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MAJOR ARTICLE

Lymphopenia Is Associated With Poor Outcomes of Patients With Community-Acquired Pneumonia and Sepsis

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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 intensive care unit (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 2203 patients with CAP and sepsis, 1347 (61%) did not have lymphopenia, while 856 (39%) did. When compared with the nonlymphopenic group, patients with sepsis and lymphopenia more frequently required ICU admission ($P = .001$), had a longer hospital length of stay ($P < .001$), and presented with a higher rate of in-hospital ($P < .001$) and 30-day mortality ($P = .001$). Multivariable analysis showed that C-reactive protein ≥15 mg/dL, lymphopenia, pleural effusion, and acute respiratory distress syndrome within 24 hours 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, being a 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 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. infection; lymphopenia; outcomes; pneumonia; sepsis.

Sepsis presents in approximately one-third of patients with severe community-acquired pneumonia (CAP), and ~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/mm^3) CAP (L-CAP); this immunotype 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 characterized by a depletion of CD4+ T lymphocytes, a greater inflammatory response, and low levels of IgG2, which were also correlated with 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 coronavirus disease 2019 (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 × 10^9 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.

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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 the hospital via the emergency department between January 2005 and December 2019. We included patients from nursing homes, as we had demonstrated that microbial etiology in this population was similar to that of CAP in people residing in their own homes [13]. We excluded patients with severe immunosuppression due to, but not limited to, human immunodeficiency viral infection, active solid or hematologic malignancy who received chemotherapy, oral corticosteroid treatment with at least 20 mg of prednisone (or equivalent) per day for at least 2 weeks, or treatment with other immunosuppressive drugs. We also excluded individuals with active tuberculosis or a confirmed alternative diagnosis. Among 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 noninterventional 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 hospitalization, accompanied by symptoms and signs of a lower respiratory tract infection. Severe CAP was diagnosed by fulfilment of at least 1 major or 3 minor criteria per guidelines set by Infectious Disease Society of America/American Thoracic Society (IDSA/ATS) [14]. Polymicrobial pneumonia was defined as pneumonia due to >1 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 24 hours 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 hospitalization. Quantification of lymphocytes was performed on blood samples collected in ethylenediaminetetraacetic acid tubes. We used automatic analyzers 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 weeks.

Cultures were collected before starting empiric antibiotic therapy at the emergency department. Bacterial etiology was considered definite if 1 of the following criteria was met: (1) positive blood culture (in the absence of an apparent extrapulmonary 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-square test or Fisher exact test, whereas continuous variables were compared using the *t* test or nonparametric Mann-Whitney *U* test.

Time to 30-day mortality was analyzed 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 ($P < .20$) were incorporated into the multivariable regression model. Final variable selection was performed using the backward stepwise selection method (likelihood ratio) ($P_{in} < .05$; $P_{out} > .10$). Odds ratios (ORs) and their 95% 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 ($P < .20$). 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 the ICU. Areas under the receiver operating characteristic curve (AUC) 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 1000 bootstrap samples and bias-corrected, accelerated 95% CIs [23]. We used the multiple imputation method [24] for missing data in multivariable analyses. When analyzing 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 $<1000/mm^3$ and based on lymphocyte quartiles.

The level of significance was set at .05 (2-tailed), and all analyses were performed using IBM SPSS, version 25.0 (IBM Corp., Armonk, NY, USA).

RESULTS

We identified 4521 consecutive patients admitted to the emergency department for CAP during the study period, ultimately excluding 2318 (51%) from the analysis (Supplementary Figure 1). The final study population therefore comprised 2203 (49%) patients with CAP and sepsis.

Comparison of Patients With CAP and Sepsis, Presenting With and Without Lymphopenia

Of the 2203 patients with CAP and sepsis, 1347 (61%) did not have lymphopenia, while 856 (39%) did. Table 1 summarizes demographic and clinical characteristics of patients according to the presence or absence of lymphopenia. When compared with the nonlymphopenic group, patients in the lymphopenic group were more likely to be male, receive inhaled corticosteroids less often, had a lower rate of influenza vaccination, and presented 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, bacteremia, multilobar infiltration, and septic shock.

An etiologic diagnosis was achieved more often in the lymphopenic group (47% vs 39%; $P < .001$). Atypical pathogens were more frequently detected in the nonlymphopenic group (2% vs 6%; $P = .001$); *Legionella pneumophila* was more common in the lymphopenic group (7% vs 3%; $P = .022$) than in the nonlymphopenic group.

