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BRIEF REPORT

Pure Viral Sepsis Secondary to Community-Acquired Pneumonia in Adults: Risk and Prognostic Factors

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We investigated the risk and prognostic factors of pure viral sepsis in adult patients with community-acquired pneumonia (CAP), using the Sepsis-3 definition. Pure viral sepsis was found in 3% of all patients (138 of 4028) admitted to the emergency department with a diagnosis of CAP, 19% of those with CAP (138 of 722) admitted to the intensive care unit, and 61% of those (138 of 225) with a diagnosis of viral CAP. Our data indicate that males and patients aged ≥65 years are at increased risk of viral sepsis.

Keywords. Sepsis; viral sepsis; virus; community-acquired pneumonia.

Improved molecular diagnostic techniques have increasingly revealed a high prevalence of viral pneumonia over recent years. Globally, it is now estimated that 100 million cases of viral pneumonia occur annually, with the incidence varying by seasonality, geographic location, and age group [1]. Respiratory viruses are detected as etiological agents in almost one third of cases of community-acquired pneumonia (CAP) [2–5] and in 7%–36% of patients with severe CAP with a defined microbial etiology [2, 3]. Recently, Jain et al [2] analyzed 2320 cases of pneumonia detected by intensive microbiological diagnosis, including viral molecular techniques. A microbial etiology was identified in 853 cases (38%). The 3 main causes were respiratory viruses (23%), bacteria (11%), and coinfections (3%), indicating the clear prominence of a viral etiology. CAP is often complicated by sepsis, which is a multifactorial process for which staging is necessary to provide personalized treatments that target individual needs [6]. Viral sepsis has been defined as a severe inflammatory response to viral infection [7], and unlike bacterial sepsis, its prevalence in adults with CAP is unknown.

We aimed to investigate the prevalence, risks, and prognostic factors associated with pure viral sepsis in adult patients with CAP, using the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) criteria [6].

METHODS

We performed a retrospective observational study of consecutive adult patients with a diagnosis of CAP admitted to the Hospital Clinic of Barcelona from the emergency department between 2005 and 2017. We excluded nonhospitalized patients and those with severe immunosuppression, active tuberculosis, viral bacterial coinfection, and unavailable data. We selected patients with pure viral CAP and compared those with and without sepsis. Severe CAP was defined according to the American Thoracic Society/Infectious Diseases Society of America guidelines [8]. Sepsis was defined as the presence of pneumonia and an increase of ≥2 points in the Sequential Organ Failure Assessment score [6]. Diagnosis of respiratory virus infection was made on the basis of results of serologic analysis, immunofluorescence assay, and cell cultures from 2005 to 2007. However, diagnosis was based on results of polymerase chain reaction (PCR) and/or culture of nasopharyngeal swab samples from 2008 to 2017. 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). The criteria for etiological diagnosis are available in a previous report [3]. The main clinical outcome was in-hospital mortality. Secondary outcomes included length of hospital stay, intensive care unit (ICU) admission, mortality among patients admitted to the ICU, length of ICU stay, need for mechanical ventilation, 30-day mortality, and 1-year mortality. Patients were followed for one year. For publication purposes, the study was approved by the ethics committee of our institution (Comité Ètic d'Investigació Clínica; registration no. 2009/5451). The need for written informed consent was waived because of the noninterventional study design.

Statistical Analysis

Logistic regression analyses were used to examine the association between sepsis and risk factors. First, each risk factor was tested individually. Then, all risk factors that showed an association in the univariate model ($P < .10$) were added to the multivariable model. Finally, backward stepwise selection ($P_{in} < .05$ and $P_{out} > .10$) was used to determine factors associated with sepsis.

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Generalized linear model analyses were performed to determine the influence of the risk factors on in-hospital mortality. Models were defined using a binomial probability distribution and a logit link function, using inverse probability of treatment weights (IPTWs) to account for biases due to observed confounders. First, each risk factor was tested individually. Second, a propensity score for patients with sepsis was developed. IPTW used the propensity score to form a weight. Finally, the weight and the year of admission were incorporated in the multivariable weighted logistic regression model for in-hospital mortality, which included all risk factors and showed an association in the univariate analyses ($P < .10$), and backward stepwise elimination was performed to detect the factors associated with in-hospital mortality.

We used the multiple imputation method for missing data in the multivariable analyses.

The level of significance was set at 0.05 (2-tailed). All analyses were performed using IBM SPSS Statistics, version 25.0 (Armonk, NY).

RESULTS

Study Population

We identified 4028 consecutive patients admitted to the emergency department with a diagnosis of CAP during the study period. A total of 2760 patients (68%) were hospitalized, of whom 225 (8%) were found to have a pure viral CAP. Thirty-six patients (23%) had severe CAP.

