Lymphopenia is associated with poor outcomes of patients with community-acquired pneumonia and sepsis

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Viewpoint: Lymphopenia was independently associated with the risk of ICU admission and higher in-hospital and 30-day mortality in patients with CAP and sepsis. Early identification of lymphopenia could help identify septic patients with CAP who require or will shortly require critical care.
Abstract

Background: Lymphopenia is a marker of poor prognosis in patients with community-acquired pneumonia (CAP), yet its impact on outcomes in patients with CAP and sepsis remains unknown. We aim to investigate the impact of lymphopenia on outcomes, risk of ICU admission and mortality in CAP patients with sepsis.

Methods: This was a retrospective, observational study of prospectively collected data from an 800-bed tertiary teaching hospital (2005-2019).

Results: Of the 2,203 patients with CAP and sepsis, 1,347 (61%) did not have lymphopenia, while 856 (39%) did. When compared to the non-lymphopenic group, patients with sepsis and lymphopenia more frequently required intensive care unit (ICU) admission (p=0.001), had a longer hospital length of stay (p<0.001), and presented with a higher rate of in-hospital (p<0.001) and 30-day mortality (p=0.001). Multivariable analysis showed that C-reactive protein ≥15 mg/dL, lymphopenia, pleural effusion and acute respiratory distress syndrome within 24h of admission were risk factors for ICU admission; age ≥80 years was independently associated with decreased ICU admission. In addition, age (≥80 years), chronic renal disease, chronic neurologic disease, nursing home resident, lymphopenia and pleural effusion were independently associated with increased 30-day mortality, whereas pneumococcal vaccination, diabetes mellitus and fever were independently associated with reduced 30-day mortality.

Conclusions: Lymphopenia was independently associated with the risk of ICU admission and higher in-hospital and 30-day mortality in patients with CAP and sepsis. Early identification of lymphopenia could help identify septic patients with CAP who require or will shortly require critical care.

Keywords: sepsis; pneumonia; lymphopenia; infection; outcomes
Introduction

Sepsis presents in approximately one-third of patients with severe community-acquired pneumonia (CAP), and approximately 74% of patients with sepsis present with lymphopenia [1–3]. Our group recently reported a particular immunophenotype of patients with CAP, which we named lymphopenic (<724 lymphocytes/mm³) CAP (L-CAP), and was found to be associated with increased severity and mortality [2]. We also observed that half of the patients with CAP showed lymphopenia upon hospital admission despite no history of immunosuppression [2], with similar findings previously reported [4,5]. L-CAP is characterised by a depletion of CD4+ T lymphocytes, a greater inflammatory response, and low levels of IgG2, which were also correlated with a greater severity in presentation and worse prognosis in patients with CAP [6]. Lymphopenia was also related to severity and poorer outcomes in patients with influenza virus-derived CAP and COVID-19 [7–9]. Lymphopenia was also reported to be an independent predictor of mortality in primary care pneumonia [10]. The same study furthermore showed that a low lymphocyte count (1-2 ×10⁹ cells/L) was associated with an increase in short- and long-term mortality when compared with higher lymphocyte counts[10]. Finally, baseline lymphopenia was reported to be associated with an elevated risk of infections such as pneumonia in the general population [11]. Hence the importance of early identification of CAP patients with lymphopenia [12].

We hypothesize that lymphopenia in patients with CAP and sepsis is associated with higher severity and mortality. Therefore, the objectives of the present study were to investigate the impact of lymphopenia on risk factors for ICU admission and mortality in patients with CAP and sepsis, as well as patient outcomes.
Methods

Study design and patients

This was a retrospective, observational study of data prospectively collected from the Hospital Clinic of Barcelona, Spain. We enrolled all consecutive, adult patients with a diagnosis of CAP admitted to hospital via the emergency department between January 2005 and December 2019. We included patients from nursing homes, as we had demonstrated that microbial aetiology in this population was similar to that of CAP in people residing in their own homes [13]. We excluded patients with severe immunosuppression due, but not limited to, human immunodeficiency viral infection, active solid or haematologic malignancy who received chemotherapy, oral corticosteroid treatment with at least 20 mg of prednisone (or equivalent) per day for at least two weeks, or treatment with other immunosuppressive drugs. We also excluded individuals with active tuberculosis or a confirmed alternative diagnosis. Amongst all subjects with CAP, we selected patients with sepsis and performed a comparison between those with and without lymphopenia.

Patient Consent Statement

For publication purposes, the study was approved by the Ethics Committee of our institution (register: 2009/5451). The need for written informed consent was waived due to the non-interventional study design.

Definitions

Lymphopenic patients were defined as those with <724 lymphocytes/mm$^3$ [2]. Pneumonia (CAP) was defined as the appearance of a new pulmonary infiltrate on chest X-ray during hospitalisation, accompanied by symptoms and signs of a lower respiratory tract infection. Severe CAP was diagnosed by fulfilment of at least one major or three minor criteria per guidelines set by Infectious Disease Society of America/American Thoracic Society.
Polymicrobial pneumonia was defined as pneumonia due to more than one pathogen.

Prior antibiotic treatment was defined as the intake of antibiotics during the week before hospital admission. The appropriateness of empiric antibiotic treatment was determined according to multidisciplinary guidelines for the management of CAP [15].

Sepsis was defined as the presence of pneumonia and an increase of ≥2 points in the Sequential Organ Failure Assessment (SOFA) score per criteria of the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) [16]. The presence of sepsis was evaluated upon hospital admission during diagnosis of CAP. The presence of acute respiratory distress syndrome (ARDS) was evaluated within the first 24h of hospital admission based on the Berlin definition [17].