Data were available for empiric antibiotic treatment in 2149 (98%) patients. The most frequent regimens were ß-lactam plus fluoroquinolone (32%) and ß-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 nonlymphopenic group (23% vs 15%; $P < .001$). Inappropriate empiric antibiotic therapy rates were comparable (5% and 5%; $P = .756$).

Outcomes of Patients With CAP and Sepsis, Presenting With and Without Lymphopenia

Patients with lymphopenia required ICU admission more frequently (25% vs 32%; $P = .001$), had a longer hospital length of stay (8 days vs 9 days; $P < .001$), and presented with higher in-hospital (8% vs 12%; $P < .001$) and 30-day mortality (8% vs 12%; $P = .001$) (Table 2). Per the presence or absence of lymphocytopenia, Kaplan-Meier curves for 30-day survival in the entire population and in the subgroup of ICU patients are shown in Figures 1 and 2, respectively.

When lymphopenia was defined as $<1000/mm^3$, it was associated with a longer length of hospital stay and higher in-hospital and 30-day mortality rates (Supplementary Table 1). We also analyzed patient outcomes according to lymphocyte

Table 1. Characteristics of Patients With CAP and Sepsis According to the Presence or Absence of Lymphopenia

Variable	Lymphopenia (<724 Lymphocytes/mm^3)		*P* Value
	No (n = 1347)	Yes (n = 856)	
Age, mean (SD), y	72.1 (15.8)	72.4 (16.3)	.303
Male sex, No. (%)	830 (62)	583 (68)	.002
Current smoker, No. (%)	262 (20)	157 (19)	.555
Current alcohol user, No. (%)	188 (14)	107 (13)	.353
Previous antibiotic in last week, No. (%)	297 (23)	165 (20)	.117
Influenza vaccine, No. (%)	635 (53)	329 (45)	<.001
Pneumococcal vaccine, No. (%)	236 (20)	151 (21)	.758
Previous inhaled corticosteroids, No. (%)	308 (23)	155 (18)	.007
Previous systemic corticosteroids, No. (%)	72 (6)	41 (5)	.569
Prior pneumonia (last year), No. (%)	192 (15)	123 (15)	.843
Comorbidities, No. (%)[a]	1020 (76)	630 (74)	.203
Chronic respiratory disease	570 (43)	324 (39)	.048
Chronic cardiovascular disease	232 (17)	123 (14)	.079
Diabetes mellitus	347 (26)	212 (25)	.685
Chronic neurologic disease	295 (23)	174 (21)	.284
Chronic renal disease	129 (10)	84 (10)	.859
Chronic liver disease	65 (5)	44 (5)	.728
Previous malignancy	93 (7)	107 (13)	<.001
Nursing home resident, No. (%)	139 (10)	85 (10)	.799
Dyspnea, No. (%)	1010 (77)	611 (73)	.066
Pleuritic pain, No. (%)	420 (32)	238 (29)	.119
Fever, No. (%)	953 (72)	616 (73)	.468
Deterioration in sensorium, No. (%)	374 (28)	221 (26)	.328
Respiratory rate, median (IQR), breaths/min	24 (21–32)	24 (21–32)	.632
C-reactive protein, median (IQR), mg/dL	17.7 (8.9–26.7)	19.5 (8.8–28.8)	.012
Neutrophils, median (IQR), cells/mm^3	11.4 (8.1–16.3)	7.9 (3.8–12.3)	<.001
Creatinine, median (IQR), mg/dL	1.2 (0.9–1.6)	1.3 (0.9–1.7)	.024
White blood cell count, median (IQR), cells/mm^3	14.2 (10.3–19.6)	9.3 (4.9–13.7)	<.001
PSI risk class IV–V, No. (%)[b]	634 (67)	401 (72)	.053
Severe CAP, No. (%)	407 (38)	330 (49)	<.001
Bacteremia, No. (%)[c]	97 (10)	138 (21)	<.001
Pleural effusion, No. (%)	182 (14)	118 (14)	.789
Multilobar infiltration, No. (%)	363 (27)	273 (32)	.013
Acute respiratory distress syndrome, No. (%)	83 (6)	68 (8)	.106
Acute renal failure, No. (%)	471 (36)	322 (38)	.183
Septic shock, No. (%)	129 (10)	107 (13)	.028
Do-not-resuscitate order, No. (%)	121 (9)	90 (11)	.162
Empiric antibiotic therapy, No. (%)			
Monotherapy	432 (33)	205 (25)	<.001
Fluoroquinolones	305 (23)	126 (15)	<.001
β-lactams	121 (9)	76 (9)	.933
Other therapy	6 (0.4)	3 (0.3)	>.999
Combination therapies	882 (67)	630 (75)	<.001
β-lactams plus fluoroquinolones	402 (31)	284 (34)	.098
β-lactams plus macrolides	358 (27)	254 (30)	.112
Other combination therapies	122 (9)	92 (11)	.191
Appropriate empiric treatment, No. (%)	1123 (95)	699 (95)	.756

Percentages were calculated with nonmissing data only.