Descriptive Data of the Overall Population

Among the 225 cases of pure viral CAP, the most common respiratory viruses were influenza A virus (52% [118 cases]), rhinovirus (13% [30]), respiratory syncytial virus (10% [23]), parainfluenza virus (8% [18]), adenovirus (8% [16]), influenza B virus (7% [15]), and coronavirus (2% [4]). We did not observe any change in the prevalence of viral CAP over the study period ($P = .65$). The mean age (±SD) was 66 ± 19 years, and the sex of 126 (56%) was male. Most patients (66% [146]) had ≥1 comorbidity, with chronic respiratory disease (in 37%) and diabetes mellitus (in 22%) being the most frequent. Despite bacterial pathogens were not isolated, patients received empirical antibiotic therapy. Monotherapy was reported for 84 patients (40%); fluoroquinolones and β-lactams were the most common agents administered. A total of 127 patients (60%) received combination therapy, with the most frequent combinations comprising a β-lactam plus a macrolide (27% [56 patients]) and a β-lactam plus a fluoroquinolone (26% [54]).

The median length of hospital stay was 7 days (interquartile range, 5–12 days); in-hospital mortality was 7% (16 patients). A total of 43 patients (19%) were admitted to the ICU, of whom 23 (53%) required mechanical ventilation; the median length of ICU stay was 7 days (interquartile range, 4–12 days), and ICU mortality was 7% (3 patients). Thirty-day mortality was 4% (10 patients), and 1-year mortality was 8% (17).

Comparison of the Sepsis and Nonsepsis Groups

Among all patients with a diagnosis of pure viral CAP, 138 (61%) presented with sepsis, and 9 (7%) presented with septic shock at admission. Table 1 summarizes the main clinical characteristics. The sepsis group had a greater mean age, a greater proportion of males, and a greater prevalence of comorbidities (especially chronic respiratory diseases), compared with the nonsepsis group. There was no statistically significant difference in symptoms (fever, cough, pleuritic pain, purulent expectoration, or dyspnea) between the 2 groups. At admission, a greater proportion of patients in the sepsis group presented with an elevated respiratory rate and lower lymphocyte levels, compared with patients in the nonsepsis group. There was no statistically significant difference in the distribution of respiratory viruses between the 2 groups. Thus, we did not find any association between the type of virus and the presence or absence of sepsis (in the nonsepsis group, influenza virus was found in 59% [51 patients] and non–influenza virus in 41% [36], compared with 59% [82] and 41% [56], respectively, in the sepsis group; $P > .99$). More patients in the sepsis group were classified as having a pneumonia severity index of IV–V, indicating severe CAP.

Overall, 92 patients (41%) received antiviral therapy with oseltamivir. The percentage of patients who received antiviral therapy was similar between the 2 groups (47% vs 42%; $P = .43$). Forty-four patients (33%) with sepsis were treated empirically with antibiotic monotherapy. The sepsis group received fluoroquinolone-based monotherapy less frequently than the nonsepsis group (27% vs 44%; $P = .008$). Antimicrobial therapy was inappropriate (ie, nonconcordant with published guidelines) in 4 cases (3%) in the sepsis group, but there was no significant difference from the nonsepsis group (4%).

Risk Factors for Viral Sepsis

Among the variables associated with viral sepsis in the univariate logistic regression analysis, age ≥65 years and male sex remained independent risks factors for viral sepsis in the multivariable analysis (Table 2). Internal validation of the logistic regression model by using bootstrapping with 1000 samples demonstrated robust results for all variables included in the model, with small 95% confidence intervals (CIs) around the original coefficients.

Outcomes

No statistically significant difference was observed between the two groups in terms of in-hospital mortality, ICU mortality, length of ICU stay, 30-day mortality, and 1-year mortality (Table 1). However, patients with sepsis showed longer length of hospital stay, were more frequently admitted to ICU and needed

Table 1. Characteristics of and Outcomes Among Patients Admitted to the Emergency Department With Community-Acquired Pneumonia (CAP), by Viral Sepsis Status

