–81), PPV 86% (95% CI 79–91), NPV 75% (95% CI 63–84) and AUC 0.80 (95% CI 0.73–0.87).

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Conclusion: Our CAP diagnostic algorithm may help reduce CAP misdiagnosis and optimize the use of chest CT scan. **P. Loubet, Clin Microbiol Infect 2020;26:382.e1–382.e7**

Introduction

Community-acquired pneumonia (CAP) is a frequent motive for consultation in emergency departments (ED) and a major cause of mortality and morbidity in many countries [1–4]. Besides typical presentation, CAP diagnosis may sometimes be complex due to the lack of specificity of clinical presentation, which may differ according to patients' backgrounds, and due to the absence of microbiological documentation in more than half of the cases [5]. CAP diagnosis relies on the combination of non-specific clues providing from patients' history, physical examination, and results of current biological tests and chest X-ray.

In recent years, new approaches have been proposed to improve CAP diagnosis using (a) markers of inflammation that correlate with infection (C-reactive protein (CRP) and procalcitonin (PCT), and (b) microbiological detection techniques such as multiplex polymerase chain reaction (mPCR) that have enhanced the ability to detect respiratory bacteria and viruses. However, none of these is specific to CAP and they have never been assessed together as diagnostic criteria in addition to history and physical examination.

Furthermore, several studies have recently challenged information provided by chest X-ray, showing a superiority of chest computed tomography scan (CT scan) in some patients "with a decrease in" or "in decreasing" the rate of false positive and false negative CAP diagnoses established using chest X-ray [6–8]. Cases of CAP diagnosed only by CT scan have been shown to have the same microbiological profile and to be as severe as those detected by chest X-ray, raising the question of its wide use in ED [9]. However, cost and availability of CT scan make it difficult to perform in every patient with suspected CAP.

The objective of this study was to integrate into the usual CAP diagnostic pathway (patient background, clinical characteristics, standard biology and chest X-ray), data provided by biomarkers and PCR in order to (a) develop and validate a simple CAP diagnostic score and (b), based on this score, create a CAP diagnostic algorithm, which identifies the patients in whom CAP diagnosis requires the use of a CT scan.

Methods

Study population and data collection

We performed a *post hoc* analysis of the ESCAPED study (NCT01574066) which was a multicentre, prospective, interventional study conducted between November 2011 and January 2013, in the emergency department (ED) of four tertiary teaching hospitals in Paris, France, aiming at exploring the impact of systematic early chest CT scan on diagnosis in patients visiting the emergency department with clinically suspected CAP [6,10].

Consecutive adult patients presenting to the ED with a clinical suspicion of non-severe CAP (classes 0, 1 and 2 on the CRB65 score) were prospectively enrolled. Clinical suspicion of CAP was based on the investigator's own judgement and inclusion criteria (new onset of systemic features (at least one among sweat, fever, chills, aches and pain, temperature 38°C) and symptoms of an acute lower respiratory tract illness (at least one among: cough, sputum production, dyspnoea, chest pain, altered breathing sounds).

Besides clinical examination and blood sample collection, all patients systematically underwent at admission to the ED, chest X-ray and CT scan and PCRs on nasopharyngeal swabs to detect respiratory viruses, intracellular bacteria, *Bordetella pertussis* and *Streptococcus pneumoniae* (please see supplementary material).

An adjudication committee including three experts in infectious diseases, pneumology and radiology reviewed patient records using clinical, biological, microbiological (except PCR results) and X-ray and CT scan data at admission, as well as day 28 follow-up data, to classify the final diagnostic probability of CAP according to four categories: definite, probable, possible and excluded CAP.

Statistical analysis

Overview of the statistical analysis

A four-step process was conducted to create a CAP diagnostic algorithm. First, we determined predictive factors of confirmed CAP using data available at baseline but excluding CT scan results. Second, we created a diagnostic score for CAP based on the previously identified predictive factors (P-ESCAPED score). Third we estimated, using a grey zone approach, the value for which the scores did not provide conclusive information and for which the use of CT scan may be valuable resulting in the creation of an algorithm (P-ESCAPED algorithm). Fourth, we assessed the performance of our score and algorithm compared to the gold standard. Fifth, as PCRs on nasopharyngeal swabs are currently not available in every setting, we repeated this four-step process excluding the PCR results to create simplified (s)-ESCAPED score and algorithm. Finally, we validated our findings in an independent cohort of 200 patients older than 65 years consecutively admitted at the Department of Internal Medicine, Rehabilitation and Geriatrics at Geneva University Hospitals, Switzerland from the emergency department with CAP suspicion [8]. All patients had a chest CT scan within the 24 hr following inclusion and the reference standard for CAP diagnosis was adjudicated by a panel of three experts in the field supported by a radiologist expert.