Abbreviations: CAP, community-acquired pneumonia; IQR, interquartile range; PSI, pneumonia severity index.

[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 nonlymphopenic group and 673 patients in the lymphopenic group were used to calculate percentages).

quartiles (<531 vs 531–874.4 vs 874.4–1350 vs ≥1350 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 subgroup of ICU patients are

Table 2. Clinical Outcomes According to Lymphopenia in Patients With CAP and Sepsis

Variable	Lymphopenia (<724 Lymphocytes/mm^3)		*P* Value
	No (n = 1347)	Yes (n = 856)	
Hospital length of stay, median (IQR), d	8 (6; 13)	9 (6; 15)	<.001
In-hospital mortality, No. (%)	104 (8)	105 (12)	<.001
ICU admission, No. (%)	340 (25)	270 (32)	.001
ICU mortality, No. (%)[a]	26 (8)	24 (9)	.579
Mechanical ventilation, No. (%)[b]			.122
Noninvasive	84 (7)	67 (10)	.118
Invasive	103 (9)	76 (11)	.245
30-d mortality, No. (%)	103 (8)	101 (12)	.001

Abbreviations: CAP, community-acquired pneumonia; ICU, intensive care unit; IQR, interquartile range.

[a]Calculated only for patients admitted to the ICU (340 patients in the nonlymphopenic group and 270 patients in the lymphopenic group were used to calculate the percentages).

[b]Patients who received noninvasive ventilation initially but later needed subsequent intubation were included in the invasive mechanical ventilation group.

shown in Supplementary Figures 2 and 3, respectively. Similar outcomes according to lymphocyte quartiles were observed among 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 was independently associated with decreased ICU admission. The AUC was 0.70 (95% CI, 0.67–0.73) for the predictive model of ICU admission. Internal validation of the final model was conducted with a bootstrapping procedure with 1000 samples, demonstrating robust results inasmuch as all variables remained significant with small 95% CIs around the original coefficients.

When using <1000 lymphocytes/mm^3 as a cutoff 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 <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 increased 30-day mortality, while pneumococcal vaccine, diabetes mellitus, and fever were independently associated with decreased 30-day mortality. The AUC was 0.59 (95% CI, 0.53–0.66) 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, 0.56–0.81) (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

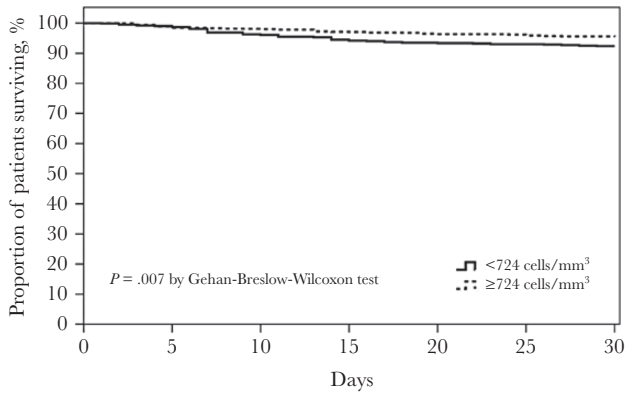

Figure 1. Kaplan-Meier survival curves for 30-day mortality in patients with community-acquired pneumonia and sepsis in relation to their lymphocyte counts (<724 vs ≥724 lymphocytes/mm^3).

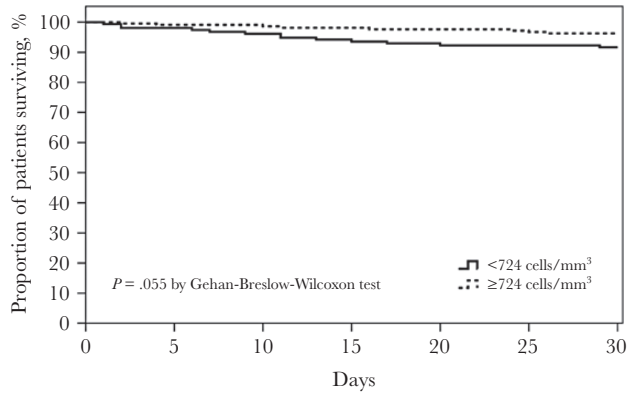

Figure 2. Kaplan-Meier survival curves for 30-day mortality in intensive care unit patients with community-acquired pneumonia and sepsis in relation to their lymphocyte counts (<724 vs ≥724 lymphocytes/mm^3).