Variable	Viral Sepsis		P[a]
	Absent (n = 87)	Present (n = 138)	
Age, y, mean ± SD	61 ± 22	69 ± 17	.004
Age ≥65 y	38 (44)	88 (64)	.003
Male sex	40 (46)	86 (62)	.016
Current smoker	16 (19)	32 (23)	.42
Current alcohol consumer	9 (10)	13 (9)	.80
Previous antibiotic therapy	27 (33)	40 (31)	.67
Influenza vaccination	32 (39)	56 (45)	.41
Pneumococcal vaccination	12 (15)	26 (20)	.28
Previous inhaled corticosteroid therapy	9 (11)	25 (19)	.11
Previous systemic corticosteroid therapy	5 (6)	7 (5)	>.99
Previous episode of pneumonia	8 (10)	24 (18)	.10
Comorbidity[b]	46 (54)	100 (73)	.004
Chronic respiratory disease	24 (29)	57 (43)	.044
Chronic cardiovascular disease	9 (11)	16 (12)	.81
Diabetes mellitus	13 (16)	35 (26)	.076
Neurological disease	10 (12)	26 (19)	.15
Chronic renal disease	2 (2)	11 (8)	.076
Chronic liver disease	5 (6)	4 (3)	.30
Nursing home admission	6 (7)	12 (9)	.66
Cough	69 (81)	116 (85)	.50
Purulent sputum	43 (52)	79 (59)	.35
Dyspnea	52 (63)	95 (69)	.31
Pleuritic pain	23 (28)	31 (23)	.47
Fever	74 (86)	102 (76)	.059
Respiratory rate, breaths/min	22 (20–24)	24 (24–30)	<.001
C-reactive protein level, mg/dL	16.4 (6.0–25.7)	16.3 (7.8–24.4)	.89
Lymphocyte count, cells/mm^3	1026 (636–1612)	819 (535–1330)	.039
Microbial etiology			
Influenza A virus	46 (53)	72 (52)	.92
Rhinovirus	12 (14)	18 (14)	.87
Respiratory syncytial virus	11 (13)	12 (10)	.34
Parainfluenza virus (1–3)	4 (5)	14 (11)	.14
Adenovirus	5 (6)	11 (8)	.53
Influenza B virus	5 (6)	10 (7)	.66
Coronavirus	3 (4)	1 (1)	.30
Other respiratory viruses	1 (1)	0 (0)	.39
PSI			
Score	63 (43–90)	97 (74–119)	<.001
Risk class IV–V[c]	8 (24)	52 (58)	.001
Severe CAP[d]	4 (7)	32 (31)	<.001
Pleural effusion	8 (11)	9 (7)	.34
Multilobar pneumonia	23 (26)	35 (25)	.86
Septic shock at admission	0 (0)	9 (7)	.013
Do-not-resuscitate order	2 (3)	10 (8)	.14
Length of hospital stay, d	6 (4–10)	9 (6–14)	<.001
ICU admission[e]	7 (8)	36 (26)	.001
Mortality	0 (0)	3 (8)	>.99
Length stay	7 (4–22)	7 (4–11)	.60
Mechanical ventilation[f]			.007
Not ventilated	67 (97)	93 (82)	.002
Noninvasive	1 (1)	10 (9)	.055
Invasive	1 (1)	11 (10)	.032

Table 1. Continued

Variable	Viral Sepsis		
	Absent (n = 87)	Present (n = 138)	P[a]
Mortality			
In-hospital	5 (6)	11 (8)	.54
30 d	5 (6)	5 (4)	.51
1 y	6 (7)	11 (8)	.78

Data are no. (%) of patients or median value (interquartile range), unless otherwise indicated. Percentages were calculated using the number of patients with nonmissing data as the denominator.

Abbreviations: ICU, intensive care unit; PSI, pneumonia severity index.

[a]Categorical variables were compared using the χ^2 test or the Fisher exact test. Continuous variables were compared using the *t* test or the nonparametric Mann-Whitney *U* test. Values <.05 indicate statistically significant differences.

[b]Patients may have >1 comorbid condition.

[c]Stratified according to 30-d mortality risk for community-acquired pneumonia: classes I–III (≤90 points) have a low mortality risk, and classes IV–V (>90 points) have the highest mortality risk.

[d]Severe CAP was defined according to the American Thoracic Society/Infectious Diseases Society of America major and minor criteria.

[e]Seven patients without and 36 with sepsis were used to calculate the percentages.

[f]Patients who initially received noninvasive ventilation but subsequently needed intubation were included in the invasive mechanical ventilation group.

more frequently invasive mechanical ventilation than patients without sepsis.

Factors Associated With In-Hospital Mortality

In the propensity-adjusted logistic regression multivariable analysis of in-hospital mortality using the weighted data, after exclusion of patients with septic shock at admission and those with do-not-resuscitate orders, pure viral sepsis was not associated with in-hospital mortality (odds ratio, 0.77; 95% CI, .18–3.17). All variables remained significant after the bootstrapping procedure, with a small 95% CIs around the original coefficients.

