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Original article

SEVERE COMMUNITY-ACQUIRED PNEUMONIA IN PATIENTS WITH SEASONAL INFLUENZA

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Abstract

Introduction: Seasonal influenza is most commonly presented as light upper respiratory disease. However, globally around 3-5 million severe cases and 290,000 – 650,000 deaths are registered during seasonal epidemics. Severe pneumonia is a common respiratory complication and the main cause for hospitalization and death.

Aim: To present the characteristics of patients with seasonal influenza and severe community-acquired pneumonia.

Materials and methods: A prospective, group-comparative clinical study was conducted at the Clinic for Infectious Diseases and Febrile Conditions in a three-year period. A total of 98 adult patients with clinically and laboratory-confirmed influenza and pneumonia as a complication were analyzed. The study included demographic and general data, clinical symptoms and signs, as well as complications. The influenza virus was confirmed through a nasopharyngeal swab using the method of real time RT-PCR (real-time reverse polymerase chain reaction).

Results: Severe pneumonia requiring extensive monitoring and treatment was registered in 32/98 (32.7%) patients, with a mean age of 54.6±16.9 years. ARDS as the most serious complication occurred in 7/32 (7.14%) patients. Diffuse bilateral consolidation was found only in patients with sCAP. In our study, the mortality rate in the group of patients with sCAP was 31.25%

Conclusion: Timely treatment, as well as determining the critical point when respiratory complications usually begin, is of crucial importance in preventing death in patients with seasonal nfluenza and severe pneumonia.

Keywords: seasonal influenza, severe apneumonia

Introduction

Seasonal influenza is a respiratory viral infection caused by influenza viruses A(H3N2), A (H1N1), and B, that occurs annually every winter and causes seasonal epidemics. Although influenza most commonly presents as a mild upper respiratory disease, globally around 3-5 million severe cases and 290,000-650,000 deaths are registered every year. Multi-systemic

complications, respiratory being with the highest rate, are the main cause for hospitalization, severe clinical presentation and fatal outcome[1-4]. Pneumonia is the most common respiratory complication, which is presented like primarily viral, secondary bacterial and mixed pneumonia which is most difficult to be distinguished. It is estimated that more than 30-40% of influenza patients contracted pneumonia, most frequently presented like community-acquired pneumonia (CAP). Mortality rates range from 6-29% and up to 50% in severe pneumonia[5-7].

Severe community-acquired pneumonia (sCAP) is defined as CAP that requires ICU admission or mechanical ventilation or vasopressor support. IDSA/ATS 2007 criteria for sCAP included 3 or more minor criteria (respiratory rate > 30 breaths/min, PaO2/FIO2 ratio <250, multi-lobar infiltrates, confusion/disorientation, uremia (blood urea nitrogen level >20 mg/dl), leukopenia (white blood cell count of 4,000 cells/ml), thrombocytopenia (platelet count of 100,000/ml), hypothermia (core temperature of 36.8 C), hypotension requiring aggressive fluid resuscitation and one or more major criteria (septic shock with need for vasopressors and respiratory failure requiring mechanical ventilation)[8,9].

It is estimated that around one third of the patients with severe pneumonia end up at the ICU and 26% of them are in need of mechanical ventilation. sCAP is the most common cause for development of ARDS (acute respiratory distress syndrome), a pathological condition with a mortality rate of over 80% and a systemic inflammatory response with multiorgan failure leading to the development of sepsis. Two large observational studies, one monocentered from Spain, and the second one from USA reported the same sCAP statistical data. They estimated CAP incidence at ICU of 145/100,000 adults, and high sCAP in-hospital mortality of 38%, range 23–50%[8-10].

Materials and methods

A prospective, group-comparative clinical study was conducted at the University Clinic for Infectious Diseases and Febrile Conditions in a three-year period. A total of 98 patients, aged ≥16 years, with clinically and laboratory confirmed seasonal influenza and pneumonia as a complication were analyzed. On admission, the following parameters were noted: demographic characteristics, comorbidities, clinical signs of the disease, laboratory-biochemical characteristics, as well as complications. Pneumonia was confirmed with chest radiography. For determining the presence of the influenza virus, nasopharyngeal smear was used.

Data was statistically analyzed using the program SPSS for Windows 13.0, employing relevant statistical methodologies. The value of $p<0.05$ was considered to be statistically significant, and the value of $p<0.01$ highly significant.

