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C-reactive protein to rule out complicated pneumococcal disease manifestations: a retrospective cohort study in adults with pneumococcal bacteraemia

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ABSTRACT

Objectives: To explore the negative predictive value (NPV) of C-reactive protein (CRP) at admission to exclude complicated disease manifestations of pneumococcal disease.

Methods: A Dutch multicentre retrospective cohort study was conducted between 01-01-2012 and 30-06-2020. Adults with positive blood cultures for *Streptococcus pneumoniae*, whose CRP was measured at admission and whose infection focus was known, were included. Electronic medical and microbiological records were reviewed.

Results: Of the 832 bacteraemic patients enrolled, 30% had complicated manifestations of pneumococcal disease; most frequent were pleural effusion (8.9%), pleural empyema (5.4%) and meningitis (7.5%). Compared to solitary pneumonia, patients with pleural effusion and empyema presented with higher CRP levels. Although low CRP levels did not exclude complicated disease in general, a CRP level < 114 mg/L at admission could reliably exclude empyema among adult pneumonia patients with an NPV of 93% and a specificity of 26%. However, in cases where pleural fluid was present, CRP levels were mostly > 114 mg/L, such that suspicion of empyema could only be ruled out in a minority of cases (10%).

Conclusions: Complicated manifestations are prevalent in adult pneumococcal bacteraemia. Low blood CRP levels can reliably exclude the development of pulmonary empyema. Practical value may be largest in settings without thoracic imaging at hand.

Introduction

Streptococcus pneumoniae (*S. pneumoniae*) is the most common cause of community-acquired pneumonia (CAP) worldwide (van der Poll and Opal, 2009). Most cases of adult pneumococcal pneumonia stay confined to the lung alveoli, from which patients can fully recover. Other patients have a more complicated course of disease associated with pulmonary complications, including pleural effusion, empyema and multilobar consolidations or abscesses (Cilloniz et al., 2012). Patients can also present with extrapulmonary manifestations such as endocarditis, meningitis and peritonitis (van der Poll and Opal, 2009). When these complications arise, the bacterium has often disseminated from the blood stream (Randle et al., 2011). A study of 343 patients with bacteraemic pneumococcal infections in the Netherlands showed a high incidence of pleural empyema in 10% of cases (Cremers et al.,

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2014). This is a complication of bacterial pneumonia that requires more extensive antibiotic treatment and therapeutic drainage compared with solitary pneumonia, and is associated with a heavily protracted course of disease and high mortality (Ahmed and Zangan, 2012; Maffey et al., 2019). Early diagnosis of complicated pneumococcal infections in primary care as well as in the emergency department is important, so that treatment can be adjusted in time, which might prevent further deterioration (Centers for Disease Control and Prevention, 2017). When complicated disease can be ruled out at an early stage, unnecessary diagnostics can be avoided and (antibiotic) therapy confined, contributing to more effective and patient-friendly healthcare.

C-reactive protein (CRP) is known to increase in patients with invasive pneumococcal disease (IPD) (Cilloniz et al., 2012; Ma et al., 2002). It is an acute phase protein that is produced in and excreted by the liver as a reaction to circulating cytokines originating from an infection site (Pepys, 1981). The C in CRP originally referred to capsular polysaccharides of *S. pneumoniae*, to which CRP reacted (Levine, 2010; Tamayose et al., 2015). It is a sensitive inflammatory parameter as it reacts quickly upon inflammatory changes, and has a short half-life (Young et al., 1991). Previous research has shown that high CRP levels at admission are an independent predictor of the occurrence of lung necrosis or lung abscesses in children with CAP (Hsieh et al., 2004). In children, a high specificity and negative predictive value for identifying CAP with consolidations have been found (Alcoba et al., 2017). In primary care in the Netherlands, the guideline for the management of respiratory infections describes increased CRP levels to be associated with bacterial pneumonia in adults (Verheij ThJM, 2011). Furthermore, CRP as a measure to exclude complicated infections is proven to be a cost-effective diagnostic intervention for many examples in infectious disease management (Oppong et al., 2013).