Data collection, evaluation and microbiologic diagnosis

Demographic variables, comorbidities, and physiologic parameters were collected at the emergency department within 24 hours of admission. The Pneumonia Severity Index (PSI) and SOFA score were calculated at admission [18,19]. We recorded whether patients had specific complications, including multilobar infiltration, pleural effusions, ARDS [17], septic shock [3] and acute renal failure [20] during hospitalisation. Quantification of lymphocytes was performed on blood samples collected in ethylenediaminetetraacetic acid tubes. We used automatic analysers available at the central laboratory following standard operating procedures approved for clinical use. All laboratory data were gathered at the time of patient admission. Further details are reported elsewhere [21]. All surviving patients were visited or contacted by telephone within 30 days of discharge; hospital records and the Catalunya Health Department database were reviewed at the 1-year mark.

Microbiologic diagnosis was performed in respiratory, urinary and blood samples. Blood
cultures, sputum cultures and urine samples for *Streptococcus pneumoniae* and *Legionella pneumophila* antigen detection were obtained within 24 hours of hospital admission. When available, pleural fluid, tracheobronchial aspirates (TBAS) and bronchoalveolar lavage (BAL) samples were collected for Gram and Ziehl-Nielsen staining, and processed for detection of bacterial, fungal and mycobacterial pathogens. Blood samples for serology of atypical pathogens and respiratory virus were collected at admission and thereafter between the third and sixth week.

Cultures were collected before starting empiric antibiotic therapy at the emergency department. Bacterial aetiology was considered definite if one of the following criteria was met: 1) positive blood culture (in the absence of an apparent extra-pulmonary focus); 2) positive bacterial culture of pleural fluid or transthoracic needle aspiration samples; 3) positive urinary antigen for *Legionella pneumophila* (Binax Now *Legionella pneumophila* urinary Antigen Test; Trinity Biotech, Bray, Ireland); 4) positive urinary antigen for *S. pneumoniae* (Binax Now *Streptococcus pneumoniae* urinary Antigen Test; Emergo Europe, The Hague, The Netherlands); 5) bacterial growth in cultures of TBAS (≥10^5 cfu/ml) in protected specimen brush (≥10^3 cfu/ml) or BAL (≥10^4 cfu/ml). More details about microbiologic diagnosis have been reported previously[21].

Respiratory viruses were diagnosed by serology, immunofluorescence assay (IFA), and isolation in cell cultures between 2005 and 2007. However, polymerase chain reaction (PCR) and/or cultures of nasopharyngeal swab samples were used in diagnosis between 2008 and 2019. Two independent, nested, multiplex real-time PCR tests were used to detect human *influenza viruses* (A, B, and C), respiratory syncytial virus, *adenoviruses*, *parainfluenza viruses* (1–4), *coronaviruses* (229E and OC43), *enteroviruses* and *rhinoviruses* (A, B, and C).
Outcomes

The primary outcome was 30-day mortality. Secondary outcomes were in-hospital mortality, ICU admission, ICU mortality and the need for mechanical ventilation.

Statistical analysis

We report the number and percentage of patients for categorical variables; the median (first quartile; third quartile) for continuous variables with non-normal distributions; and the mean (standard deviation) for continuous variables with normal distributions. Categorical variables were compared using the chi-squared test or Fisher’s exact test, whereas continuous variables were compared using the t-test or nonparametric Mann-Whitney U test.

Time to 30-day mortality was analysed by Kaplan–Meier survival curves, which were then compared using the Gehan–Breslow–Wilcoxon test. Univariate and multivariable logistic regression analyses [22] were performed to identify variables associated with ICU admission. Factors showing an association in the univariate analyses (p<0.20) were incorporated into the multivariable regression model. Final variable selection was performed using the backward stepwise selection method (likelihood ratio) (p<0.05, p_out>0.10). Odds ratios (ORs) and their 95% confidence intervals (CIs) were calculated. The Hosmer–Lemeshow goodness-of-fit test was performed to assess the overall fit of the model. Associations with 30-day mortality were also tested by univariate and multivariable analyses, with similar inclusion criteria applied for the Cox regression analysis (p<0.20). Hazard ratios (HRs) and their 95% CIs were calculated. Proportional hazards assumptions were tested with log-minus-log plots. To investigate the fit of the final model, we evaluated deviance residuals. A subgroup analysis also examined 30-day mortality for patients admitted to ICU. Areas under the receiver operating characteristic curve (AUCs) of the
multivariable models were then calculated to predict both ICU admission and 30-day mortality. The internal validity of the prediction models was assessed using ordinary nonparametric bootstrapping with 1,000 bootstrap samples and bias-corrected, accelerated 95% CIs [23]. We used the multiple imputation method [24] for missing data in multivariable analyses. When analysing factors associated with ICU admission and 30-day mortality, we excluded 236 patients with septic shock, as other studies had shown that septic shock was the main risk factor for mortality in patients with severe CAP [25,26]. We also excluded an additional 211 patients who had do-not-resuscitate (DNR) orders.

Additional analyses on patient outcomes were performed considering lymphopenia as a total lymphocyte count <1,000/mm$^3$ and based on lymphocyte quartiles.

Level of significance was set at 0.05 (two-tailed), and all analyses were performed using IBM SPSS Version 25.0 (IBM Corp., Armonk, NY, USA).

**Results**

We identified 4,521 consecutive patients admitted to the emergency department for CAP during the study period, ultimately excluding 2,318 (51%) from the analysis (see Supplementary Figure 1). The final study population therefore comprised 2,203 (49%) patients with CAP and sepsis.