Statistical analysis is further described in (please see supplementary material).

Ethics

The ethics committee (Comité de Protection des Personnes – CPP 1, Paris, France) approved the study protocol and patient informed consent procedures. All enrolled patients provided written informed consent before inclusion.

Results

Characteristics of study subjects and CAP classification

All the 319 patients enrolled in the ESCAPED study were included for analysis. Characteristics of the participants are displayed in Table 1. Based on the day 28 adjudication committee, 51%

Table 1
Characteristics of the 319 patients included in the ESCAPED score study according to the adjudication committee classification

	Total, $n = 319$	Excluded CAP, $n = 156$	Confirmed CAP, $n = 163$	p
Background characteristics				
Men, *n* (%)	164 (51)	80 (51)	84 (51)	0.96
Median age, years (IQR)	68 (51–81)	68 (53–84)	67 (49–79)	0.25
Age ≥ 65 years, *n* (%)	177 (55)	85 (54)	92 (56)	0.73
Chronic disease, *n* (%)				
Cancer	32 (12)	16 (10)	16 (10)	0.90
Chronic heart failure	39/318 (12)	19/155 (12)	20 (12)	0.99
Chronic respiratory disease	99/318 (31)	45/155 (29)	44 (27)	0.69
Immunocompromised status	30/306 (10)	17/149 (11)	13/157 (8)	0.39
Influenza vaccination in current season, *n* (%)	118/295 (40)	56/142 (39)	62/153 (41)	0.85
Updated pneumococcal vaccination[a], *n* (%)	45/273 (16)	19/136 (14)	26/137 (19)	0.24
Study centre, *n* (%)				
Bichat hospital	73 (23)	38 (24)	35 (21)	0.14
Cochin hospital	103 (32)	54 (35)	49 (30)	
Pitié-Salpêtrière hospital	71 (22)	34 (22)	37 (23)	
Tenon hospital	72 (23)	30 (19)	42 (26)	
Clinical presentation, *n* (%)				
Antibiotics administration before emergency department, *n* (%)	111/319 (35)	43/156 (28)	68/163 (42)	0.006
Fever (≥38°C)	112/317 (38)	42/155 (27)	70/162 (43)	0.002
Cough	240/317 (76)	108/155 (70)	132/162 (81)	0.025
Chest pain	103/318 (32)	44 (28)	59/162 (36)	0.11
Sputum production	147/318 (46)	66 (42)	81/162 (50)	0.17
Dyspnoea	229/318 (72)	118 (76)	111 (68)	0.12
Myalgia	59/318 (19)	23/156 (15)	36/162 (22)	0.07
Unilateral crackles	105/316 (33)	42/155 (27)	63/161 (39)	0.02
Biologic data, *n* (%)				
White blood cell ≥ 7000/mm^3	166/272 (61)	61/130 (47)	105/142 (74)	0.001
Procalcitonin ≥0.25 ug/L	110/257 (43)	41/123 (33)	69/134 (51)	0.019
C-reactive protein ≥50 mg/L	161/265 (61)	50/131 (38)	111/134 (83)	0.001
Positive PCR result (except rhinovirus) in nasopharyngeal swab	65/255 (25)	20/123 (16)	45/132 (34)	0.001
Positive Rhinovirus PCR in nasopharyngeal swab	21/255 (8)	15/123 (12)	6/132 (5)	0.04
Radiologic data (chest X-ray), *n* (%)				
Parenchymal infiltrate	188/308 (61)	69/152 (45)	119/156 (76)	0.001
Air bronchograms	68 (21)	25 (16)	43 (26)	0.014
Pulmonary nodule/mass	11 (3)	6 (4)	5 (3)	0.72
Underlying pulmonary disease	45/305 (14)	26/148 (18)	19/157 (12)	0.21

CAP, community-acquired pneumonia; IQR, interquartile range.
[a] If concerned by pneumococcal vaccine recommendation.