However, it is unknown if the blood CRP level at admission can be used to rule out complicated manifestations of pneumococcal infections in adults, and more specifically if it can be used to differentiate between solitary pneumonia or pneumonia with empyema. The latter can be useful, as 50% of IPD patients present with pleural effusion, whereas pleural empyema is established in a minority of cases (Cremers et al., 2014). Therefore, the aim of this study was to find a cut-off point for the blood CRP level at admission below which a complicated course of IPD can be excluded; it aimed for a negative predictive value $>$ 90%.

Materials and method

Study population

A retrospective multicentre cohort study was conducted. The study population included all adult ($\geq$ 18 years old) hospitalized patients with positive blood cultures for *S. pneumoniae* between 01-01-2012 and 30-06-2020 in three participating hospitals (Radboudumc Nijmegen, Canisius-Wilhelmina Ziekenhuis (CWZ) Nijmegen, and Rijnstate Arnhem). These hospitals included one academic tertiary care hospital and two secondary care hospitals in the southeast of the Netherlands, which provide care for around 800,000 inhabitants. Based on a relatively sparse distribution of CRP levels within clinical syndromes observed in a previous cohort, this study aimed to include at least 60 cases of meningitis and empyema. Patients were excluded when the CRP at admission or the focus of infection was unknown, or when patients had not given permission for their data to be used for scientific purposes in general. Patients who were transferred to another hospital during hospitalization were excluded. The study procedures were approved by the Medical Ethical Committees of all participating hospitals.

Data collection

A database was created including coded clinical data. Electronical medical records and microbiological data were reviewed. The researchers working in the different hospitals regularly discussed how to interpret findings, so that consensus could be provided, ensuring comparable methods of data entry.

Clinical characteristics and definitions

Data included demographics, medical history, immunocompromising conditions (Camille Nelson Kotton, 2019) and additional predisposing conditions. Clinical history, physical examination and clinical chemistry were determined at admission. Clinical diagnoses were based on blood, sputum and cerebrospinal fluid cultures. Furthermore, parameters about hospital stay and discharge were collected. A more detailed description of all characteristics is provided in Supplement 1. Complicated pneumococcal infections were defined as expanded infection inside or outside the lungs. Intrapulmonary complicated disease manifestations were empyema, pleural effusion (without empyema) or other . Extrapulmonary disease included meningitis, arthritis, peritonitis, endocarditis or other . Patients could therefore have multiple diagnoses at the same time.

Measurement methods of CRP

The three participating hospitals used different methods to measure the CRP at admission. Radboudumc and CWZ used the C8000 systems of Roche (c702); the range is 0.5-700 mg/L (reference value $<$ 10 mg/L), with a reproducibility rate of 3.5%. Rijnstate used the Siemens Atellica, with a range of 4-912 mg/L and a reproducibility rate of 6.8%.

Data analysis

The population was divided into two groups: non-complicated infections and complicated disease manifestations. Non-complicated infections were defined as solitary pneumonia. Complicated manifestations included pleural effusion, empyema, meningitis, peritonitis, endocarditis and arthritis. The primary parameter was the CRP value at admission in mg/L. Normality was tested using the Shapiro-Wilk test. For non-normally distributed variables the Kruskal-Wallis test was used to compare continuous variables and the independent sample t-test for normally distributed variables. For nominal variables, the Chi-square test was used (Petrie and Sabin, 2009). Cases with missing values were only excluded from analysis of the particular missing variable.

Histograms were made to visualise the distribution of CRP per clinical manifestation of IPD. Complicated disease categories (composite outcome as well as specific syndromes) were compared to solitary pneumonia cases. For each comparison a ROC curve was used to determine the optimal CRP cut-off point with a negative predictive value of $>$ 90% in combination with a maximum specificity. The multiple regression analysis was performed using backward elimination based on significant contribution to the outcome. Variables found to be statistically significant in the univariate analyses were included for backward elimination.

All analyses were performed using IBM SPSS version 26.0. P-values of $<$ 0.05 were considered statistically significant. For univariate analyses, no correction for multiple testing was applied.