**Comparison of patients with CAP and sepsis, presenting with and without lymphopenia**

Of the 2,203 patients with CAP and sepsis, 1,347 (61%) did not have lymphopenia, while 856 (39%) did. Table 1 summarises demographic and clinical characteristics of patients according to the presence or absence of lymphopenia. When compared to the non-lymphopenic group, patients in the lymphopenic group were more likely to be male, receive inhaled corticosteroids less often, have a lower rate of influenza vaccination, and present with more chronic respiratory diseases and prior malignancies as comorbidities. Additionally,
lymphopenic patients showed higher C-reactive protein and creatinine levels, as well as lower neutrophil and overall white blood cell counts within 24 hours of hospital admission. The lymphopenic group also presented with higher rates of severe CAP, bacteraemia, multilobar infiltration and septic shock.

An aetiologic diagnosis was achieved more often in the lymphopenic group (47% vs. 39%; p<0.001). Atypical pathogens were more frequently detected in the non-lymphopenic group (2% vs. 6%; p=0.001); *Legionella pneumophila* was more common in the lymphopenic group (7% vs. 3%, p=0.022) than in the non-lymphopenic group.

Data were available for empiric antibiotic treatment in 2,149 (98%) patients. The most frequent regimens were β-lactam plus fluoroquinolone (32%) and β-lactam plus macrolide (28%). No differences in empiric antibiotic therapy were present between groups, except for a more frequent administration of fluoroquinolones in monotherapy in the non-lymphopenic group (23% vs. 15%, p<0.001). Inappropriate empiric antibiotic therapy rates were comparable (5% and 5%; p=0.756).

**Outcomes of patients with CAP and sepsis, presenting with and without lymphopenia**

Patients with lymphopenia required ICU admission more frequently (25% vs. 32%; p=0.001); had a longer hospital length of stay (8 days vs. 9 days; p<0.001); and presented with a higher in-hospital (8% vs. 12%; p<0.001) and 30-day mortality (8% vs. 12%; p=0.001). (Table 2). Per the presence or absence of lymphocytopenia, Kaplan–Meier curves for 30-day survival in the entire population and in the sub-group of ICU patients are shown in Figures 1 and 2, respectively.

When lymphopenia was defined as <1,000/mm³, it was associated with a longer length of hospital stay, and higher in-hospital and 30-day mortality rates (Supplementary Table 1). We also analysed patient outcomes according to lymphocyte quartiles (<531 vs. 531-874.4 vs. 874.4-1,000 vs. ≥1,000/mm³).
874.4-1,350 vs. ≥1,350 lymphocytes/mm$^3$) (Supplementary Table 2). In relation to lymphocyte quartiles, Kaplan–Meier survival curves for 30-day mortality in the entire population and in the sub-group of ICU patients are shown in Supplementary Figures 2 and 3, respectively. Similar outcomes according to lymphocyte quartiles were observed amongst patients.

**Risk factors for ICU admission in patients with CAP and sepsis**

The univariate logistic regression analysis identified several variables significantly associated with ICU admission in patients with CAP and sepsis (Table 3). In the multivariable analysis, C-reactive protein ≥15 mg/dL, lymphopenia, pleural effusion and ARDS were risk factors for ICU admission in patients with sepsis, while age ≥80 years were independently associated with decreased ICU admission. The AUC was 0.70 (95% CI 0.67 to 0.73) for the predictive model of ICU admission. Internal validation of the final model was conducted with a bootstrapping procedure with 1,000 samples, demonstrating robust results inasmuch as all variables remained significant with small 95% CIs around the original coefficients.

When using <1,000 lymphocytes/mm$^3$ as a cut-off for lymphopenia, the latter was not found to be a risk factor for ICU admission (Supplementary Table 3). Conversely, the analysis according to lymphocyte quartile showed that presenting with lymphocyte counts below 531 lymphocytes/mm$^3$ constituted a risk factor for ICU admission (Supplementary Table 4).

**Factors associated with 30-day mortality in patients with CAP and sepsis**

In the multivariable analysis (Table 4), age (≥80 years), chronic renal disease, chronic neurologic disease, nursing home resident, lymphopenia and pleural effusion were independently associated with an increased 30-day mortality, while pneumococcal vaccine, diabetes mellitus and fever were independently associated with a decreased 30-day mortality. The AUC was 0.59 (95% CI 0.53 to 0.66) for the multivariable model of 30-day
mortality. In the subgroup of patients requiring ICU admission, age (≥80 years), chronic respiratory disease, chronic liver disease, lymphopenia and acute renal failure were factors associated with 30-day mortality (AUC 0.68 [95% CI 0.56 to 0.81]) (Table 5). Internal validation demonstrated robust results for all included variables in both multivariable models, with small 95% CIs around the original coefficients. In an additional analysis of factors associated with the risk of 30-day mortality, lymphopenia with a cut-off of <1,000 lymphocytes/mm$^3$ was not a risk factor for such mortality in the entire population and in the sub-group of ICU patients (Supplementary Tables 5 and 6). However, when we repeated the analysis including the variable according to lymphocyte quartiles, lymphopenia (<531 lymphocytes/mm$^3$) was a risk factor for 30-day mortality in the entire population, yet not in the sub-group of ICU patients (Supplementary Tables 7 and 8).

**Discussion**

In this large cohort of hospitalised patients with CAP and sepsis, when compared with non-lymphopenia patients, we found that lymphopenia was associated with an increased risk of ICU admission, mechanical ventilation, longer length of stay, and in-hospital and 30-day mortality. We further found that 39% of patients with CAP and sepsis had lymphopenia, and such a high percentage is suggestive of lymphopenia being associated to a more severe clinical presentation of CAP.

