Pure viral sepsis secondary to Community-Acquired Pneumonia in adults: risk and prognostic factors

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Summary: Pure viral sepsis affected 3% of all patients admitted with a diagnosis of community-acquired pneumonia and 19% of those admitted to intensive care unit. Males and patients aged ≥65 years were at increased risk of viral sepsis.

Abstract

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 admitted to the emergency department with a diagnosis of CAP (138 out of 4,028), 19% of all CAP patients admitted to the intensive care unit (ICU) (138 out of 722) and 61% of all patients with a diagnosis of viral CAP (138 out of 225). Our data indicate that males and patients aged ≥65 years are at increased risk of viral sepsis.

Key words: sepsis; viral sepsis; virus; community-acquired pneumonia

Background

Improvements in molecular diagnostic techniques have increasingly shown 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 account for 7% - 36% of patients with severe CAP and a defined microbial etiology[2,3]. Recently, Jain et al.[2] analyzed 2,320 cases of pneumonia detected by intensive microbiological diagnosis, including viral molecular techniques. A microbial etiology was identified in 853 (38%) cases. The three main causes were respiratory viruses (23%), bacteria (11%), and co-infections (3%), indicating the clear prominence of 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 non-hospitalized patients, patients with severe immunosuppression, active tuberculosis, viral bacterial co-infections, and unavailable data. We selected patients with pure viral CAP and compared those with and without sepsis. Severe CAP was defined according to the ATS/IDSA guidelines[8]. Sepsis was defined as the presence of pneumonia and an increase of ≥2 points in the Sequential Organ Failure Assessment score [6]. Respiratory viruses were diagnosed by serology, immunofluorescence assay (IFA), and isolation in cell cultures from 2005 to 2007. However, diagnosis was performed by 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, ICU admission, ICU mortality, 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*, register: 2009/5451). The need for written informed consent was waived because of the non-interventional 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 ($p<0.10$) were added to the multivariable model. Finally, a backward stepwise selection ($p_{in}<0.05$, $p_{out}>0.10$) was used to determine factors associated with sepsis.

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 (PS) for patients with sepsis was developed. IPTW used the PS 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, including all risk factors which showed an association in the univariate analyses ($p<0.10$), and calculated in a stepwise backward elimination procedure.

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

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

Results

Study population

We identified 4,028 consecutive patients admitted to the emergency department with a diagnosis of CAP during the study period; 2,760 patients (68%) were hospitalized and 225 (8%) of them were found to have a pure viral CAP; 36 (23%) of them showed 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%; n=118), rhinovirus (13%; n=30), respiratory syncytial virus (10%; n=23), parainfluenza virus (8%; n=18), adenovirus (8%; n=16), influenza B virus (7%; n=15), and coronavirus (2%; n=4). We did not observe any change in the prevalence of viral CAP over the study period (p=0.65). The mean (SD) age was 66 (19) years and 126 (56%) were males. Most patients (66%; n=146) had at least one comorbidity, with chronic respiratory disease (37%) and diabetes mellitus (22%) being the most frequent. Despite bacterial pathogens were not isolated, patients received empiric antibiotic therapies. Monotherapy was reported in 84 patients (40%): fluoroquinolones and β-lactams were the most common agents administered; 127 patients (60%) received a combination therapy, with the most frequent association being a β-lactam plus a macrolide (27%; n=56) and a β-lactam plus a fluoroquinolone (26%; n=54).

The median (Q1; Q3) length of hospital stay was 7 (5; 12) days, in-hospital mortality was 7% (n=16). A total of 43 patients (19%) were admitted to ICU, 23 (53%) of whom required mechanical ventilation; the median length of ICU stay was 7 (4; 12) days, and ICU mortality was 7% (n=3). Thirty-day mortality was 4% (n=10), and 1-year mortality was 8% (n=17).

Comparison of the sepsis and non-sepsis groups

Among all patients diagnosed with pure viral CAP, 138 (61%) presented with sepsis and 9 (7%) with septic shock at admission. Table 1 summarizes the main clinical characteristics. The sepsis group included patients who were older, more frequently males, and had more comorbidities (especially chronic respiratory diseases) compared with the non-sepsis group. There was no statistically significant difference in symptoms (fever, cough, pleuritic pain, purulent expectoration or dyspnoea) between the two groups. At admission, patients in the sepsis group presented with elevated respiratory rate and lower lymphocyte levels more frequently than patients in the non-sepsis group. There was no statistically significant difference in the distribution of respiratory viruses between the two groups. Thus, we did not find any association between the type of virus and the presence or absence of sepsis (non-sepsis group: influenza virus 59% (n=51), non-influenza virus 41% (n=36) vs. sepsis group: influenza virus 59% (n=82), non-influenza virus 41% (n=56); p>0.99). More patients in the sepsis group were classified as having a Pneumonia Severity Index IV–V, indicating severe CAP.

