

THE IMPACT OF PNEUMONIA ON THE COURSE AND OUTCOME IN PATIENTS WITH SEASONAL INFLUENZA

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ABSTRACT

Introduction: Seasonal influenza, although often presented as a mild, self-limiting disease, is frequently accompanied by complications that lead to the development of a severe clinical presentation and a fatal outcome. The most common are respiratory complications, with secondary bacterial pneumonia being the leading cause.

Aim: The aim of this study is to determine the impact of pneumonia on the severity of the clinical presentation and outcome in patients with seasonal influenza.

Materials and Methods: This research is comparatively group-based and has been conducted at the University Clinic for Infectious Diseases and Febrile Conditions during a three-year period. The analysis consists of 122 adult patients with clinically and laboratory-confirmed influenza. Based on the severity of the clinical picture, the patients are divided into two groups, severe (n=87) and mild (n=35) forms of the disease. The study included demographic, general data, clinical symptoms, and signs as well as complications.

Results: Of 122 patients with seasonal influenza, complications were registered among 108(88.52%), with a significantly more frequent emergence among the group with severe influenza 93.1% vs 77.14% (p=0.012). Pneumonia was the most common 98(80.33%) and had a significant effect on disease severity (p=0.002). Complications from the types of ABI 8(6.56%), ARDS 7(5.74%), sepsis 5(4.1%), DIC 4 (3.28%) and otitis 2(1.64%) were reported only in the group with severe influenza. Acute meningoencephalitis was registered among 5(4.1%), gastroenterocolitis among 3(2.46%), and hepatic damage among 14(11.47%) of patients.

Conclusion: Pneumonia as the most common complication among patients with seasonal influenza significantly impacts the clinical course and outcome of the illness.

Keywords: influenza, complications, pneumonia

INTRODUCTION

Seasonal influenza is an acute respiratory viral infection caused by influenza viruses A (H1N1), A (H3N2) and B. Although commonly presented as a

mild to moderate self-limiting disease, it is often accompanied by numerous complications such as pneumonia, bacterial superinfections, to more severe and

invasive infections with multiorgan failure, which is also the most common reason for hospitalization, development of a severe clinical presentation and a fatal outcome [1, 2, 3, 4]. Respiratory complications are the most common in percentage, with secondary bacterial and primary viral pneumonia with mortality rates in the range of 6-29% [5, 6, 7]. Nearly one-third of patients with severe influenza have pneumonia [8, 9, 10, 11, 12]. Respiratory complications can progress to the development of ARDS (acute respiratory distress syndrome), a pathological condition with a mortality rate over 80% and a systemic inflammatory response with multiorgan failure leading to the development of sepsis.

Extrapulmonary complications involve a large number of tissue and systems. In this category are myocarditis, pericarditis or pancarditis with an 11% incident rate, toxic shock syndrome, as well as complications with the central nervous system, Guillain-Barre syndrome, Reyes syndrome, encephalitis- a condition which in certain cases reaches a mortality rate up to 30%, myositis and rhabdomyolysis, which frequently progress to the development of acute kidney failure [13,14,15].

MATERIALS AND METHODS

The study was prospective, clinical, compared within two groups and was conducted at the Clinic for Infectious Diseases and Febrile Conditions during a period of three years. It was designed to take into account ethical principles and was approved by the ethical committee of the Faculty of Medicine at Ss. Cyril and Methodius University of Skopje.

The study analyzed 122 adult patients (≥ 16 years of age) with clinically and laboratory-confirmed influenza, divided into two groups based on the severity of the clinical presentation- 87 with a severe and 35 with a mild form of influenza.

Group 1: patients with severe influenza: Defined as patients with a clinically and laboratory-confirmed influenza which meet the criteria for severe influenza: signs of respiratory weakness (dyspnea, tachypnea, hypoxia, cyanosis) such as arterial $\text{PaO}_2 < 70$ mmHg (< 9.0 KPa) and/or the need for me-

chanical ventilation and/or signs of ARDS ($\text{PaO}_2/\text{FiO}_2 \leq 200$), intensive care stay, exacerbation of an existing chronic disease.

The group of patients with severe influenza were further divided into two groups: 75 survived and 12 deceased patients.

Group 2: patients with mild influenza: Defined as patients with clinically and laboratory-confirmed influenza without signs of respiratory weakness nor pre-existing chronic illness.

The study excluded patients in whom death occurred in the first 24 hours. During admission, the following were observed: demographic characteristics, clinical signs and symptoms, as well as complications.

The presence of influenza viruses was confirmed through a nasopharyngeal swab using a method of real time RT-PCR (real-time reverse polymerase chain reaction).

The results were statistically processed through the SPSS program for Windows 13.0, with comparable statistical methods.

