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EPIDEMIC OF INFLUENZAE A H1N1 IN 2019 IN THE ZLATIBOR DISTRICT

Sažetak

Uvod: Influenza A H1N1 se širom sveta javlja sporadično ili epidemijski. Poslednjih decenija je bilo nekoliko pandemija ove bolesti sa milionima obolelih i više stotina hiljada umrlih. Klinička slika varira od asimptomatske do letalnog ishoda. Česte su pojave komplikacija od kojih je najteži akutni respiratorni distres sindrom. Pored komplikacija, na nepovoljan ishod bolesti utiče stariji uzrast, muški pol i udružena gojaznost.

Cilj istraživanja je bio da se ispita klinički tok i ishod bolesti bolesnika sa upalom pluća tokom epidemije influenze A H1N1 2019. godine u Zlatiborskom okrugu.

Metodi istraživanja: Retrogradno su prikupljeni i analizirani epidemiološki, klinički, mikrobiološki i radiografski podaci pacijenata sa influenzom A H1N1 lečenih na Odeljenju za infektivne i tropske bolesti i Jedinici intenzivne nege OB Užice. Virusološke i serološke analize su rađene na Institutu za imunologiju i virusologiju „Torlak“ u Beogradu. Dijagnoza akutnog respiratornog distres sindroma (ARDS) postavljena je prema berlinskoj definiciji. Statistička analiza obavljena je korišćenjem Statističkog paketa za društvene nauke SPSS (verzija 16.0).

Rezultati: Od ukupno 274 bolesnika, žene su činile 52,9%. Najčešći uzrast bio je od 61 do 70 godina. Komorbiditete je imalo 55,4% bolesnika, od čega 61,8% kardiovaskularne bolesti.

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C reaktivni protein bio je povišen kod 79,2% bolesnika. Upalu pluća potvrđenu radiografskim nalazom imalo je 82,8% bolesnika, od toga 51,5% obostranu. Četiri bolesnice su bile trudne, GML 5–9. Dve od njih su imale lakši klinički tok infekcije, jedna srednje težak, sa jednostranom upalom pluća. Sve tri su imale povoljan ishod bolesti. Četvrta trudnica je primljena u teškom kliničkom stanju i odmah upućena u tercijernu zdravstvenu ustanovu gde se bolest završila letalnim ishodom. U jedinici intenzivne nege lečeno je 10,2% bolesnika.

Komplikacije su nastale kod 23,7% bolesnika, od toga ARDS kod 52,3%. 55,9% bolesnika sa ARDS-om je bilo uzrasta od 61 do 70 godina, a 58,8% je bilo muškog pola. Među bolesnicima sa ARDS-om njih 94,1% je imalo udružene bolesti, najčešće KVB (85,3%). CRP je bio povišen kod 85,3% bolesnika sa ARDS-om. Kod 8,4% bolesnika bolest je imala nepovoljan tok i završila se letalnim ishodom. Među ovim bolesnicima, 65,2% su bile žene, a uzrast preko 65 godina imalo je 73,9%. Kod 95,6% ovih bolesnika bile su prisutne udružene bolesti, od kojih KVB kod 87%.

Zaključak: Tokom epidemije influenze 2019. godine u Zlatiborskom okrugu, upalu pluća, najčešće obostranu, imali su najčešće bolesnici uzrasta 61–70 godina sa udruženim kardiovaskularnim bolestima. Isti faktori rizika su uslovljavali nastanak komplikacija i nepovoljan ishod bolesti. Najčešća komplikacija i faktor rizika za letalni ishod bolesti bio je ARDS.

Ključne reči: influenza A H1N1, epidemija 2019, Zlatiborski okrug, klinički tok, ishod bolesti

Introduction

Influenza A H1N1 is a serious problem worldwide. The last decade has been marked by pandemics of this disease. About 400,000 people died from the disease in 208 countries during the 2009. pandemic. Pandemic 2015/16. covered 17 countries with about 217,000 deaths. More than 490,000 people were hospitalized for this disease during 2018/19, and about 34,000 patients had an unfavorable outcome (1). Influenza virus infection ranges from asymptomatic to multiorgan damage with respiratory complications (3). Influenza pneumonia can be a primary infection, but also a secondary bacterial one (3). Sepsis and acute respiratory distress syndrome (ARDS) are possible complications of this infection and important risk factors for a poor prognosis. In addition, the unfavorable outcome of the disease is influenced by old age, male gender and obesity, as well as cardiac surgery (4, 5).