The study was designed in accordance with the ethical principles of the Declaration of Helsinki for patients and their rights, and was approved by the Ethics Committee of the Faculty of Medicine, Ss. Cyril and Methodius University in Skopje.

Results

The analysis of 98 (100%) patients with confirmed seasonal influenza and pneumonia as a complication, guided by the recommendations of IDSA/ATS (Infectious Diseases Society of America/American Thoracic Society Criteria for defining severe community-acquired pneumonia) from 2007, which are still widely used, confirmed severe community-acquired pneumonia (sCAP) in 32/98 (32.65%) patients, (Figure 1). The remaining 66/98 (67.34%) patients did not meet these criteria, and they presented as community-acquired pneumonia (CAP).

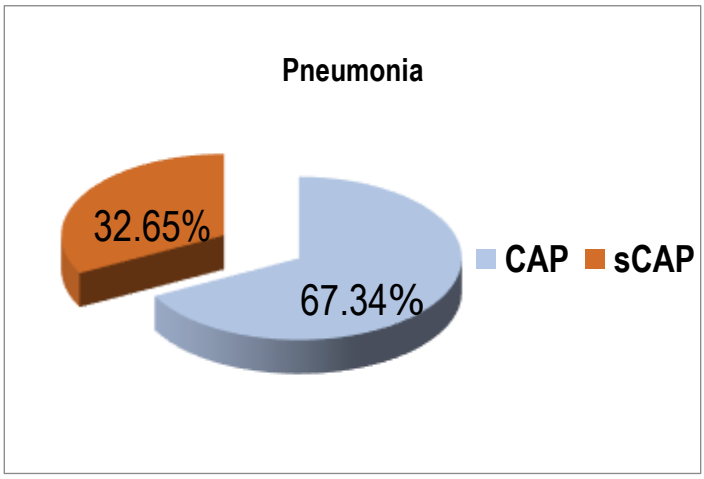

Fig. 1. Patients with seasonal influenza and pneumonia as a complication

The analysis of the demographic characteristics of patients with seasonal influenza and pneumonia as a complication showed that the male gender was predominant, accounting for 63/98 (64.28%) compared to the female gender, which accounted for 35/98 (35.72%). The mean age of patients was 54.6±16.9. The comparative analysis between the two groups confirmed a statistically significantly older age group of patients with severe pneumonia (sCAP) *vs*. those with CAP, 56.8±17.3 *vs*. 46.1±14.8 (p=0.023). Regarding the analyzed comorbidities and additional complications, they were statistically significantly more frequent in the group of patients with sCAP compared to those with CAP: 29/32 (90.62) *vs*. 38/66 (57.57), (p=0.00008) and 24/32 (75) *vs*. 8/66 (12.12) (p=0.002) (Table 1).

Table 1. Baseline characteristics of patients with seasonal influenza and pneumonia

	Pneumonia	**CAP [n (%)]**	**sCAP [n (%)]**	**P value**
	98(100)	66(67.34)	32(32.65)	
Gender [n (%)]				
male	63(64.28)	43(65.15)	20(62.5)	[a]0.889
female	35(35.72)	23(34.85)	12(37.5)	
Age (mean±SD)	54.6±16.9	46.1±14.8	56.8±17.3	[b]0.023*
Smoking history [n (%)]				
no	62(63.26)	57(86.36)	7(21.87)	[c]p<0.01
yes	36(36.70)	9(25)	25(78.12)	
Comorbidities [n (%)]				
no	31(31.63)	28(42.42)	3(9.37)	[a]0.00008**
yes	67(68.36)	38(57.57)	29(90.62)	
Comorbidities [n (%)]				
no	66(67.34)	58(87.87)	8(25)	[a]0.002**
yes	32(32.65)	8(12.12)	24(75)	

[a]p (Chi-square test), [b]p (Student's test), [c]p (Fisher exact test), *p<0.05 **p<0.01

On admission, 35/98 (35.71%) patients with seasonal influenza and pneumonia were hospitalized in the intensive care unit. Patients with sCAP were much more likely to be treated in the intensive care unit compared to patients in the CAP group, 90.62% *vs*. 9.09%, p<0.01. Acute respiratory distress syndrome (ARDS) was present in 7/98 (7.14%) patients, all in the group with severe pneumonia. Twelve of 98 (12.24%) patients, all in the sCAP group, required mechanical ventilation, p<0.018 (Table 2).