The value of $p < 0.05$ was taken as significant, and the value of $p < 0.01$ as highly significant.

RESULTS

The results of the findings yielded that of the 122 patients with influenza, complications were present among 108 (88.52%). These are significantly more often associated with a severe form ($p = 0.012$).

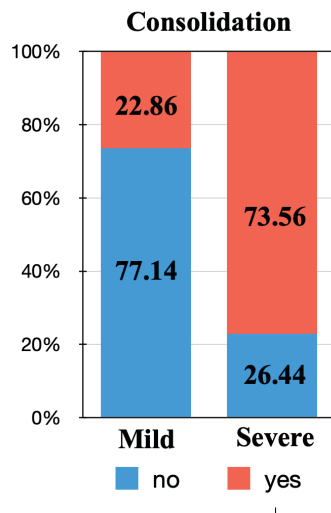
The most common complication was pneumonia, which was diagnosed among 98 (80.33%) patients, and the same had a significant influence on the severity of the illness ($p = 0.002$). Pneumonia was present among 22 (62.86%) patients with mild influenza, and among 76 (87.36%) patients with severe influenza. Bilateral pneumonia was diagnosed significantly more often among patients with severe influenza in comparison with those with mild influenza (77.01% vs 54.29% $p = 0.013$). Among 10 (11.49%) patients, all with a severe form of the disease pleural effusion was found (Table 1).

Table 1. *Complications and type of complications among patients in terms of the severity of the clinical picture*

variables	Influenza			p value
	Total n = 122	Mild n = 35	Severe n = 87	
Complications [n (%)]				
no	14(11.47)	8(22.86)	6(6.9)	^a 0.012*
yes	108(88.52)	27(77.14)	81(93.1)	
Pneumonia [n (%)]				
no	24(19.67)	13(37.14)	11(12.64)	^a 0.002**
yes	98(80.33)	22(62.86)	76(87.36)	
Bilateral Pneumonia [n (%)]				
no	36(29.51)	16(45.71)	20(22.99)	^a 0.013*
yes	86(70.49)	19(54.29)	67(77.01)	
Single Pneumonia [n (%)]				
no	110(90.16)	32(91.43)	78(89.66)	^c 1.0
yes	12(9.84)	3(8.57)	9(10.34)	
Pleural Effusion [n (%)]				
no	112(91.8)	35(100)	77(88.51)	^c 0.06
yes	10(8.2)	0	10(11.49)	
ARDS [n (%)]				
no	115(94.26)	35(100)	80(91.95)	^c 0.19
yes	7(5.74)	0	7(8.05)	
ABI [n (%)]				
no	114(93.44)	35(100)	79(90.8)	^c 0.1
yes	8(6.56)	0	8(9.2)	
DIC [n (%)]				
no	118(96.72)	35(100)	83(65.4)	^c 0.58
yes	4(3.28)	0	4(4.6)	
Meningoencephalitis [n (%)]				
no	117(95.9)	34(97.14)	83(95.4)	^c 1.0
yes	5(4.1)	1(2.86)	4(4.6)	
Sepsis [n (%)]				
no	117(95.9)	35(100)	82(94.25)	^c 0.32
yes	5(4.1)	0	5(5.75)	
Gastroenterocolitis [n (%)]				
no	119(97.54)	33(94.29)	86(98.85)	^c 0.2
yes	3(2.46)	2(5.71)	1(1.15)	
Hepatic Lesions [n (%)]				
no	108(88.52)	31(88.57)	77(88.51)	^c 1.0
yes	14(11.47)	4(11.43)	10(11.49)	
Otitis [n (%)]				
no	120(98.36)	35(100)	85(97.7)	^c 1.0
yes	2(1.64)	0	2(2.3)	

^ap (Chi-square test) ^cp (Fisher exact test) *p < 0.05 **p < 0.01

Pneumonia was confirmed through an x-ray of the lungs, where patients with severe influenza were significantly more likely to have a finding of pulmonary consolidation (73.56% vs 22.86%, $p=0.0001$) (Graph1).



Complications from the type of ARDS, ABI, DIC, sepsis and otitis were registered only among the group with severe influenza. The most frequent complication was ABI 8 (6.56%), followed by ARDS 7 (5.74%), sepsis 5 (4.1%), DIC 4 (3.28%) and otitis 2 (1.64%).

Meningocephalitis was registered among 5 (4.1%) patients, gastroenterocolitis among 3 (2.46%) patients, and hepatic damage with a rise in aminotransferases among 14 (11.47%) patients.