Results

A total of 956 patients were admitted to one of three participating hospitals during the study period with a positive blood culture for *S. pneumoniae*. Three patients were excluded as no medical

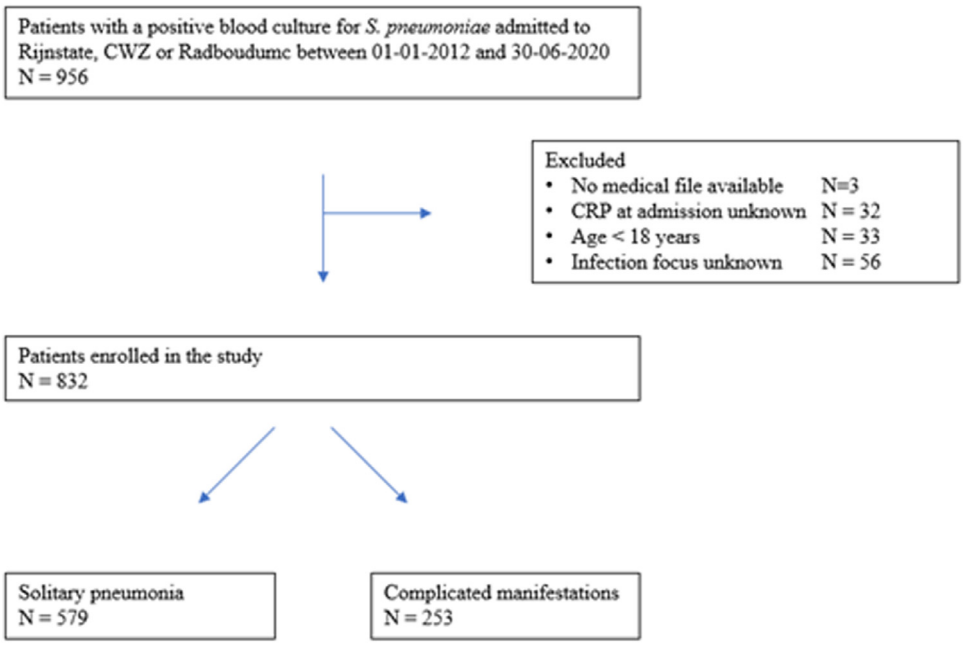

Figure 1. Inclusion of participants.

Table 1
Demographic characteristics, parameters at admission and course of disease in 579 patients with solitary pneumonia compared to 253 patients with complicated manifestations of IPD.

	Solitary pneumonia (n = 579)	All complicated manifestations (n = 253)	P-value
Demographic characteristics			
Gender (male)	306 (53)	133 (53)	0.94
Age (years)	70 (60-79)	66 (57-76)	**0.006**
Institutionalisation (independent)	554 (96)	247 (98)	0.17
Current smoking	120 (21)	51 (20)	0.20
Current alcohol abuse	30 (5)	21 (8)	0.11
Parameters at admission			
Saturation (%)	94 (91-96)	95 (91-97)	0.066
Heart rate (bpm)	102 (90-119)	104 (90-119)	0.66
Systolic blood pressure (mmHg)	122.0 (105.0-140.0)	127.0 (109.5-146.5)	0.056
Diastolic blood pressure (mmHg)	68 (58-78)	71 (63-84)	**0.014**
Temperature (°C)	38.5 (37.7-39.2)	38.5 (37.5-39.3)	0.29
C-reactive protein (mg/L)	259.0 (93.0-346.0)	306.0 (139.8-378.3)	0.15
Course of disease			
Length of stay (days)	6 (4-10)	12 (7-18)	**< 0.001**
Mechanical ventilation	47 (8)	48 (19)	**< 0.001**
Admission to intensive care unit	107 (19)	96 (38)	**< 0.001**
30-day mortality	60 (10)	42 (17)	**0.013**

Data are presented as number (percentage) or median (interquartile range)

records were available. Based on the exclusion criteria, another 121 patients were excluded, leading to 832 eligible patients who were included in the study (87%). Figure 1 shows the inclusion of participants. The number of cases with missing data for a given variable ranged from 0to 11, with an average of 1 (Supplement 2).