(163/319) and 49% (156/319) patients were classified as confirmed or excluded CAP cases, respectively (reference standard). The physicians' CAP classification in the ED at inclusion had a sensitivity of 91% (95% CI 86–95), specificity of 28% (95% CI 21–36), positive predictive value of 57% (95% CI 51–63), negative predictive value of 76% (95% CI 63–86). Its area under the curve (AUC) was 0.60 (95% CI 0.56–0.64).

PCR results were available in 80% of patients (255/319). At least one pathogen was found in 82 patients (82/255, 32%) without significant difference between excluded (69/255, 27%) and confirmed (94/255, 37%) CAP (p 0.08). Bacteria were found more frequently in confirmed CAP (16% (19/117) vs. 3% (3/112); $p < 0.001$). There was no difference between CAP groups concerning respiratory viruses (26% (32/123) vs. 30% (39/132); p 0.58) except for rhinovirus that were more likely to be found in excluded CAP (13% (15/123) vs. 5% (6/132); p 0.04) (Table S1).

CAP predictive factors

Cough, fever, chest pain, unilateral crackles, white blood cell ≥7000/mm^3, CRP ≥50 mg/L, positive PCRs result (except for rhinovirus), parenchymal infiltrate on chest X-ray were variables selected from the four different multivariate models (epidemiological, clinical, micro/biological and radiological) to create the P-ESCAPED score (Tables S2–S5) and included in the final multivariate model. Finally, five predictive factors (cough, chest pain, fever, PCR positive result (except rhinovirus) from nasopharyngeal samples, CRP ≥50 mg/L and parenchymal infiltrate on chest X-ray) were independently

Table 2
Final predictive model of community-acquired pneumonia (CAP) and median β coefficients estimated by Multivariate Poisson Regression with a robust error variance approach and Bootstrapping Procedure in the 319 patients enrolled with CAP suspicion in the P-ESCAPED score study

	Boostrap procedure[a]	
	Incidence risk ratio (95% CI)	Weight
Cough	1.4 (1.0–1.9)	1
Chest pain	1.3 (1.0–1.6)	1
Fever (≥38°C)	1.3 (1.0–1.6)	1
Positive PCR result (except rhinovirus) in nasopharyngeal swab	1.4 (1.1–1.7)	1
C reactive protein ≥50 mg/L	1.7 (1.3–2.2)	2
Parenchymal infiltrate on chest X-Ray	1.7 (1.3–2.3)	2

P-ESCAPED score includes nasopharyngeal multiplex PCR results.
[a] Results from the multivariate poisson regression with a robust error variance approach showed same values as the bootstrap procedure.

associated with confirmed CAP (Table 2). The p value of the Hosmer–Lemeshow test for the final model was 0.40 and the median AUC after bootstrap procedure was 0.78 (95% CI 0.73–0.83).

CAP diagnostic scores

After 1000 iterations using bootstrap procedure, median β coefficients of the five predictive factors were estimated for the P-ESCAPED score (Table 2). Points assigned were 2 for parenchymal infiltrate and CRP ≥50 mg/L and 1 for cough, chest pain, fever and positive PCR positive result leading to a theoretical score ranging from 0 to 8 for a given patient.

For an optimal cut-off considered to be 4, the score had a sensitivity of 78% (95% CI 71–85), specificity of 63% (95% CI 55–70), positive predictive value of 69% (95% CI 62–75), negative predictive value of 74% (95% CI 65–81) and an AUC of 0.78 0.73–0.83).

CAP diagnostic algorithms (to identify patient requiring CT-scan)

Using Youden's index determination for each bootstrapped population, we obtained a distribution for the optimal thresholds of the 1000 samples. Median of these optimal thresholds was 4, and the 95% CI of this distribution (the grey zone) was 3–5. Using the alternative approach of splitting the receiver operating characteristic curve into two curves of sensitivity and specificity (Fig. S1), an inconclusive zone spreading from 3.1 to 5.4 was retrieved. The results of the two approaches were merged and rounded as a grey zone in the score ranging from 3 to 5.

The rate of confirmed CAP increased significantly from 17% (14/84) when the score was <3 to 88% (51/58) when the score was >5. Between 3 and 5, this rate was 55% (98/177).

Based on the results of the grey zone determination, we proposed a diagnostic algorithm in which CT scan would need to be performed only in patients with a diagnostic score between 3 and 5 which represented 55% (177/319) of our sample (Fig. S2). Among patients with a score in the grey zone (3–5), 69% (68/98) of patients with confirmed CAP had an evidence of pneumonia on chest CT scan versus 13% (10/79) in patients with excluded CAP resulting in correct classification of 77% (137/177) (Table S6). Based on the algorithm, the CAP probability of the physician's classification in the ED would be modified in 145 participants (45% (145/319); 95% CI 40–51%).