The observation that lymphopenia was associated with a higher 30-day mortality in our study population is in accordance with a prior study that evaluated the usefulness of lymphopenia in predicting the short-term outcome of patients with sepsis [27]. Authors found that lymphopenia was independently associated with an increased 28-day mortality and a significantly higher requirement for ICU admission [27]. Prior, Drewry et al. [28] had studied 335 adult patients with bacteraemia and sepsis and reported that the median
lymphocyte count on day 4 after admission was an independent variable predictor for 28-day mortality. More recently, Wagner et al.[29] found a significant association between lymphocytopenia and disease severity in patients with COVID-19, being later validated in further studies and meta-analyses [30]. When we used lymphopenia at a cut-off of <1000 lymphocytes/mm³, it was associated with higher in-hospital and 30-day mortality; however, it was not a risk factor for ICU admission [2]. Lymphopenia values lower than 1000/mm³ are perhaps more accurate when considering the number of lymphocytes for prediction of different outcomes in CAP.

The main hypothesis presented by most investigators to explain the association between lymphopenia and disease severity in CAP is a deregulated immune response to infection, including the activation of different immune cells, secretion of various cytokines and subsequent activation of cellular apoptosis mechanisms (both intrinsic and extrinsic pathways) so as to cause impaired inflammatory responses [31,32]. Such a deregulated immune response would favour uncontrolled lymphocyte migration to the lungs and extra-pulmonary tissues alongside with apoptosis, and lead to secondary lymphopenia and its subsequent persistence [33,34]. These mechanisms might therefore place patients in a state of immunosuppression, leading to an increased risk of further severity and higher mortality. However, an accurate understanding of the mechanisms underlying lymphopenia is still lacking. The massive migration of lymphocytes to the lung, the adhesion to the vascular endothelium, the impaired production in the bone marrow, and an increase in apoptosis pathways during the acute phase of pneumonia may contribute to lymphopenia [8]. Immunosenescence—comprising a set of changes occurring in peripheral T lymphocytes—and the presence of chronic comorbidities may induce chronic endothelial dysfunction that could help explain lymphopenia in an elderly population with severe COVID-19 [35–37].
In addition, elevated levels of C-reactive protein, pleural effusion and ARDS were associated with the risk of ICU admission. This is in accordance with previous studies that reported an association between these variables, treatment failure and increased need for critical care in patients with CAP [38–40]. In our study, age (≥ 80 years) was associated with a lower risk of ICU admission, thus reflecting the controversial and clinically difficult decision-making process held when considering ICU admission in elderly patients. Frailty, larger burdens of comorbidities, and relatively scant studies evaluating the prognosis of very old patients with CAP admitted to the ICU are some of the major underlying causes of such complex clinical scenarios [41,42],[43].

On the other hand, pneumonia due to atypical pathogens, mostly occurs in young patients with few comorbidities and has milder clinical presentation. The fact that in our study, atypical pathogens were more frequently detected in non-lymphopenic patients, who indeed were younger and had less comorbidities, confirms prior observations [44,45]. Inversely, we observed that L. pneumophila was most commonly detected in lymphopenic patients, which is consistent with Legionella usually causing rapidly progressive and severe forms of pneumonia [46,47].

Age (≥80 years), chronic renal disease, chronic neurologic disease, nursing home resident, and pleural effusion were independently associated with increased 30-day mortality in the overall cohort. Meanwhile, in the subgroup of patients requiring ICU admission, age (≥80 years), chronic respiratory disease, chronic liver disease, lymphopenia and acute renal failure were associated with 30-day mortality. Most of these factors except lymphopenia are already well-known risk factors of mortality and severity in patients with CAP and sepsis, e.g. the PSI score include many of them. Furthermore, advanced age, residing in a nursing
home, and chronic renal and neurologic diseases favour the development of delirium in sepsis, which is associated with a prolonged hospital length of stay and increased mortality [48,49]. However, the role of lymphopenia as a risk factor of mortality in CAP with sepsis is a novel finding. Additionally, we found that previous pneumococcal vaccination, diabetes mellitus and fever were associated with a lower risk of 30-day mortality. The impact of diabetes mellitus on the outcomes of patients with sepsis remains controversial. In a study carried out in the Netherlands, no significant differences were found in short- or long-term outcomes, inflammatory biomarker levels, coagulation factor, or endothelial activation when comparing mortality in 241 diabetic and 863 non-diabetic patients with sepsis [50]. Another large study including 1.5 million critically ill patients suggested that diabetes may have a protective effect [51]. The reason could be related to a greater tolerance of sustained levels of moderate hyperglycaemia, as well as better adaptability to marked fluctuations in blood glucose levels in patients with diabetes. On the other hand, with an increased likelihood of multiorgan dysfunction, patients without diabetes may be at a disadvantage due to a compromised immune response and altered microvasculature [52]. With respect to vaccinations, *S. pneumoniae* is well known to be the main bacterial pathogen in patients with CAP and sepsis. This, therefore, highlights the importance of vaccinations in pneumonia and sepsis prevention.

Our study has some limitations, though, beginning with its retrospective nature. However, data of all patients included were collected consecutively and prospectively per our study protocol in CAP. Secondly, the study was carried out in a single-centre teaching hospital in Spain. The identified cut-off for lymphopenia validated in our centre should be confirmed and validated in future studies to increase external validity.
In conclusion, patients with CAP and sepsis presenting with lymphopenia have higher rates of ICU admission and mortality. It is, therefore, critical to identify lymphopenia in hospitalised patients with CAP and sepsis, as lymphopenia might serve to prioritise patients with CAP and sepsis who require or will shortly require critical care. Moreover, early identification of lymphopenia could impact in the treatment optimisation and the need for complementary treatments with immune modulators and drug-inducing expansion of lymphocyte counts [53,54]. Lastly, including lymphocyte count in bundles of care for patients with CAP might be an appropriate way of improving management of such patients.
Funding: This study was supported by CIBER de Enfermedades Respiratorias (CIBERES CB06/06/0028), and by 2009 Support to Research Groups of Catalonia 911, IDIBAPS. Dr Cillóniz is the recipient of the SEPAR fellowship 2018, and a grant from the Fondo de Investigación Sanitaria (PI19/00207). The sponsor had no role in the design of the study, collection and analysis of the data, or preparation of the manuscript.