Overall, 92 patients (41%) received antiviral therapy with Oseltamivir. The percentage of antiviral therapy was similar between the two groups (47% vs. 42%, p=0.43). Forty-four patients (33%) with sepsis were treated with empiric antibiotic monotherapy. The sepsis group received fluoroquinolone-based monotherapy less frequently than the non-sepsis group (27% vs. 44%, p=0.008). Antimicrobial therapy was inappropriate (non-concordant with published guidelines) in 4 cases (3%) in the sepsis group, but there was no significant difference with the non-sepsis 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 using bootstrapping with 1,000 samples demonstrated robust results for all the variables included in the model, with small 95% 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 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 excluding patients with septic shock at admission and with do-not-resuscitate orders, pure viral sepsis was not associated with in-hospital mortality (OR 0.77, 95% CI 0.18 to 3.17). All variables remained significant after the bootstrapping procedure, with a small 95% CIs around the original coefficients.

Discussion

This study has three 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 ICU, and 61% of those diagnosed with 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 an overwhelmed host response to an 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 through multiplex PCR from the nasopharynx of 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 research, Montull et al.[11] investigated the predictors of severe sepsis in CAP patients, reporting 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 (n=88) aged ≥65 years. These results are consistent with data showing that elderly patients, due to the increased prevalence of chronic conditions and age-related changes in the immune system, 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 have frequently been found in critically ill patients with pneumonia, but where mortality rates were not significantly different in patients with bacterial infection or 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 CAP. We could not find other studies addressing the issue of pure viral sepsis (defined according to the Sepsis-3 criteria) in 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 or without sepsis. Compared to other previous studies[5,15], our population received a higher proportion of antiviral therapy. However, future studies are needed to investigate why antiviral therapy 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 has not changed significantly during the 12 years 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 patients risk for viral sepsis and making a complete microbiological diagnosis in CAP.

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Table 1. Patients characteristics and outcomes according to the presence of viral sepsis

	Viral Sepsis		
	No	Yes	
Variable	**(N = 87)**	**(N = 138)**	**p-value[a]**
Age, mean (SD), years	61 (22)	69 (17)	**0.004**
Age ≥65 years, n (%)	38 (44)	88 (64)	**0.003**
Male sex, n (%)	40 (46)	86 (62)	**0.016**
Current smoker, n (%)	16 (19)	32 (23)	0.42
Current alcohol consumer, n (%)	9 (10)	13 (9)	0.80
Previous antibiotic, n (%)	27 (33)	40 (31)	0.67
Influenza vaccine, n (%)	32 (39)	56 (45)	0.41
Pneumococcal vaccine, n (%)	12 (15)	26 (20)	0.28
Previous inhaled corticosteroids, n (%)	9 (11)	25 (19)	0.11
Previous systemic corticosteroids, n (%)	5 (6)	7 (5)	>0.99
Previous episode of pneumonia, n (%)	8 (10)	24 (18)	0.10
Comorbidities, n (%)[b]	46 (54)	100 (73)	**0.004**
Chronic respiratory disease	24 (29)	57 (43)	**0.044**
Chronic cardiovascular disease	9 (11)	16 (12)	0.81
Diabetes mellitus	13 (16)	35 (26)	0.076
Neurological disease	10 (12)	26 (19)	0.15
Chronic renal disease	2 (2)	11 (8)	0.076
Chronic liver disease	5 (6)	4 (3)	0.30
Nursing-home, n (%)	6 (7)	12 (9)	0.66
Cough, n (%)	69 (81)	116 (85)	0.50
Purulent sputum, n (%)	43 (52)	79 (59)	0.35
Dyspnoea, n (%)	52 (63)	95 (69)	0.31