The aim of the study was to analyze

- epidemiological, clinical and biochemical parameters of patients with influenza A H1N1
- frequency, types and course of complications,
- epidemiological, clinical and biochemical data of patients with ARDS and patients with lethal outcome of the disease.

Methods

We were retrogradely examined patients with influenza A H1N1, treated in the Department of Infectious Diseases and the Intensive Care Unit of the General Hospital of Uzice, from January 15. to April 01. 2019. years.

We were collected epidemiological, biochemical and microbiological data, presence of comorbidities, radiography of the lungs.

Influenza A virus was detected at the Institute of Immunology and Virology „Torlak” in Belgrade by polymerase multiplication reaction (PCR) from a throat swab and determination of IgM antibody titer from serum.

The diagnosis of acute respiratory distress syndrome (ARDS) was made according to the Berlin definition, which includes

- acute clinical condition,
- clinical picture of respiratory damage (tachypnea > 20 min),
- PaO₂ < 6.6 kPa (50 mmHg),
- bilateral pulmonary infiltrates on the radiograph (6).

Hematological and biochemical analyzes from blood were performed by standard methods used in the Republic of Serbia. The etiological diagnosis of associated bacterial infections was made by identifying the causative agent from sputum/bronchial lavage culture or blood. The minimum inhibitory concentration assay was performed by the E test, according to CLSI guidelines (7).

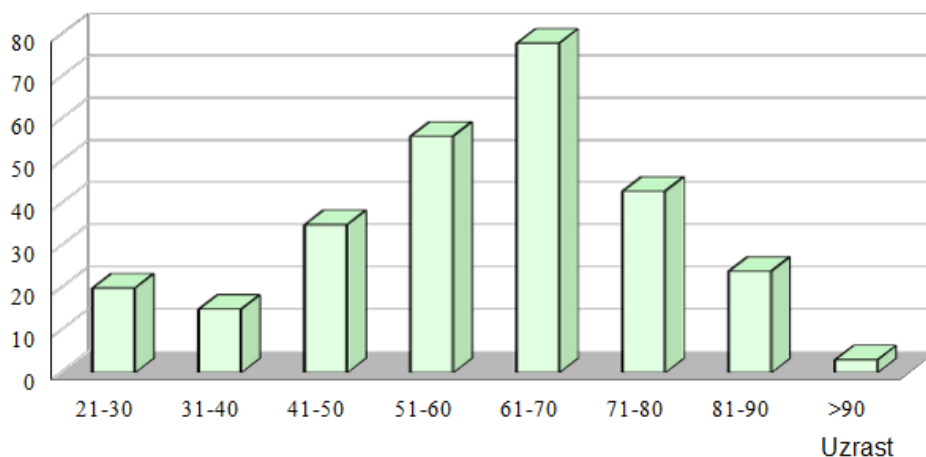
The Statistical Package for Social Sciences SPSS (version 16.0) was used for statistical analysis. A significant difference was represented by P < 0.05.

Results

From total of 274 patients, 145 (52.9%) were women, 129 (47.1%) men. It was not a statistically significant difference in gender (p > 0.05).