Conflict of interest: The authors declare that they have no conflicts of interest.

Acknowledgments: We are indebted to all participating medical and nursing colleagues for their assistance and cooperation in this study. Thank you to Anthony Armenta for providing medical editing assistance for the manuscript at hand.
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Figure Legend

Figure 1. Kaplan-Meier survival curves for 30-day mortality in patients with CAP and sepsis in relation to their lymphocyte counts (<724 vs. ≥724 lymphocytes/mm$^3$)

Figure 2. Kaplan-Meier survival curves for 30-day mortality in ICU patients with CAP and sepsis in relation to their lymphocyte counts (<724 vs. ≥724 lymphocytes/mm$^3$)
Table 1. Characteristics of patients with CAP and sepsis according to the presence or absence of lymphopenia

| Variable                                           | No (n = 1,347) | Yes (n = 856) | P-value |
|----------------------------------------------------|----------------|---------------|---------|
| Lymphopenia (<724 lymphocytes/mm³)                 |                |               |         |
| Age, mean (SD), years                              | 72.1 (15.8)    | 72.4 (16.3)   | 0.303   |
| Male sex, n (%)                                    | 830 (62)       | 583 (68)      | 0.002   |
| Current smoker, n (%)                              | 262 (20)       | 157 (19)      | 0.555   |
| Current alcohol user, n (%)                        | 188 (14)       | 107 (13)      | 0.353   |
| Previous antibiotic in last week, n (%)            | 297 (23)       | 165 (20)      | 0.117   |
| Influenza vaccine, n (%)                           | 635 (53)       | 329 (45)      | <0.001  |
| Pneumococcal vaccine, n (%)                        | 236 (20)       | 151 (21)      | 0.758   |
| Previous inhaled corticosteroids, n (%)            | 308 (23)       | 155 (18)      | 0.007   |
| Previous systemic corticosteroids, n (%)           | 72 (6)         | 41 (5)        | 0.569   |
| Prior pneumonia (last year), n (%)                 | 192 (15)       | 123 (15)      | 0.843   |
| Comorbidities, n (%)                               | 1,020 (76)     | 630 (74)      | 0.203   |
| Chronic respiratory disease                        | 570 (43)       | 324 (39)      | 0.048   |
| Chronic cardiovascular disease                     | 232 (17)       | 123 (14)      | 0.079   |
| Diabetes mellitus                                  | 347 (26)       | 212 (25)      | 0.685   |
| Chronic neurologic disease                         | 295 (23)       | 174 (21)      | 0.284   |
| Chronic renal disease                              | 129 (10)       | 84 (10)       | 0.859   |
| Chronic liver disease                              | 65 (5)         | 44 (5)        | 0.728   |
| Previous malignancy                                | 93 (7)         | 107 (13)      | <0.001  |
| Nursing home resident, n (%)                       | 139 (10)       | 85 (10)       | 0.799   |
| Dyspnoea, n (%)                                    | 1,010 (77)     | 611 (73)      | 0.066   |
| Variable                                      | No (n = 1,347) | Yes (n = 856) | P-value |
|-----------------------------------------------|----------------|---------------|---------|
| Pleuritic pain, n (%)                         | 420 (32)       | 238 (29)      | 0.119   |
| Fever, n (%)                                  | 953 (72)       | 616 (73)      | 0.468   |
| Deterioration in sensorium, n (%)             | 374 (28)       | 221 (26)      | 0.328   |
| Respiratory rate, median (Q1; Q3), breaths/min| 24 (21; 32)    | 24 (21; 32)   | 0.632   |
| C-reactive protein, median (Q1; Q3), mg/dL    | 17.7 (8.9; 26.7)| 19.5 (8.8; 28.8)| 0.012   |
| Neutrophils, median (Q1; Q3), cells/mm³      | 11.4 (8.1; 16.3)| 7.9 (3.8; 12.3)| <0.001  |
| Creatinine, median (Q1; Q3), mg/dL           | 1.2 (0.9; 1.6) | 1.3 (0.9; 1.7) | 0.024   |
| White blood cell count, median (Q1; Q3), cells/mm³| 14.2 (10.3; 19.6)| 9.3 (4.9; 13.7)| <0.001  |
| PSI risk class IV–V, n (%)                    | 634 (67)       | 401 (72)      | 0.053   |
| Severe CAP, n (%)                             | 407 (38)       | 330 (49)      | <0.001  |
| Bacteraemia, n (%)                            | 97 (10)        | 138 (21)      | <0.001  |
| Pleural effusion, n (%)                       | 182 (14)       | 118 (14)      | 0.789   |
| Multilobar infiltration, n (%)                | 363 (27)       | 273 (32)      | 0.013   |
| Acute respiratory distress syndrome, n (%)    | 83 (6)         | 68 (8)        | 0.106   |
| Acute renal failure, n (%)                    | 471 (36)       | 322 (38)      | 0.183   |
| Septic shock, n (%)                           | 129 (10)       | 107 (13)      | 0.028   |
| Do-not-resuscitate order, n (%)               | 121 (9)        | 90 (11)       | 0.162   |
| Empiric antibiotic therapy, n (%)             |                |               |         |
| Monotherapy                                   |                |               | <0.001  |
| Fluoroquinolones                              | 305 (23)       | 126 (15)      | <0.001  |
| β-lactams                                     | 121 (9)        | 76 (9)        | 0.933   |
| Other therapy                                 | 6 (0.4)        | 3 (0.3)       | >0.999  |
| Combination therapies                         | 882 (67)       | 630 (75)      | <0.001  |
| β-lactams plus fluoroquinolones               | 402 (31)       | 284 (34)      | 0.098   |
| β-lactams plus macrolides                     | 358 (27)       | 254 (30)      | 0.112   |
| Variable                              | No   | Yes   | P-value |
|--------------------------------------|------|-------|---------|
|                                      | (n = 1,347) | (n = 856) |         |
| Other combination therapies          | 122 (9) | 92 (11) | 0.191   |
| Appropriate empiric treatment, n (%) | 1,123 (95) | 699 (95) | 0.756   |