In the group of 87 patients with a severe form of influenza, complications were confirmed among 81 (93.1%), and in this test group, the most frequent complication was pneumonia, which was registered among 76 (87.36%) patients. A fatal outcome was registered among 12 (15.79%) of patients, all with pneumonia. It is of statistical significance that patients with x-ray findings of diffuse bilateral pneumonia died more frequently (71.42% vs 10.98%, $p=0.001$). The remaining complications, although more common in the group of deceased patients, did not show statistical significance (Tables 2 and 3).

Table 2. Complications and type of complications among patients in terms of the outcome

Variables	Severe Influenza			p value
	Total n = 87	Living n = 75	Deceased n = 12	
Complications [n (%)]				
no	6(6.89)	6(100)	0	°0.59
yes	81(93.1)	69(85.19)	12(14.81)	
Pneumonia [n (%)]				
no	11(12.64)	11(100)	0	°0.35
yes	76(87.36)	64(84.21)	12(15.79)	
Bilateral Pneumonia [n (%)]				
no	20(22.99)	19(95)	1(5)	°0.28
yes	67(77.01)	56(83.58)	11(16.42)	
Single Pneumonia [n (%)]				
no	78(89.65)	67(85.9)	11(14.1)	°1.0
yes	9(10.34)	8(8.89)	1(11.11)	
Pleural Effusion [n (%)]				
no	77(88.5)	65(84.42)	12(15.58)	°0.34
yes	10(11.49)	10(100)	0	
ARDS [n (%)]				
no	80(91.95)	71(88.75)	9(11.25)	°0.052
yes	7(8.05)	4(5.14)	3(42.86)	
ABI [n (%)]				
no	79(90.8)	70(88.61)	9(11.39)	°0.07
yes	8(9.19)	5(6.25)	3(37.5)	
DIC [n (%)]				
no	83(95.4)	73(87.95)	10(12.05)	°0.09
yes	4(4.6)	2(50)	2(50)	
Meningoencephalitis [n (%)]				
no	83(95.4)	71(85.54)	12(14.46)	°1.0
yes	4(4.6)	4(100)	0	
Sepsis [n (%)]				
no	82(94.25)	71(86.59)	11(13.41)	°0.53
yes	5(5.75)	4(80)	1(20)	
Gastroenterocolitis [n (%)]				
no	86(98.85)	74(86.05)	12(13.95)	°1.0
yes	1(1.15)	1(100)	0	
Hepatic Lesions [n (%)]				
no	77(88.51)	66(85.71)	11(14.29)	°1.0
yes	10(11.49)	9(90)	1(10)	
Otitis [n (%)]				
no	85(97.7)	73(85.88)	12(14.12)	°1.0
yes	2(2.3)	2(100)	0	

/°p (Chi-square test) °(Fisher exact test)

Table 3. RTG findings of the lungs among patients in terms of the outcome

Variables	Severe Influenza			‘p value
	Total n = 87	Living n = 75	Deceased n = 12	
RTG findings of the lungs [n (%)]				
no	9(10.34)	9(100)	0	0.205
yes	78(89.65)	66(84.62)	12(15.38)	
Consolidation [n (%)]				
no	23(26.44)	20(86.96)	3(13.04)	1.0
yes	64(73.56)	55(85.94)	9(14.06)	
Diffuse Bilateral Consolidation [n (%)]				
no	80(91.95)	73(89.02)	9(10.98)	0.001**
yes	7(8.04)	2(28.57)	5(71.42)	
Interstitial [n (%)]				
no	78(89.65)	66(84.62)	12(15.38)	0.35
yes	9(10.34)	9(100)	0	

DISCUSSION

In our study, the results of the tested groups of patients showed a representation of various complication which affected organic systems. Pneumonia represented one of the most common complications among patients with seasonal influenza, as confirmed in our study. [16, 17]. According to the WHO repots, during pandemics and epidemics, the largest number of cases of mortality among seasonal influenza are as a result of secondary bacterial infection presented as pneumonia. Thus, in the last pandemic report in 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, 98 (80.33%) patients had pneumonia. Of those, a total of 12 (12.24%) died, all of which were affected with severe influenza. In the group of severe influenza, pneumonia manifested itself significantly more frequently as bilateral ($p = 0.013$), with findings of lung consolidation ($p < 0.0001$), in comparison of the group with mild influenza where pneumonia manifested as unilateral with a finiding of interstitial changes in the x-ray of the lungs ($p = 0.012$). The figures correlate with a large number of global studies where pneumonia was registered not only as the most frequent complication, but also as the most common cause for admission in intensive care, need for mechanical ventilation and a fatal outcome. It is important to identify penumonia associated with high-risk

patients in order to administer timely diagnosis and adequate clinical treatment [21, 22].

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. In our study, 7 (8.05%) patients with ARDS were registered in the group with severe influenza, of which 3 (42.86%) died [23, 24].