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 = 1664)[a]

	Univariate			Multivariable[b]		
Variable	OR	95% CI	*P* Value	OR	95% CI	*P* Value
Age ≥80 y	0.32	0.24–0.42	<.001	0.31	0.23–0.41	<.001
Male sex	1.33	1.04–1.71	.024	-	-	-
Previous inhaled corticosteroids	0.98	0.74–1.29	.884	-	-	-
Previous systemic corticosteroids	1.16	0.66–2.03	.606	-	-	-
Antibiotic use in the last week	0.90	0.68–1.19	.442	-	-	-
Chronic respiratory disease	0.96	0.76–1.21	.708	-	-	-
Chronic cardiovascular disease	0.76	0.54–1.05	.099	-	-	-
Chronic renal disease	0.63	0.40–0.99	.046	-	-	-
Chronic liver disease	1.16	0.67–2.00	.593	-	-	-
Diabetes mellitus	0.85	0.65–1.11	.224	-	-	-
Chronic neurologic disease	0.63	0.46–0.87	.005	-	-	-
Previous pneumonia	0.70	0.49–0.99	.043	-	-	-
Nursing home resident	0.62	0.39–0.99	.044	-	-	-
Fever	0.91	0.70–1.18	.474	-	-	-
Deterioration in sensorium	0.90	0.68–1.19	.464	-	-	-
C-reactive protein ≥15 mg/dL	1.55	1.21–1.98	<.001	1.39	1.07–1.79	.012
Lymphopenia (<724 lymphocytes/mm^3)	1.32	1.04–1.67	.022	1.37	1.07–1.76	.013
Pleural effusion	1.85	1.35–2.53	<.001	1.81	1.30–2.52	<.001
Acute respiratory distress syndrome	5.74	3.63–9.09	<.001	6.14	3.78–9.96	<.001
Acute renal failure[c]	1.22	0.96–1.55	.108	-	-	-
Streptococcus pneumoniae	1.36	1.03–1.79	.033	-	-	-
Respiratory virus	1.23	0.85–1.77	.267	-	-	-

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 with 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.

Abbreviations: ICU, intensive care unit; OR, odds ratio.

[b]Hosmer-Lemeshow goodness-of-fit test, *P* = .597.

[c]Variable highly correlated with another independent variable and therefore not included in the multivariable model.

with a cutoff of <1000 lymphocytes/mm^3 was not a risk factor for such mortality in the entire population or in the subgroup 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 subgroup of ICU patients (Supplementary Tables 7 and 8).

DISCUSSION

In this large cohort of hospitalized patients with CAP and sepsis, when compared with nonlymphopenia 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 with a more severe clinical presentation of CAP.

The observation that lymphopenia was associated with 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]. The authors found that lymphopenia was independently associated with increased 28-day mortality and a significantly higher requirement for ICU admission [27]. Prior, Drewry et al. [28] had studied 335 adult patients with bacteremia 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, which was later validated in further studies and meta-analyses [30]. When we used lymphopenia at a cutoff of <1000 lymphocytes/mm^3, it was associated with higher in-hospital and 30-day mortality; however, it was not a risk factor for ICU admission [2]. Lymphopenia values <1000 / mm^3 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

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 = 1664)[a]