Of all 832 patients, 739 (88% of 832) had pneumonia and 579 patients (70% of 832) had a non-complicated course, thus only having solitary pneumonia. Complicated manifestations were determined in 253 patients with at least one of the following diagnoses: empyema, pleural effusion, meningitis, peritonitis, endocarditis, arthritis or other. The demographic characteristics, parameters at admission and course of disease of these two groups are described in Table 1.

The solitary pneumonia group had an older age compared with the complicated group: 70 years (60-79) vs. 66 years (57-76) ($p = 0.006$). The male to female range was almost 1:1 in both groups, as well as the percentage of current smokers and alcohol dependency. The complicated group had a higher median CRP level at admission (306 mg/L vs. 259 mg/L), although this was not statistically significant ($p = 0.15$). They had a significantly longer length of hospital stay (median 12 days vs. 6 days; $p < 0.001$). Also, the percentage of patients that had to be mechanically ventilated or had to be admitted to the intensive care unit (ICU) was significantly higher in the complicated group (19% vs. 8%; $p<0.001$) and 38% vs. 19%; $p < 0.001$), respectively. The mortality within 30 days of admission was higher in the complicated group (17% vs. 10%; $p = 0.013$).

The CRP measured at admission was not significantly different between men (255 mg/L, IQR 97-345) and women (283 mg/L, IQR 115-359) ($p = 0.15$). Comparing the CRP at admission between survivors 30 days after hospitalization (263 mg/L, IQR 100-347) and patients deceased within 30 days after hospitalization (289 mg/L, IQR 122-355), no significant difference was found ($p = 0.13$).

Of the 253 patients with complicated IPD, 63% (160) had complicated pneumonia. Complicated pneumonia included pleural effusion (46%), empyema (28%) and meningitis (8%) (Figure 2a). Sole

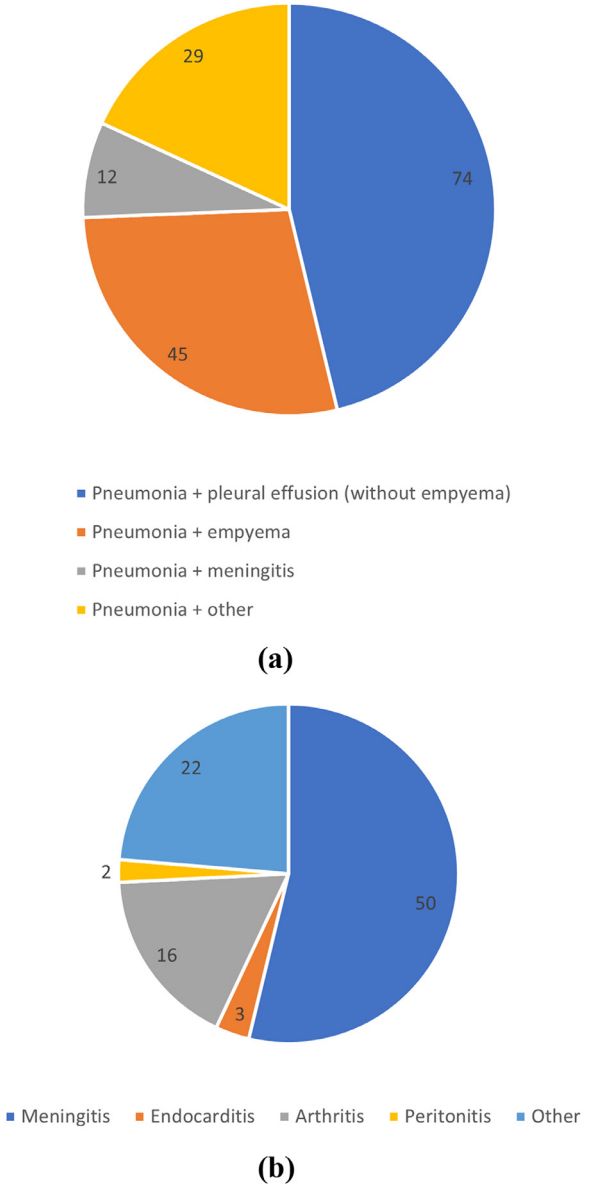

Figure 2. a Frequencies of complicated pneumonia in bacteraemic patients with pneumococcal disease. b. Frequencies of diseases other than pneumonia in bacteraemic patients with pneumococcal disease.