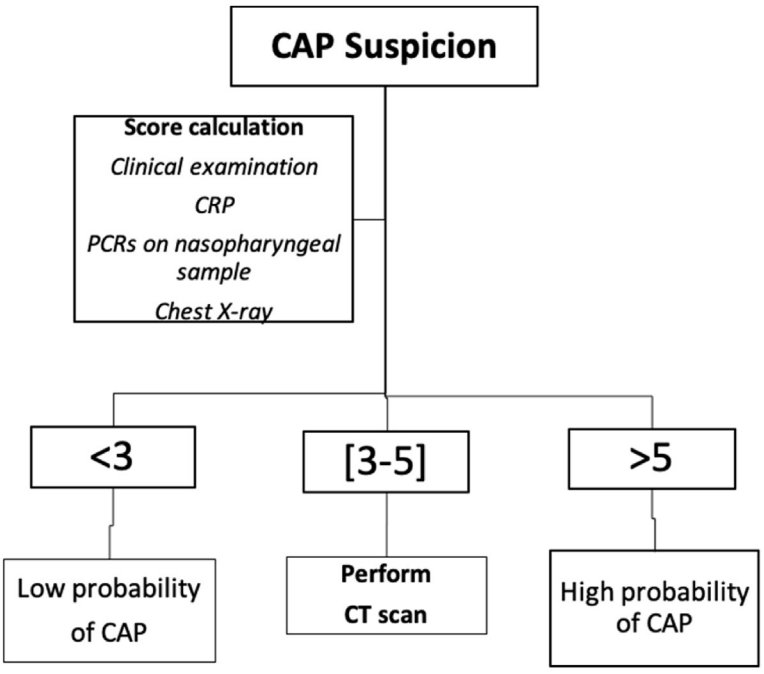
Our diagnostic algorithm (score calculation + CT scan according to score values) had a sensitivity of 73% (95% CI 66–80), specificity of 89% (95% CI 83–94), positive predictive value of 88% (95% CI 81–93), negative predictive value of 76% (95% CI 69–82) and an AUC of 0.81 (95% CI 0.77–0.85) (Fig. 1). Diagnostic strategy without the inclusion of PCR results (s-ESCAPED) are displayed in the supplementary material.

External validation

In the validation cohort, P-ESCAPED algorithm and S-ESCAPED algorithm had similar performance as in the derivation cohort with an AUC of 0.80 (0.73–0.87) and 0.79 (0.74–0.85) respectively. Accuracy of the algorithms with and without PCRs results in the validation cohort is displayed in Table 3.

Discussion

We have developed two two-step diagnostic algorithms integrating new diagnostic tools into current diagnosis approach for patients visiting ED for suspected CAP.



Score calculation: cough=1, chest pain=1, fever ≥ 38°C =1, PCR positive result (except rhinovirus) in nasopharyngeal swab = 1, CRP ≥ 50 mg/L = 2 and parenchymal infiltrate on chest X-ray = 2.

Fig. 1. P-ESCAPED diagnostic algorithm proposed in CAP suspicion in Emergency Department including nasopharyngeal PCRs results. CAP, community-acquired pneumonia; CRP, C-reactive protein; CT, computed tomography.

Table 3
Diagnostic performances of emergency department physician in charge of the patients, P-ESCAPED algorithm and S-ESCAPED algorithm in the diagnosis of community acquired pneumonia in derivation and validation cohorts