Abbreviations: CAP, community-acquired pneumonia; PSI, pneumonia severity index; Q1, first quartile; Q3, third quartile; SD, standard deviation. Percentages calculated with non-missing data only. a May have >1 comorbid condition. b Stratified according to 30-day mortality risk for CAP: classes I–III (≤90 points) had low mortality risk while classes IV–V (>90 points) had the highest mortality risk. c Calculated only for patients with blood samples (983 patients in the non-lymphopenic group and 673 patients in the lymphopenic group were used to calculate percentages).
### Table 2. Clinical outcomes according to lymphopenia in patients with CAP and sepsis

| Variable                        | Lymphopenia (<724 lymphocytes/mm³) | No (n = 1,347) | Yes (n = 856) | P-value |
|--------------------------------|------------------------------------|----------------|---------------|---------|
| Hospital length of stay, median (Q1; Q3), days | 8 (6; 13) | 9 (6; 15) | <0.001 |
| In-hospital mortality, n (%) | 104 (8) | 105 (12) | <0.001 |
| ICU admission, n (%) | 340 (25) | 270 (32) | 0.001 |
| ICU mortality, n (%)<sup>a</sup> | 26 (8) | 24 (9) | 0.579 |
| Mechanical ventilation, n (%)<sup>b</sup> | 84 (7) | 67 (10) | 0.118 |
| Non-invasive | 103 (9) | 76 (11) | 0.245 |
| Invasive | 103 (8) | 101 (12) | 0.001 |
| 30-day mortality, n (%) | 103 (8) | 101 (12) | 0.001 |

Abbreviations: ICU, intensive care unit; Q1, first quartile; Q3, third quartile. <sup>a</sup> Calculated only for patients admitted to the ICU (340 patients in the non-lymphopenic group and 270 patients in the lymphopenic group were used to calculate the percentages). <sup>b</sup> Patients who received non-invasive ventilation initially but later needed subsequent intubation were included in the invasive mechanical ventilation group.
Table 3. Univariate logistic regression analysis for variables associated with ICU admission and independent predictors of ICU admission determined by multivariable logistic regression analysis (N = 1,664)\textsuperscript{a}

| Variable                                                      | Univariate |           | Multivariable |           |
|---------------------------------------------------------------|------------|-----------|---------------|-----------|
|                                                               | OR         | 95% CI    | P-value       | OR        | 95% CI    | P-value |
| Age ≥80 years                                                 | 0.32       | 0.24 to 0.42 | <0.001       | 0.31       | 0.23 to 0.41 | <0.001 |
| Male sex                                                      | 1.33       | 1.04 to 1.71 | 0.024        | -         | -         | -       |
| Previous inhaled corticosteroids                              | 0.98       | 0.74 to 1.29 | 0.884        | -         | -         | -       |
| Previous systemic corticosteroids                             | 1.16       | 0.66 to 2.03 | 0.606        | -         | -         | -       |
| Antibiotic use in the last week                               | 0.90       | 0.68 to 1.19 | 0.442        | -         | -         | -       |
| Chronic respiratory disease                                  | 0.96       | 0.76 to 1.21 | 0.708        | -         | -         | -       |
| Chronic cardiovascular disease                                | 0.76       | 0.54 to 1.05 | 0.099        | -         | -         | -       |
| Chronic renal disease                                         | 0.63       | 0.40 to 0.99 | 0.046        | -         | -         | -       |
| Chronic liver disease                                         | 1.16       | 0.67 to 2.00 | 0.593        | -         | -         | -       |
| Diabetes mellitus                                             | 0.85       | 0.65 to 1.11 | 0.224        | -         | -         | -       |
| Chronic neurologic disease                                   | 0.63       | 0.46 to 0.87 | 0.005        | -         | -         | -       |
| Previous pneumonia                                           | 0.70       | 0.49 to 0.99 | 0.043        | -         | -         | -       |
| Nursing home resident                                         | 0.62       | 0.39 to 0.99 | 0.044        | -         | -         | -       |
| Fever                                                         | 0.91       | 0.70 to 1.18 | 0.474        | -         | -         | -       |
| Deterioration in sensorium                                    | 0.90       | 0.68 to 1.19 | 0.464        | -         | -         | -       |
| C-reactive protein ≥15 mg/dL                                  | 1.55       | 1.21 to 1.98 | <0.001       | 1.39       | 1.07 to 1.79 | 0.012 |
| Lymphopenia (<724 lymphocytes/mm\textsuperscript{3})         | 1.32       | 1.04 to 1.67 | 0.022        | 1.37       | 1.07 to 1.76 | 0.013 |
| Pleural effusion                                              | 1.85       | 1.35 to 2.53 | <0.001       | 1.81       | 1.30 to 2.52 | <0.001 |
| Acute respiratory distress syndrome                           | 5.74       | 3.63 to 9.09 | <0.001       | 6.14       | 3.78 to 9.96 | <0.001 |
| Variable                        | Univariate |         |         | Multivariable |
|--------------------------------|------------|---------|---------|---------------|
|                                | OR         | 95% CI  | P-value | OR            | 95% CI | P-value |
| Acute renal failure\(^c\)     | 1.22       | 0.96 to 1.55 | 0.108  | -             | -      | -       |
| Streptococcus pneumoniae      | 1.36       | 1.03 to 1.79 | 0.033  | -             | -      | -       |
| Respiratory virus             | 1.23       | 0.85 to 1.77 | 0.267  | -             | -      | -       |