meningitis was identified in 20% of the complicated cases, and other complicated manifestations included spondylodiscitis, pericarditis, erysipelas, cerebritis and cholangitis (Figure 2b). Figure 3 demonstrates the distribution of CRP values for adult pneumococcal bacteremia cases with solitary pneumonia (i.e. uncomplicated) and for those with empyema, meningitis and pleural effusion without empyema established. The CRP value at admission for empyema (363mg/L, IQR 311-462) was significantly higher than solitary pneumonia (259 mg/L, IQR 93-346; p<0.001). For meningitis, the CRP value at admission was significantly lower than for solitary pneumonia (200 mg/L, IQR 87-325; p = 0.024). For pleural effusion, the CRP was significantly higher (322 mg/L, IQR 163-413; p = 0.038). For arthritis (322 mg/L, IQR 171-357), peritonitis (107 mg/L, IQR 32-253) and endocarditis (356 mg/L, IQR 259-431) the CRP at admission was not significantly different from solitary pneumonia cases (p-values 0.69, 0.10, 0.41, respectively).

Table 2 displays solitary pneumonia patients compared to those with empyema, meningitis, and pleural effusion without empyema established. Empyema cases had symptoms longer before consulting a doctor compared with solitary pneumonia cases: 4 days (2-5) vs. 3 days (1-5) (p = 0.04). Their length of stay was more than twice as long: 15 days (12-21) compared to 6 days (4-10) (p <0.001). Patients with empyema were more often admitted to the ICU (44% vs. 19%; p<0.001) and had to be mechanically ventilated more often (27% vs. 8%; p< 0.001). The 30-day mortality was also higher compared with solitary pneumonia cases (20% vs. 10%; p = 0.049).

Meningitis cases were more often associated with alcohol dependency compared with solitary pneumonia (15% vs 5%; p = 0.004). The length of stay was more than twice as long (14 days, IQR 10-25; p<0.001). This group more often required mechanical ventilation (32%; p<0.001), and admission to the ICU (58%; p < 0.001) and 30-day mortality were higher (21%; p = 0.013). Patients with meningitis less often had COPD as a comorbidity (11% vs 29%; p = 0.002). When comparing the pleural effusion group to the solitary pneumonia group, the pleural effusion group had a longer length of stay (10 days, IQR, 6-16; p = 0.005).

For all patients diagnosed with pneumonia (solitary and with complicated manifestations), the CURB-65 score was calculated based on parameters at admission. Supplement 3 shows the random distribution of CRP values across CURB-65 scores, also when comparing complicated manifestations with solitary pneumonia. Therefore, the height of CRP at admission did not reflect the clinical severity of the pneumonia, in terms of likelihood of survival.

To differentiate from uncomplicated solitary pneumonia, for neither the composite endpoint, nor meningitis or pleural effusion specifically, a CRP cut-off point with an NPV > 90% could be identified, as was expected from the large overlap in lower CRP values. However, from the ROC-curve for empyema compared to solitary pneumonia cases, a valid cut-off point could be established at a CRP value of 114 mg/L at admission. The area under the curve was 0.747. The NPV was 93%, the sensitivity 98% and the specificity 26% compared with solitary pneumonia. When translating the cut-off for CRP found for empyema to the study population, empyema could be directly ruled out based on blood CRP levels in 26% of pneumonia patients (192 out of 739 patients). For the group with pleural effusion (with or without empyema) seen on imaging, 10% (12 out of 119) had a CRP < 114 mg/L at admission.