Table 2. Admission to ICU, mechanical ventilation and ARDS in patients with seasonal influenza and CAP and sCAP

	Pneumonia n=98	CAP [n (%)] n=66	sCAP [n (%)] n=32	P value
	98(100)	66(67.34)	32(32.65)	
ICU admission [n (%)]				
no	63(64.28)	60(90.90)	3(9.37)	[c]p<0.01
yes	35(35.71)	6(9.09)	29(90.62)	
ARDS[n (%)]				
no	91(92.85)	66(100)	25(78.12)	[c]p<0.01
yes	7(7.14)	0	7(21.87)	
MV[n (%)]				
no	86(87.75)	66(100)	20(62.5)	[c]0.018*
yes	12(12.24)	0	12(37.5)	

[a]p (Chi-square test) [c]p (Fisher exact test) *p<0.05 **p<0.01

The analysis of chest x-ray findings on admission showed that consolidation on x-ray was significantly more often observed in patients with sCAP: 31/32 (96.87%) *vs*. 40/66 (60.60%) with CAP, p<0.0001. Diffuse bilateral consolidation was registered only in patients with sCAP (Table 3).

Table 3. X-ray findings of the lungs in patients with seasonal influenza and pneumonia

	Pneumonia	CAP [n (%)]	sCAP [n (%)]	P value
	98(100)	66(67.34)	32(32.65)	
Consolidation [n (%)]				
no	29(29.59)	26(39.40)	1(3.12)	[a]<0.0001
yes	71(72.44)	40(60.60)	31(96.87)	
Diffuse bilateral consolidation [n (%)]				
no	91(92.85)	66(100)	25(78.12)	[c]<0.001
yes	7(7.14)	0	7(21.87)	

[a]p (Chi-square test) [c]p (Fisher exact test) *p<0.05 **p<0.01

In-hospital mortality rate in patients with seasonal influenza and pneumonia in our study was 13/98 (13.26%). Mortality rate in the sCAP group was 10/32 (31.25%), which correlates with world-referred mortality.

Discussion

Seasonal influenza is associated with a large number of complications and systemic manifestations from different tissues and organs. Community-acquired pneumonia is the most common complication of seasonal influenza, which is often the cause of a severe clinical course, and death[11,12].

Community-acquired pneumonia (CAP) is an acute inflammation of the lung parenchyma acquired outside the hospital. It is most often caused by bacteria (S*treptococcus pneumoniae, Haemophilus influenzae, Mycoplasma pneumoniae, Legionella species*), and viruses (influenza, SARS-CoV, respiratory syncytial virus). It is presented by a general infectious syndrome with additional lower respiratory symptomatology (chest pain, dyspnea, tachypnea). Diagnosis is based on lung x-ray, and treatment is empiric. It is the leading cause of morbidity and mortality in adults, as well as the leading cause of emergency room visits. Every year, WHO reports about 450 million cases and 3 million deaths[8,13].

A separate entity is represented by severe community-acquired pneumonia (sCAP) which is a major global health challenge, especially among patients requiring intensive care. It

is defined as CAP that requires ICU admission, mechanical ventilation or vasopressor support and is characterized with a high mortality rate. Differentiating sCAP from CAP is necessary to ensure appropriate and timely therapeutic approach, as well as the need for timely monitoring and placement of patients in intensive care units[14,15].

Pneumonia is as one of the most common complications among patients with seasonal influenza, which was also confirmed in our study[16,17]. According to the WHO repots, during pandemics and epidemics, the largest number of mortality cases among patients with influenza are a result of secondary bacterial infection manifested as pneumonia. Thus, in the last pandemic report from 2009, 29% of all patients developed a bacterial co-infection, which increased the chance of a fatal outcome[18,19]. Most of these patients had positive bacterial culture in the sputum. The most common bacteria were *Staphylococcus aureus* and *Streptococcus pneumoniae*[20].