Abbreviations: CI, confidence interval; OR, odds ratio. Data are shown as estimated ORs (95% CIs) of the explanatory variables in the sepsis group. The OR represents the odds that the presence of ICU admission will occur given exposure of the explanatory variable, compared to the odds of the outcome occurring in the absence of that exposure. The P-values are based on the null hypothesis that all ORs relating to an explanatory variable equal unity (no effect). \(^a\) Excluded 236 patients with septic shock, 34 patients with missing data regarding septic shock, 211 patients who had do-not-resuscitate orders and 58 with missing data regarding a do-not-resuscitate order. \(^b\) Hosmer–Lemeshow goodness-of-fit test, \(p=0.597\). \(^c\) Variable highly correlated with another independent variable and therefore not included in the multivariable model.
Table 4. Univariate Cox regression analysis for variables associated with 30-day mortality and independent predictors of 30-day mortality determined by multivariable Cox regression analysis (N = 1,664)\(^a\)

| Variable                                | Univariate |              |          | Multivariable |              |          |
|-----------------------------------------|------------|--------------|----------|---------------|--------------|----------|
|                                         | HR         | 95% CI       | P-value  | HR            | 95% CI       | P-value  |
| Age ≥80 years                            | 3.99       | 2.55 to 6.24 | <0.001   | 2.87          | 1.80 to 4.57 | <0.001   |
| Male sex                                | 1.12       | 0.73 to 1.73 | 0.596    | -             | -            | -        |
| Influenza vaccine                       | 0.89       | 0.59 to 1.33 | 0.565    | -             | -            | -        |
| Pneumococcal vaccine                    | 0.57       | 0.31 to 1.05 | 0.071    | 0.49          | 0.27 to 0.92 | 0.025    |
| Previous inhaled corticosteroids        | 1.31       | 0.83 to 2.05 | 0.247    | -             | -            | -        |
| Previous systemic corticosteroids       | 0.75       | 0.24 to 2.36 | 0.620    | -             | -            | -        |
| Antibiotic use in the last week         | 1.21       | 0.77 to 1.92 | 0.408    | -             | -            | -        |
| Chronic respiratory disease             | 1.00       | 0.67 to 1.51 | 0.993    | -             | -            | -        |
| Chronic cardiac disease                 | 1.57       | 0.97 to 2.53 | 0.064    | -             | -            | -        |
| Chronic renal disease                   | 2.78       | 1.69 to 4.55 | <0.001   | 2.64          | 1.59 to 4.38 | <0.001   |
| Chronic liver disease                   | 0.97       | 0.36 to 2.65 | 0.956    | -             | -            | -        |
| Diabetes mellitus                       | 0.48       | 0.27 to 0.85 | 0.011    | 0.42          | 0.24 to 0.75 | 0.003    |
| Chronic neurologic disease              | 3.33       | 2.12 to 5.00 | <0.001   | 2.48          | 1.61 to 3.81 | <0.001   |
| Previous pneumonia                      | 0.88       | 0.49 to 1.58 | 0.663    | -             | -            | -        |
| Nursing home resident                   | 3.56       | 2.21 to 5.74 | <0.001   | 2.17          | 1.31 to 3.61 | 0.003    |
| Fever                                   | 0.44       | 0.30 to 0.67 | <0.001   | 0.49          | 0.32 to 0.73 | 0.001    |
| Deterioration in sensorium              | 1.99       | 1.31 to 3.02 | 0.001    | -             | -            | -        |
| C-reactive protein ≥15 mg/dL            | 0.72       | 0.48 to 1.08 | 0.111    | -             | -            | -        |
| Lymphopenia (<724 lymphocytes/mm\(^3\)) | 1.73       | 1.15 to 2.59 | 0.008    | 1.94          | 1.29 to 2.93 | 0.001    |
| Pleural effusion                        | 1.81       | 1.10 to 2.97 | 0.018    | 1.90          | 1.15 to 3.14 | 0.013    |
| Acute respiratory distress syndrome     | 1.63       | 0.76 to 3.53 | 0.211    | -             | -            | -        |

\(^a\) doi: 10.1093/ofid/ofab169/6209395
| Variable                              | HR  | 95% CI       | P-value | HR  | 95% CI       | P-value |
|--------------------------------------|-----|--------------|---------|-----|--------------|---------|
| Acute renal failure \(^b\)           | 2.72| 1.81 to 4.09 | <0.001  | -   | -            | -       |
| Appropriate empiric antibiotic       | 0.99| 0.36 to 2.68 | 0.977   | -   | -            | -       |
| treatment                            |     |              |         |     |              |         |
| *Streptococcus pneumoniae*           | 1.05| 0.64 to 1.74 | 0.846   | -   | -            | -       |
| Respiratory virus                    | 0.68| 0.32 to 1.48 | 0.334   | -   | -            | -       |