The multiple regression analysis showed that a high blood CRP level was the primary predictor for empyema compared with solitary pneumonia. In addition, COPD appeared protective of empyema (Supplement 4). If empyema was compared with pleural effusion, CRP and the leucocyte count at admission were factors that were positively associated with empyema. However, an ROC curve for blood leucocyte count at admission yielded no cut-off point with an NPV > 90% to rule out empyema in the presence of pleural fluid.

Discussion

This 8.5-year retrospective study in two secondary hospitals and one tertiary hospital in the Netherlands revealed that 30% of all adults with pneumococcal bacteraemia had complicated disease manifestations. Patients with empyema and pleural effusion had significantly higher CRP levels at admission compared to patients with solitary pneumonia. Meningitis cases had a significantly lower CRP level compared to solitary pneumonia patients. Although a low blood CRP level at admission did not exclude complicated disease in general, a CRP level < 114 mg/L at admission could reliably rule out empyema among adult pneumonia patients with an NPV of 93%.

A limitation of the study was that the feasibility of focal puncture and culture was at the discretion of the attending physician.

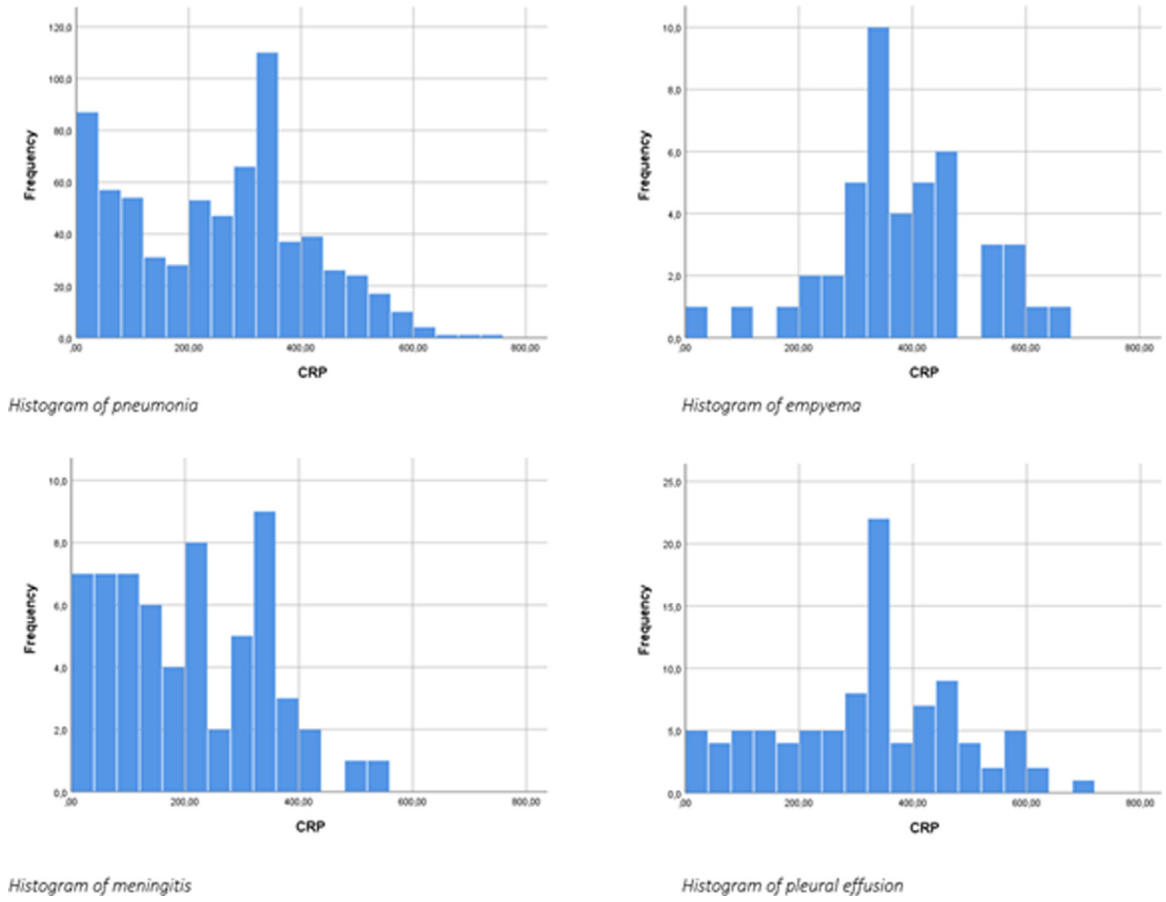

Figure 3. Distribution of C-reactive protein (CRP) for pneumonia, empyema, meningitis and pleural effusion without empyema patients with bacteraemic pneumococcal disease.