DISCUSSION

This study has 3 main findings. First, pure viral sepsis defined according to the Sepsis-3 criteria was found in 3% of all patients admitted with a diagnosis of CAP, 19% of those admitted to

Table 2. Findings of Logistic Regression Analysis to Detect Significant Risk Factors for Pure Viral Sepsis Among 225 Patients Admitted to the Emergency Department With Community-Acquired Pneumonia

Variable	Univariate[a]		Multivariable	
	OR[b] (95% CI)	P[c]	OR[b] (95% CI)	P[c]
Age ≥65 y	2.27 (1.31–3.92)	.003	2.59 (1.46–4.58)	.001
Male sex	1.94 (1.13–3.35)	.017	2.26 (1.28–4.01)	.005
Chronic pulmonary disease		.037		
No	1		…	
Bronchiectasis	1.54 (.27–8.71)	.62	…	
COPD	2.80 (1.20–6.56)	.018	…	
Asthma	0.51 (.17–1.52)	.23	…	
Other	2.21 (.88–5.55)	.093	…	
Chronic renal disease	3.68 (.80–17.02)	.095	…	
Diabetes mellitus	1.76 (.90–3.44)	.10	…	

Data are estimated ORs (95% CIs) of the explanatory variables for sepsis.

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; OR, odds ratio.

[a]The variables analyzed in the univariate analysis were as follows: age, sex, smoking status, alcohol consumption, influenza vaccination, pneumococcal vaccination, previous inhaled corticosteroid therapy, previous systemic corticosteroid therapy, previous antibiotic therapy in last week, chronic pulmonary disease, chronic cardiovascular disease, chronic renal disease, chronic liver disease, diabetes mellitus, chronic neurologic disease, and nursing home admission (*P* = .51).

[b]Defined as the probability of being in the sepsis group divided by the probability of being in the nonsepsis group.

[c]Based on the null hypothesis that all ORs relating to an explanatory variable equal unity (ie, that there was no effect).

the ICU, and 61% of those with a diagnosis of pure viral CAP. Second, male sex and age ≥65 years were shown to be risk factors for pure viral sepsis. Third, pure viral sepsis was not found to be a risk factor for in-hospital mortality.

Sepsis is a life-threatening organ dysfunction due to the host's overwhelming response to infection. Although respiratory viruses are reported to be important causative agents of severe CAP [9], the prevalence of pure viral sepsis is not fully known. A recently published study investigated the role of virus detection by multiplex PCR of nasopharyngeal samples from clinically septic patients during a winter season [10]. The authors reported that respiratory viruses, including influenza A virus, human metapneumovirus, coronavirus, and respiratory syncytial virus were detected in 70% of adult patients with sepsis. In another study, Montull et al [11] investigated the predictors of severe sepsis in patients with CAP and found that 38% of patients presented with severe sepsis and that 0.5% were identified to have respiratory viruses as casual agents. The proportion of patients with pure viral sepsis was slightly higher in our study population, but we think that this was due to our use of the new Sepsis-3 definition. Montull et al also highlighted the association between older age and development of viral sepsis, which was in line with our finding that viral sepsis affected 64% of patients (88) aged ≥65 years. These results are consistent with data showing that, because of the increased prevalence of chronic conditions and age-related changes in the immune system, elderly patients are more susceptible to infectious diseases and sepsis. It is also possible that the endothelium is fragile in this population [12]. Male sex was another risk factor for pure viral sepsis, consistent with data that men typically have more chronic comorbidities and a higher incidence of CAP than women [13].

We observed that viral sepsis was not a risk factor for in-hospital mortality in patients without septic shock. Our data support those of previous studies in which respiratory viruses were frequently found in critically ill patients with pneumonia but mortality rates did not significantly differ between patients with bacterial infection and those with viral infection [9, 10, 14]. This highlights the need to identify patients at higher risk of viral sepsis and the importance of a complete microbiological diagnosis in cases of CAP. We could not find other studies addressing the issue of pure viral sepsis (defined according to the Sepsis-3 criteria) in case of CAP in a large inpatient adult cohort.

Finally, we observed that 41% of patients with viral CAP received oseltamivir therapy, without differences between patients with and those without sepsis. Compared with other previous studies [5, 15], our population received a higher proportion of antiviral therapy. However, future studies are needed to investigate why the frequency of antiviral therapy use among patients hospitalized with CAP is not high, since current guidelines strongly recommend early treatment with oseltamivir in patients with influenza [8].

Some limitations must be addressed. First, although the protocol used for CAP diagnosis in our hospital did not change substantially during the 12-year study, we cannot discount the effect of changes in microbiological diagnosis over this period. Second, regarding microbiological diagnosis, more-rapid PCR diagnostic tests for influenza virus and respiratory syncytial virus were used during the influenza season. Third, the indications for oseltamivir therapy were only extended in 2009, before which it was only used to treat severe cases of viral infection.

In conclusion, in our cohort, pure viral sepsis affected 61% of patients with a diagnosis of viral CAP, supporting the importance of stratifying patient risk for viral sepsis and making a complete microbiological diagnosis in cases of CAP.

Notes

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Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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