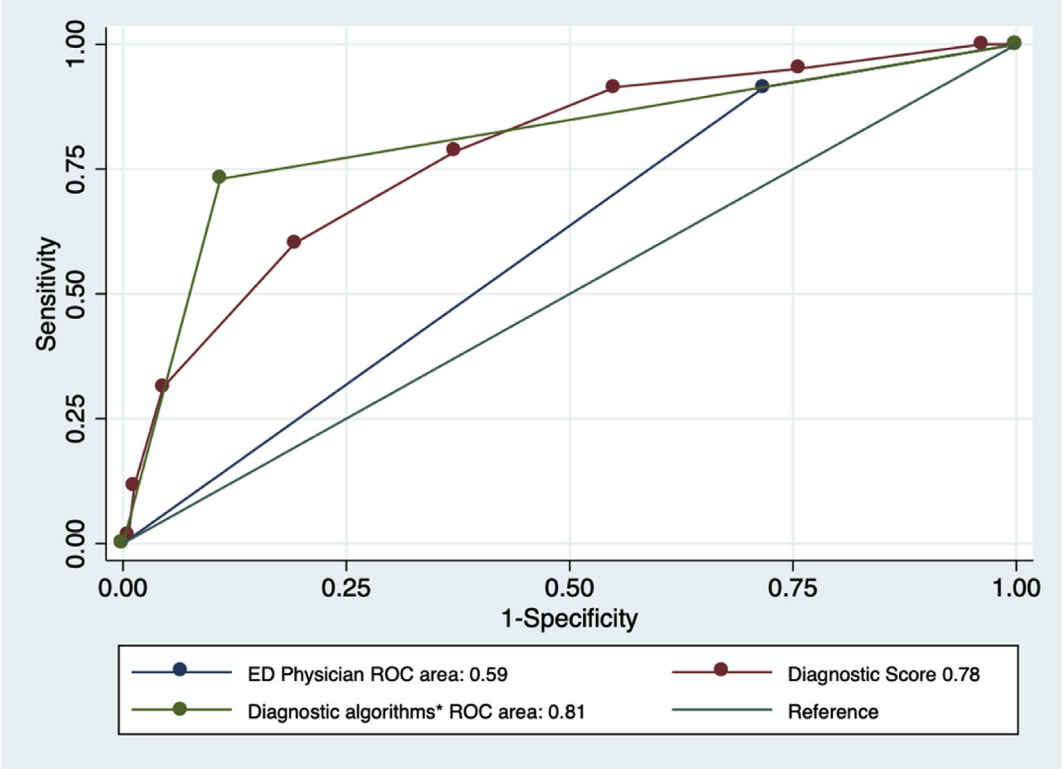
	ED physician ($n = 319$)	P-ESCAPED algorithm derivation cohort ($n = 319$)	P-ESCAPED algorithm validation cohort ($n = 200$)	S-ESCAPED algorithm derivation cohort ($n = 319$)	S-ESCAPED algorithm validation cohort ($n = 200$)
AUC (95% CI)	0.60 (0.56–0.64)	0.81 (0.77–0.85)	0.80 (0.73–0.87)	0.81 (0.77–0.86)	0.79 (0.74–0.85)
Sensitivity (95% CI)	91% (86–95)	73% (66–80)	88% (81–92)	72% (64–79)	88% (80–92)
Specificity (95%CI)	28% (21–36)	89% (83–94)	72% (60–81)	91% (85–95)	70% (58–80)
Positive predictive value (95% CI)	57% (51–63)	88% (81–93)	86% (79–91)	89% (82–94)	85% (78–90)
Negative predictive value (95% CI)	76% (63–86)	76% (69–82)	75% (63–84)	76% (70–82)	73% (62–83)

P-ESCAPED algorithm includes nasopharyngeal PCRs results.

In the P-ESCAPED score (including PCR results), the probability of CAP was considered to be low with a score <3. Conversely, CAP probability was considered to be high if the score was >5. We showed that neither ESCAPED score alone would be accurate enough in the diagnosis of CAP in all patients, but would allow identification of specific patients whose scores were between 3 and 5 for the P-ESCAPED score and 3 and 6 for the s-ESCAPED score, for whom a CT scan would be decisive. Of interest, we have shown that AUCs increased markedly, from 0.6 using a standard diagnostic approach to 0.8 when applying our algorithms (see Fig. 2).

The population of the ESCAPED study was composed of individuals in whom the positive or negative diagnosis of CAP is difficult because of their characteristics (old age, high rate of comorbidities, frequent previous use of antibiotics before consultation) but similar to those individuals visiting ED for suspected CAP. The inclusion of patients during 12 consecutive months, the multicentre design of the study and the use of a multidisciplinary adjudication committee increased the external and the internal validities of the study. Of note, to avoid tautology, the adjudication committee was blinded to PCRs, PCT and CRP results.