The group of patients with pleural effusion but no convincing evidence of empyema may have contained missing cases of empyema. This is one of the reasons why it was analysed as a separate group. Antibiotic treatment duration among patients with pleural effusion was considerably longer compared with solitary pneumonia (16.9 ± 1.6 vs. 9.5 ± 0.3 days). Although the pleural effusion group may have been heterogeneous, proxies of severe disease (ICU admission, hospital stay, mortality and antibiotic treatment duration) were not related to CRP levels – which were generally > 114 mg/L within this group, limiting the impact of potential misclassifications for ruling out empyema. The strengths of this study were the high representativeness of a large population of consecutive patients with proven invasive pneumococcal disease attending three different hospitals over a period of 8.5 years. Furthermore, this was one of the first studies to document CRP as a means of excluding empyema in an adult population.

The adult pneumococcal bacteraemia cohort was comparable to an American study in the beginning of the 21st century, where 85% of adult patients with IPD were diagnosed with pneumonia (Rueda et al., 2010). They found a 30-day mortality of 16.2%, which was comparable with the current 12.0%. The current study found that 16.1% of bacteraemic pneumococcal pneumonia cases developed pleural effusion or empyema (10% and 6.1%, respectively). Also, a Spanish study of 626 adults diagnosed with pneumococcal community-acquired pneumonia (31% bacteraemic) described frequent pleural effusion in 22% of cases, although empyema was confirmed in 2.9% (Cilloniz et al., 2012). The study found that patients with pulmonary complications had a longer length of stay in the hospital and were more often admitted to the ICU, which was also reflected in the current results. For CAP caused by any aetiology, a prospective study by Chalmers et al. showed that 7.2% of patients developed complicated parapneumonic effusion or empyema (Chalmers et al., 2008). These studies suggest that pulmonary complications of pneumonia may be more likely to occur in bacteraemic infection or in cases of pneumococcal aetiology. In line with the current results, another study by Chalmers identified CRP to be the strongest contributor predicting the development of complicated parapneumonic effusion or empyema, and COPD to be protective (Chalmers et al., 2009). An explanation might be that COPD patients consult an expert while their symptoms are still in an early phase and therefore disease can be confined sooner.

CRP is one of the first parameters measured at admission. This is confirmed by the fact that of the initial 956 patients, CRP was not measured in only 32 (3.3%) cases. Among pneumonia patients, a cut-off value of 114 mg/L below which the NPV for empyema was 93% was found. In 26% of pneumonia patients in this study, empyema could have been directly ruled out based on blood CRP levels, and 2% of empyema patients (1 out of 45) would have been missed. If a higher CRP cut-off value would have been chosen, the percentage of low suspects for empyema would have substantially increased. Although this could further decrease additional investigation, it comes at the expense of the NPV. To avoid missed empyema cases, it was felt that the CRP cut-off value of 114 mg/L was the most acceptable.

In the current study, thoracic imaging was readily performed. Of patients with pleural effusion but without confirmed empyema, 10% (12 out of 119 patients) had a CRP < 114 mg/L at admission. Therefore, in the current selection of proven IPD patients, once pleural effusion had been visualized, only a few cases of empyema could have been excluded based on blood CRP levels.

Table 2
General characteristics, parameters at admission, course of disease and comorbidities in bacteraemic patients with pneumococcal disease for solitary pneumonia, empyema, meningitis and pleural effusion without empyema.