Variable	Viral Sepsis No (N = 87)	Viral Sepsis Yes (N = 138)	p-value[a]
Pleuritic pain, n (%)	23 (28)	31 (23)	0.47
Fever, n (%)	74 (86)	102 (76)	0.059
Respiratory rate, median (IQR), rpm	22 (20; 24)	24 (24; 30)	**<0.001**
C-reactive protein, median (IQR), mg/Dl	16.4 (6.0; 25.7)	16.3 (7.8; 24.4)	0.89
Lymphocytes, median (IQR), cell/mm^3	1,026 (636; 1,612)	819 (535; 1,330)	**0.039**
Microbial etiology			
Influenza A virus, n (%)	46 (53)	72 (52)	0.92
Rhinovirus, n (%)	12 (14)	18 (14)	0.87
Respiratory syncitial virus, n (%)	11 (13)	12 (10)	0.34
Parainfluenza virus (1-3), n (%)	4 (5)	14 (11)	0.14
Adenovirus, n (%)	5 (6)	11 (8)	0.53
Influenza B virus, n (%)	5 (6)	10 (7)	0.66
Coronavirus, n (%)	3 (4)	1 (1)	0.30
Other respiratory viruses, n (%)	1 (1)	0 (0)	0.39
PSI score, median (IQR)	63 (43; 90)	97 (74; 119)	**<0.001**
PSI risk class IV–V, n (%)[c]	8 (24)	52 (58)	**0.001**
Severe CAP, n (%)[d]	4 (7)	32 (31)	**<0.001**
Pleural effusion, n (%)	8 (11)	9 (7)	0.34
Multilobar, n (%)	23 (26)	35 (25)	0.86
Septic shock at admission, n (%)	0 (0)	9 (7)	**0.013**
Do-not-resuscitate order, n (%)	2 (3)	10 (8)	0.14
Length of hospital stay, median (IQR), days	6 (4; 10)	9 (6; 14)	**<0.001**
ICU admission, n (%)	7 (8)	36 (26)	**0.001**

	Viral Sepsis		
	No	**Yes**	
Variable	**(N = 87)**	**(N = 138)**	**p-value[a]**
ICU mortality, n (%)[e]	0 (0)	3 (8)	>0.99
Length of ICU stay, median (IQR), days[e]	7 (4; 22)	7 (4; 11)	0.60
Mechanical ventilation, n (%)[f]			**0.007**
Not ventilated	67 (97)	93 (82)	**0.002**
Non-invasive	1 (1)	10 (9)	0.055
Invasive	1 (1)	11 (10)	**0.032**
In-hospital mortality, n (%)	5 (6)	11 (8)	0.54
30-day mortality, n (%)	5 (6)	5 (4)	0.51
1-year mortality, n (%)	6 (7)	11 (8)	0.78

Abbreviations: CAP indicates community acquired pneumonia; ICU, intensive care unit; IQR, interquartile range; PSI, pneumonia severity index; SD, standard deviation. Percentages calculated on non-missing data. [a] Categorical variables were compared using the χ2 test or the Fisher exact test. Continuous variables were compared using the t test or the nonparametric Mann-Whitney U test. [b] May have >1 comorbid condition. [c] Stratified according to 30-day mortality risk for community-acquired pneumonia: classes I–III (≤90 points) have low mortality risk and classes IV–V (>90 points) have the highest mortality risk. [d] Severe CAP was defined according to the ATS/IDSA major and minor criteria. [e] 7 patients in the no sepsis group and 36 patients in the sepsis group were used to calculate the percentages. [f] Patients who initially received non-invasive ventilation but needed subsequently intubation were included in the invasive mechanical ventilation group.

Table 2. Significant risk factors for pure viral sepsis in the logistic regression analyses (N = 225)

	Univariate[a]			Multivariable[b]		
Variable	**OR**	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**
Age ≥65 years	2.27	1.31 to 3.92	0.003	2.59	1.46 to 4.58	0.001
Male sex	1.94	1.13 to 3.35	0.017	2.26	1.28 to 4.01	0.005
Chronic pulmonar disease			0.037	-	-	-
No	1	-	-	-	-	-
Bronchiectasis	1.54	0.27 to 8.71	0.62	-	-	-
COPD	2.80	1.20 to 6.56	0.018	-	-	-
Asthma	0.51	0.17 to 1.52	0.23	-	-	-
Other	2.21	0.88 to 5.55	0.093	-	-	-
Chronic renal disease	3.68	0.80 to 17.02	0.095	-	-	-
Diabetes mellitus	1.76	0.90 to 3.44	0.10	-	-	-

Abbreviations: CI indicates confidence interval; COPD, chronic obstructive pulmonary disease; OR, odds ratio. Data are shown as estimated ORs (95% CIs) of the explanatory variables in the sepsis group. OR is defined as the probability of being in the sepsis group divided by the probability of being in the no-sepsis group. The P-values are based on the null hypothesis that all ORs relating to an explanatory variable equal unity (no effect). [a] The variables analyzed in the univariate analysis were as follows: age, gender, smoking status, alcohol consumption, influenza vaccine, pneumococcal vaccine, previous inhaled corticosteroids, previous systemic corticosteroids, previous antibiotic in last week, chronic pulmonary disease, chronic cardiovascular disease, chronic renal disease, chronic liver disease, diabetes mellitus, chronic neurologic disease, and nursing home residency, p=0.51.