	Univariate			Multivariable		
Variable	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Age ≥80 y	3.99	2.55–6.24	<.001	2.87	1.80–4.57	<.001
Male sex	1.12	0.73–1.73	.596	-	-	-
Influenza vaccine	0.89	0.59–1.33	.565	-	-	-
Pneumococcal vaccine	0.57	0.31–1.05	.071	0.49	0.27–0.92	.025
Previous inhaled corticosteroids	1.31	0.83–2.05	.247	-	-	-
Previous systemic corticosteroids	0.75	0.24–2.36	.620	-	-	-
Antibiotic use in the last week	1.21	0.77–1.92	.408	-	-	-
Chronic respiratory disease	1.00	0.67–1.51	.993	-	-	-
Chronic cardiac disease	1.57	0.97–2.53	.064	-	-	-
Chronic renal disease	2.78	1.69–4.55	<.001	2.64	1.59–4.38	<.001
Chronic liver disease	0.97	0.36–2.65	.956	-	-	-
Diabetes mellitus	0.48	0.27–0.85	.011	0.42	0.24–0.75	.003
Chronic neurologic disease	3.33	2.12–5.00	<.001	2.48	1.61–3.81	<.001
Previous pneumonia	0.88	0.49–1.58	.663	-	-	-
Nursing home resident	3.56	2.21–5.74	<.001	2.17	1.31–3.61	.003
Fever	0.44	0.30–0.67	<.001	0.49	0.32–0.73	.001
Deterioration in sensorium	1.99	1.31–3.02	.001	-	-	-
C-reactive protein ≥15 mg/dL	0.72	0.48–1.08	.111	-	-	-
Lymphopenia (<724 lymphocytes/mm^3)	1.73	1.15–2.59	.008	1.94	1.29–2.93	.001
Pleural effusion	1.81	1.10–2.97	.018	1.90	1.15–3.14	.013
Acute respiratory distress syndrome	1.63	0.76–3.53	.211	-	-	-
Acute renal failure[b]	2.72	1.81–4.09	<.001	-	-	-
Appropriate empiric antibiotic treatment	0.99	0.36–2.68	.977	-	-	-
Streptococcus pneumoniae	1.05	0.64–1.74	.846	-	-	-
Respiratory virus	0.68	0.32–1.48	.334	-	-	-

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 2 levels of an explanatory variable (the hazard rate is the risk of death [ie, 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).

Abbreviation: HR, hazard ratio.

[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.

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 favor uncontrolled lymphocyte migration to the lungs and extrapulmonary tissues alongside 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 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 [41–43].

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 nonlymphopenic patients, who indeed were younger and had fewer comorbidities, confirms prior observations [44, 45].

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)[a]

	Univariate			Multivariable		
Variable	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Age ≥80 y	5.49	2.31–13.03	<.001	6.75	2.60–17.50	<.001
Male sex	0.71	0.30–1.72	.452	-	-	-
Influenza vaccine	1.00	0.41–2.40	.992	-	-	-
Pneumococcal vaccine	0.58	0.13–2.47	.457	-	-	-
Previous inhaled corticosteroids	2.17	0.90–5.24	.084	-	-	-
Previous systemic corticosteroids	2.20	0.51–9.43	.290	-	-	-
Antibiotic use in the last week	1.46	0.57–3.76	.435	-	-	-
Chronic respiratory disease	2.32	0.96–5.60	.061	2.61	1.08–6.33	.033
Chronic cardiac disease	2.58	1.00–6.65	.050	-	-	-
Chronic renal disease	3.66	1.23–10.88	.020	-	-	-
Chronic liver disease	3.46	1.02–11.75	.047	8.53	2.18–33.48	.002
Diabetes mellitus	1.00	0.36–2.72	.993	-	-	-
Chronic neurologic disease	1.89	0.69–5.15	.216	-	-	-
Previous pneumonia	0.77	0.18–3.32	.729	-	-	-
Nursing home resident	1.75	0.41–7.53	.450	-	-	-
Fever	1.27	0.47–3.48	.637	-	-	-
Deterioration in sensorium	1.43	0.56–3.70	.456	-	-	-
C-reactive protein ≥15 mg/dL	0.54	0.23–1.27	.157	-	-	-
Lymphopenia (<724 lymphocytes/mm^3)	2.30	0.95–5.55	.064	2.57	1.06–6.24	.037
Pleural effusion	1.32	0.48–3.61	.586	-	-	-
Acute respiratory distress syndrome	1.15	0.34–3.90	.825	-	-	-
Acute renal failure	3.66	1.48–9.06	.005	3.52	1.38–8.95	.008
Appropriate empiric antibiotic treatment	1.62	0.22–12.08	.637	-	-	-
Streptococcus pneumoniae	1.32	0.51–3.41	.562	-	-	-
Respiratory virus	0.36	0.05–2.70	.322	-	-	-

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 2 levels of an explanatory variable (the hazard rate is the risk of death [ie, 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).

Abbreviations: HR, hazard ratio; ICU, intensive care unit.

[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.

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, being a 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; for example, the PSI score includes many of them. Furthermore, advanced age, residing in a nursing home, and chronic renal and neurologic diseases favor 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 for 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 nondiabetic 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 hyperglycemia, 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, the data of all patients included were collected consecutively and prospectively per our study protocol in CAP. Second, the study was carried out in a single-center teaching hospital in Spain. The identified cutoff for lymphopenia validated in our center 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 hospitalized patients with CAP and sepsis, as lymphopenia might serve to prioritize patients with CAP and sepsis who require or will shortly require critical care. Moreover, early identification of lymphopenia could impact treatment optimization 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.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases online*. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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