	Solitary pneumonia (n = 579)	Empyema (n = 45)	P-value	Meningitis* (n = 62)	P-value	Pleural effusion (n = 74)	P-value
General characteristics of population							
Gender (male)	306 (53)	26 (58)	0.52	35 (57)	0.070	37 (50)	0.71
Age (years)	70 (60-79)	64 (56-75)	0.25	65 (58-73)	0.94	67 (59-79)	0.30
Current smoking	120 (21)	9 (20)	0.67	12 (19)	0.21	19 (26)	0.72
Current alcohol abuse	30 (5)	3 (7)	0.81	9 (15)	**0.004**	4 (5)	0.92
Parameters at admission							
Saturation (%)	94 (91-96)	92 (90-96)	0.17	95 (94-97)	**< 0.001**	93 (88-96)	0.19
Heart rate (bpm)	102 (90-119)	109 (94-121)	0.12	99 (85-113)	0.30	110 (97-121)	0.10
Diastolic blood pressure (mmHg)	68 (58-78)	70 (62-80)	0.19	80 (66-92)	**< 0.001**	66 (56-80)	0.49
Systolic blood pressure (mmHg)	122 (105-140)	120 (108-138)	0.72	148 (124-172)	**<0.001**	119 (100-143)	0.70
Temperature (°C)	38.5 (37.7-39.2)	38.0 (37.4-38.8)	**0.006**	39.2 (38.4-40.0)	**0.001**	38.2 (37.3-39.0)	0.30
CRP (mg/L)	259 (93-346)	363 (311-462)	**<0.001**	200 (87-325)	**0.024**	322 (163-413)	**0.038**
Duration of symptoms before admission (days)	3.0 (1.0-5.0)	4.0 (2.0-5.0)	**0.041**	1.5 (1.0-4.0)	0.092	3.0 (1.0-5.5)	0.78
Leucocyte count (*10^9/L)	145 (96-204)	146 (91.5-239)	0.74	156 (100-216)	0.59	143 (97-192)	0.71
Course of disease							
Length of stay (days)	6 (4-10)	15 (12-21)	**< 0.001**	14 (10-25)	**< 0.001**	10 (6-16)	**0.005**
Mechanical ventilation	47 (8)	12 (27)	**< 0.001**	20 (32)	**< 0.001**	8 (11)	0.44
Admission to ICU	107 (19)	20 (44%)	**< 0.001**	36 (58)	**< 0.001**	20 (27)	0.084
30-day mortality	60 (10)	9 (20)	**0.049**	13 (21)	**0.013**	12 (16)	0.067
Comorbidities							
Liver disease	15 (3)	0	0.27	2 (3)	0.78	1 (1)	0.51
History of cancer	185 (32)	13 (29)	0.64	14 (23)	0.12	15 (20)	**0.035**
Immune suppression	149 (26)	3 (7)	**0.004**	10 (16)	0.091	13 (18)	0.12
COPD	170 (29)	6 (13)	**0.019**	7 (11)	**0.002**	18 (24)	0.34

Data are presented as number (percentage) or median (interquartile range)
CRP: C-reactive protein; ICU: intensive care unit; COPD: chronic obstructive pulmonary disease
* Of which meningitis + pneumonia (n = 12) or meningitis only (n = 50)

Beyond, patient categories that may benefit more from ruling out infectious empyema (directly at presentation) are those with uncertainty about the infectious nature of the disease episode, barriers to pleural fluid aspiration, or those without thoracic imaging at hand. The validity of these findings should be investigated in these populations, especially in low-resource settings where additional factors like nutritional status may influence CRP response dynamics. Furthermore, in time, CRP levels might diverge between patients who do and do not recover without empyema treatment.

Complicated pneumococcal disease manifestations are still very common. C-reactive protein can be used to differentiate between a solitary pneumonia and empyema at admission among adults with bacteraemic pneumococcal pneumonia. Applying these findings may be practical in various settings, for example without imaging at hand. Further prospective studies are needed to validate these findings in populations with larger expected impact on clinical decision-making.

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Conflict of interest statement

The authors declare no conflict of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2021.08.011.

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