There are increasing data in the literature supporting the interest of chest CT-scan to establish or exclude CAP diagnosis. First, systematic chest CT scan allows the identification of CAP in patients with normal chest X-ray, a situation which was reported to occur in 9–13% of patients in different studies [6,9]. Of importance, Upchurch et al. [9] stated that CAP only visualized on CT scan occurred in patients with the same clinical presentations, the same responsible microorganisms and who had the same clinical outcomes as patients with CAP visualized on chest X-ray, underlying the importance of diagnosing these CAP. Second, two studies found that systematic chest CT scan also limits overdiagnosis in 30–40% of



Note:
*P-ESCAPED & S-ESCAPED had the same ROC area value

Fig. 2. Comparison of AUC between Emergency Department Physician, P-ESCAPED score P-ESCAPED Algorithm and S-ESCAPED Algorithm in the diagnosis of community acquired pneumonia. ROC, receiver operating characteristic.

patients [6,8]. Overall, a change in the probability of a CAP diagnosis was around one patient out of two in these studies [3,5]. Based on the ESCAPED algorithms, the need for CT scan can be limited to half of our population when applying P-ESCAPED score and to two-thirds of them when applying s-ESCAPED score.

There are few studies in the literature on CAP diagnostic score. Those published, on the one hand, mostly concern CAP in primary care [9–11], and on the other hand, do not use the modern gold standard. So far, the score from Schierenberg et al. [12] developed for primary care has demonstrated the highest discriminative accuracy. This score is based on clinical symptoms (absence of runny nose and presence of breathlessness, crackles and diminished breath sounds on auscultation, tachycardia, and fever) associated with CRP >30 mg/L.

As PCR was available in the settings of our study, but not in all emergency departments all around the world, we decided to create two separate analyses, with and without PCR results. We found that their positivity for any pathogen except rhinovirus was significantly associated with the diagnosis of CAP, but not sufficient in itself (score weight equal to 1) showing that combining nasopharyngeal PCR result with other arguments toward CAP allows a better interpretation of each isolated piece of information. We decided not to consider rhinovirus in our analysis because it was the only pathogen that was significantly associated with the absence of CAP. This is in line with the literature where the significance of rhinovirus detection in respiratory specimens from pneumonia patients is a subject of some debate and with the above-mentioned Van Vugt score. Of note, the inclusion of PCR results in the P-ESCAPED score decreased the grey zone width (i.e. increased the level of confidence) in adding information, and consequently reduced the number of patients for whom CT-scan was needed to correctly establish CAP diagnosis. It has to be underlined that the PCR result mainly gives information on the presence or absence of a respiratory pathogen. Whether this pathogen is responsible for the acute respiratory infection is difficult to establish with certainty. For these reasons, we think that the interpretation of an isolated PCR result is confusing and should be thus associated with clinical data, biological tests and CT scan results.

The reliable performance of our algorithms was confirmed, showing even higher sensitivity, in another independent cohort that used similar methods in a different population of patients with CAP suspicion.

Some limitations of our study should be acknowledged. We did not use other microbiological results (sputum samples, blood cultures, urinary antigens) in order to be in line with the data available within the few hours after ED admission. Neither did we address the issue of cost-effectiveness of the procedure including multiplex PCR and CT scan nor its impact on ED delays and activity. Indeed, our algorithms raise several unanswered questions. We must analysed, first, whether the costs generated by additional CT scans will be offset by costs avoided related to a better diagnosis and treatment of CAPs. Second, even if these additional costs are not offset and ESCAPED algorithm is more expensive, we must also analysed whether this strategy is cost-effective (i.e. quality-adjusted life years saved worth the money that has been spent to implement to implement this strategy). Third, we must assess, whether performing these additional CT scans is logistically feasible in imaging departments. Concerning this last point, we have estimated from data of one of the university hospital from the ESCAPED study that the use of the P-ESCAPED algorithm would result in an 1.3% increase in the CT scan activity of this hospital. Fourth, whether the time interval to obtain the results of multiplex respiratory panels in its current use will postpone the use of CT scan and thus may jeopardize the treatment initiation. Finally, although fewer than half of our patients were younger than 65 years, it has to be underlined that we only validated our algorithms in a cohort of patients older than 65, which could impact the performance of the algorithms.

Conclusion

Our scores make possible the identification of patients who would benefit the most from a chest CT scan in ED. Our strategy could streamline the use of CT scan and PCR in suspected CAP, improve CAP diagnosis process and thus improve quality of care. Randomized clinical trials evaluating the impact of using the ESCAPED algorithms on patients' prognosis and the cost-effectiveness of the proposed strategies should be considered.

Transparency declaration

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ESCAPED (Early CT-Scan for Community-Acquired Pneumonia at the Emergency Department) study group.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2019.06.026.

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