In our study, according to IDSA/ATS 2007 criteria for sCAP, 32 (32.65%) of patients were classified in the group with sCAP, and the remaining 66 (67.34%) who did not meet those criteria were classified as CAP group. In terms of gender, males were predominant in both groups - sCAP/CAP (65.15% and 62.5%). This is in agreement with most studies that identify male gender as a risk factor for influenza and pneumonia[21]. A completely different result compared to our study was reported in one study conducted in Canada, in which 72% of patients who died were female[22]. Patients' age in our study had a significant influence on the development of sCAP and illness outcome. Patients in the sCAP group were significantly older that those in the CAP group, with average age of 56.8±17.3 *vs*. 46.1±14.8 (p=0.023). This finding, together with data from a large number of studies point out to adult patients as a vulnerable group, with risk to progress into a severe form of the illness and/or death. Thus, certain preventive and therapeutic measures in primary and secondary health care may have significant influence on the outcome.

The analysis of identified associated comorbidities showed that patients in the sCAP group had additional chronic conditions more often than patients in the CAP group, 29(90.62) *vs*. 38(57.57). The registered comorbidities significantly influenced the outcome ($p<0.01$). A large number of studies show that patients with one or more comorbidities must be hospitalized in intensive care units, and some of them are at risk of death[23,24].

In the group of sCAP patients, pneumonia manifested itself signifcantly more frequently with findings of lung consolidation on x-ray ($p<0.0001$), in comparison to the group with CAP. These findings correlate with a large number of global studies in which pneumonia was registered not only as the most frequent complication, but also as the most common cause of admission to the intensive care unit, often requiring mechanical ventilation and associated with a fatal outcome. It is important to identify penumonia most commonly associated with high-risk patients, in order to make a timely diagnosis and an adequeate clinical treatment[25,26].

In our study, 35/98(35.71%) patients were treated in the intensive care unit, and 29 (90.62%) of them belonged to the group with severe pneumonia. The remaining 6(9.09%) patients who belonged to the group with influenza and CAP stayed in the intensive care unit due to other complications from the central nervous system, renal system and multi-organ involvement.

A very common complication in patients with influenza, especially during the pandemic of 2009, was acute respiratory distress syndrome, a life-threatening condition with a mortality rate of 40-80% and the need of extracorporeal membrane oxygenation, which was the most common cause of a fatal outcome[27,28]. In our study, 7(21.87%) patients were registered with ARDS, all from the sCAP group. Mechanical ventilation was used in 12(37.5%), all from the sCAP group.

The mortality rate in our study was much higher in the group of patients with sCAP, which is in correlation with the mortality rate reported in relevant worldwide studies. The

mortality rate varies among published studies, and it ranges from 10% to as high as 50%, which depends on the different conditions and criteria according to which patients were analyzed as well as the criteria for admission to intensive care units [29,30]. Thus, the study performed in China showed that from 60 patients with severe form of influenza, 44% were treated at the intensive care unit and the lethality was 14.7%[31,32].

Taking into account the seriousness and severity of the clinical picture in patients with seasonal influenza and pneumonia as a complication, it is necessary to pay special attention to the need for implementation and timely initiation of appropriate antimicrobial and antiviral therapy. Following the recommendations of the relevant world associations (IDSA Guidelines for the Diagnosis, Treatment, Chemoprophylaxis, and Institutional Outbreak Management of Seasonal Influenza 2018, ATS/IDSA Diagnosis and Treatment of Adults with Community-acquired Pneumonia 2019, ERS/ESICM/ESCMID/ALAT guidelines for the management of severe community-acquired pneumonia 2023), the use of osaltamivir is recommended for all patients (outpatients and hospitalized) with confirmed influenza and pneumonia, regardless of the duration since the onset of symptoms, with the strongest recommendation for use in the first 48 hours after the onset of symptoms. The latest and first official guidelines for sCAP recommend multiplex PCR testing of lower respiratory samples, use of procalcitonin levels to manage the length of therapy, but also empiric therapy with osaltamivir for all patients with sCAP during the influenza season (ERS/ESICM/ESCMID/ALAT 2023)[13,15,31].

Conclusion

Severe pneumonia, as a complication in patients with seasonal influenza, significantly worsens the clinical course and increases mortality rate. Therefore, timely treatment, the implementation of adequate medical procedures as well as determination of the critical point when the respiratory complications usually begin are of crucial importance in preventing the most severe outcomes in patients with seasonal influenza and pneumonia. Official guidelines postulated by relevant international associations guide us in achieving this goal, on one hand, and, on the other hand, they also open further discussion and inquiries regarding the treatment of this type of patients.

Conflict of interest statement. None declared.

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