Abbreviations: CI, confidence interval; HR, hazard ratio. Data are shown as estimated HRs (95% CIs) of the explanatory variables in the 30-day mortality group. The HR is defined as the ratio of the hazard rates corresponding to the conditions described by two levels of an explanatory variable (the hazard rate is the risk of death [i.e., the probability of death], given that the patient has survived up to a specific time). The P-value is based on the null hypothesis that all HRs relating to an explanatory variable equal unity (no effect). \(^a\) Excluded 236 patients with septic shock, 34 patients with missing data regarding septic shock, 211 patients who had do-not-resuscitate orders and 58 with missing data regarding a do-not-resuscitate order. \(^b\) Variable highly correlated with another independent variable and therefore not included in the multivariable model.
Table 5. Univariate Cox regression analysis for variables associated with 30-day mortality and independent predictors of 30-day mortality determined by multivariable Cox regression analysis in ICU patients (N = 368)\textsuperscript{a}

| Variable                              | Univariate | Multivariable |
|---------------------------------------|------------|---------------|
|                                       | HR         | 95% CI        | P-value | HR         | 95% CI        | P-value |
| Age ≥80 years                          | 5.49       | 2.31 to 13.03 | <0.001  | 6.75       | 2.60 to 17.50 | <0.001  |
| Male sex                              | 0.71       | 0.30 to 1.72  | 0.452   | -          | -             | -       |
| Influenza vaccine                     | 1.00       | 0.41 to 2.40  | 0.992   | -          | -             | -       |
| Pneumococcal vaccine                  | 0.58       | 0.13 to 2.47  | 0.457   | -          | -             | -       |
| Previous inhaled corticosteroids      | 2.17       | 0.90 to 5.24  | 0.084   | -          | -             | -       |
| Previous systemic corticosteroids     | 2.20       | 0.51 to 9.43  | 0.290   | -          | -             | -       |
| Antibiotic use in the last week       | 1.46       | 0.57 to 3.76  | 0.435   | -          | -             | -       |
| Chronic respiratory disease           | 2.32       | 0.96 to 5.60  | 0.061   | 2.61       | 1.08 to 6.33  | 0.033   |
| Chronic cardiac disease               | 2.58       | 1.00 to 6.65  | 0.050   | -          | -             | -       |
| Chronic renal disease                 | 3.66       | 1.23 to 10.88 |        | 0.020      | -             | -       |
| Chronic liver disease                 | 3.46       | 1.02 to 11.75 | 0.047   | 8.53       | 2.18 to 33.48 | 0.002   |
| Diabetes mellitus                     | 1.00       | 0.36 to 2.72  | 0.993   | -          | -             | -       |
| Chronic neurologic disease            | 1.89       | 0.69 to 5.15  | 0.216   | -          | -             | -       |
| Previous pneumonia                    | 0.77       | 0.18 to 3.32  | 0.729   | -          | -             | -       |
| Nursing home resident                 | 1.75       | 0.41 to 7.53  | 0.450   | -          | -             | -       |
| Fever                                 | 1.27       | 0.47 to 3.48  | 0.637   | -          | -             | -       |
| Deterioration in sensorium            | 1.43       | 0.56 to 3.70  | 0.456   | -          | -             | -       |
| C-reactive protein ≥15 mg/dL          | 0.54       | 0.23 to 1.27  | 0.157   | -          | -             | -       |
| Variable                              | Univariate |           |           | Multivariable |           |           |
|--------------------------------------|------------|-----------|-----------|---------------|-----------|-----------|
|                                      | HR         | 95% CI    | P-value   | HR            | 95% CI    | P-value   |
|                                      |            |           |           |               |           |           |
| Lymphopenia (<724 lymphocytes/mm$^3$) | 2.30       | 0.95 to 5.55 | 0.064     | 2.57          | 1.06 to 6.24 | 0.037     |
| Pleural effusion                     | 1.32       | 0.48 to 3.61 | 0.586     | -             | -         | -         |
| Acute respiratory distress syndrome  | 1.15       | 0.34 to 3.90 | 0.825     | -             | -         | -         |
| Acute renal failure                  | 3.66       | 1.48 to 9.06 | 0.005     | 3.52          | 1.38 to 8.95 | 0.008     |
| Appropriate empiric antibiotic treatment | 1.62      | 0.22 to  |           | 0.637         | -         | -         |
|                                      |            | 12.08     |           |               |           |           |
| *Streptococcus pneumoniae*          | 1.32       | 0.51 to 3.41 | 0.562     | -             | -         | -         |
| Respiratory virus                    | 0.36       | 0.05 to 2.70 | 0.322     | -             | -         | -         |

Abbreviations: CI, confidence interval; HR, hazard ratio. Data are shown as estimated HRs (95% CIs) of the explanatory variables in the 30-day mortality group. The HR is defined as the ratio of the hazard rates corresponding to the conditions described by two levels of an explanatory variable (the hazard rate is the risk of death [i.e., the probability of death], given that the patient has survived up to a specific time). The P-value is based on the null hypothesis that all HRs relating to an explanatory variable equal unity (no effect). a Excluded 187 patients with septic shock, 11 patients with missing data regarding septic shock, 30 patients who had do-not-resuscitate orders and 27 with missing data regarding a do-not-resuscitate order.
Figure 1

The graph shows the proportion of patients surviving over days. The survival rates for <724 cells/mm³ and ≥724 cells/mm³ are compared using the Gehan-Breslow-Wilcoxon test. The p-value is 0.007, indicating a statistically significant difference between the two groups.
Figure 2

Proportion of patients surviving (%)

\( p = 0.055 \) by Gehan-Breslow-Wilcoxon test

- \(< 724 \text{ cells/mm}^3\)
- \( \geq 724 \text{ cells/mm}^3\)

Days