In terms of neurological complications in our study, they had a dominant presence in the group with severe influenza (4.6% vs 2.86%), however this did not show statistical significance, most likely due to the small group of patients. Retrospective studies in the United States found an 8.5% increase in neurological complications in patients with seasonal influenza [25]. Neurological complications mainly concern conditions such as meningoencephalitis, focal neurological deficit, encephalopathy, and other conditions which have an abnormal electrographic findings. Life-threatening require early diagnosis, timely antiviral therapy, and a appropriate strategy for active immunization in the population. In other studies, the precentage of prevalence of neurological complications ranged from 1.6% to 6.8%. The studies concern both adult and pedaitric populations [26, 27]. In our study, the patients with neurological complications were presented most frequently with a clinical picture of encephalitis and meningoencephalitis.

In our study, 8 (6.56%) patients had acute kidney failure and all were of the group affected by severe influenza. They were treated in the in-

tensive care unit where three of them died. These patients had other accompanying complications, such as pneumonia and sepsis. According to the literature, the most common reason for the development of acute kidney failure among patients with influenza is acute rhabdomyolysis, which occurs as a result of aggression and inflammatory response which the virus manifests in the muscular fibers. This condition is most frequent among younger populations (28). Inflammatory mediators such as C-peptide, procalcitonin, serum amyloid A, CRP and others, which are elevated in the early phase of the bacterial infections, frequently present themselves as early complications among patients with influenza, especially those with enlarged body weight as a risk factor (29). According to the study of Vallejos A, acute kidney failure among patients with AH1N1 influenza most frequently manifests within the first week of the development of refractory oliguria, requiring immediate haemodialysis in 10 to 50% of patients as a result of the body's systemic inflammatory response accompanied by the virus, hypotension and shock [30].

Sepsis and septic shock are also one of the most commonly reported causes of death among patients with severely-complicated influenza treated in the intensive care units. This complication is much more common in patients with co-morbid conditions such as chronic obstructive pulmonary disease, as well as in adult patients over 65 years of age. Patients who develop septic shock and require mechanical ventilation are at a much higher risk of death and polymicrobial infection. [31].

CONCLUSION

In our study group, pneumonia stood as the most common complication and as such had a significant impact on the severity of the disease. Bilateral consolidation in the x-ray findings was of significant value with respect to the lethal outcome in patients with seasonal influenza. Pneumonia was registered as a complication in all deceased patients, but the x-ray findings of diffuse bilateral pneumonia had a statistically significant effect on the outcome. Early recognition of complications will allow for the implementation of adequate medical procedures that will contribute to adequate treatment and reduction in mortality.

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Резиме

ВЛИЈАНИЕТО НА ПНЕВМОНИЈАТА НА ТЕКОТ И НА ИСХОДОТ КАЈ ПАЦИЕНТИТЕ СО СЕЗОНСКА ИНФЛУЕНЦА

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Вовед: Сезонската инфлуенца, иако најчесто се презентира како лесно самолимитирачко заболување, неретко е придружена со компликации што се причина за развој на тешка клиничката слика и смртен исходот. Најчести се респираторните компликации, а како водечка се издвојува секундарната бактериска пневмонија. Целта на оваа студија е да се одреди влијанието на пневмонијата на тежината на клиничката слика и исходот кај пациентите со сезонска инфлуенца.

Материјал и методи: Истражувањето е проспективно, групно, споредбено и е изведено на Универзитетската клиника за инфективни болести и фебрилни состојби во текот на тригодишен период. Анализирани се 122 возрасни пациенти со клинички и лабораториски потврдена инфлуенца. Врз основа на тежината на клиничката слика пациентите се поделени во две групи, тешка (n = 87) и лесна (n = 35) форма на болеста. При вклучување во студијата бележени се демографски, општи податоци, клинички симптоми и знаци како и компликации.

Резултати: Од 122 пациенти со сезонска инфлуенца, компликации беа регистрирани кај 108 (88,52%), со сигнификантно почесто јавување во групата со тешка инфлуенца 93,1% vs 77,14% (p = 0,012). Процентуално најзастапена е пневмонијата 98(80,33%) и таа значително влијаеше на тежината на болеста (p = 0,002). Компликации од типот на АБИ 8 (6,56%), АРДС 7 (5,74%), сепса 5 (4,1%), ДИК 4 (3,28%) и отитис 2 (1,64%) беа регистрирани само во групата со тешка инфлуенца. Кај 5 (4,1%) пациенти е регистриран акутен менингоенцефалитис, гастроентероколитис кај 3 (2,46%), а хепатално оштетување кај 14 (11,47%) пациенти.

Заклучок: Пневмонијата како најчеста компликација кај пациентите со сезонска инфлуенца значајно влијае на клиничкиот тек и на исходот на болеста.

Клучни зборови: инфлуенца, компликации, пневмонија