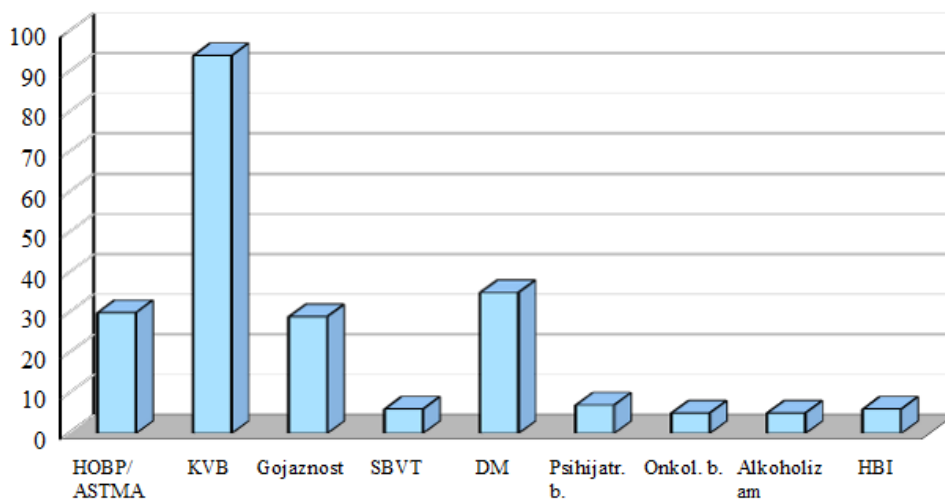
The age of the patients ranged from 42 to 93 years, average 59.9 +/- 16.3. The largest number of patients was aged 61 to 70 years. The age of the patients is shown in Graph 1.

Graph 1. Age of patients with influenza A H1N1



152 patients (55.4%) had comorbidities, of which the most common were cardiovascular diseases (CVD), (61.8%) ($p < 0.01$) (Graph 2).

Graph 2. Comorbidities of patients with influenza A H1N1

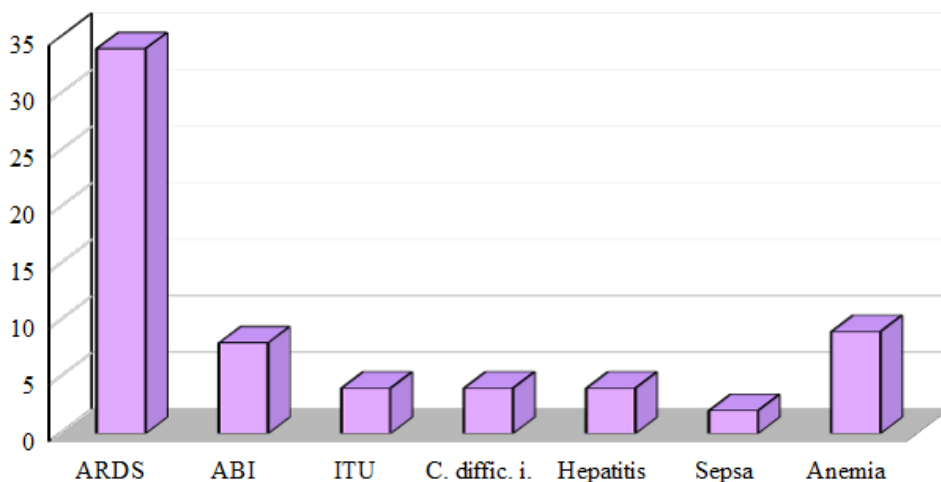


A quarter of patients had leukocytosis, while leukopenia was observed in 14.2%. C reactive protein (CRP) was elevated in 217 (79.2%) patients ($p < 0.01$). CRP values ranged from 0.2 to 499 mg/L. In 227 (82.8%) patients pneumonia was confirmed by radiographic findings ($p < 0.01$), most often bilateral (51.5%). Laboratory parameters and radiographic findings of the lungs are shown in Table 1.

Table 1. Laboratory parameters and radiographic findings of the lungs of patients with influenza A H1N1

Characteristics	Number of patients (%)	P
WBC > 11x10 ⁹ /L	70 (25.5)	0.00
WBC < 4.0x10 ⁹ /L	39 (14.2)	0.00
Hb < 120 g/L	80 (30.3)	<0.01
RBC < 4.0x10 ¹² /L	63 (23)	0.00
PLT < 150x10 ⁹ /L	69 (25.2)	0.00
CRP > 10 mg/L	217 (79.2)	<0.01
X-ray pneumonia left	34 (12.4)	<0.01
X-ray pneumonia right	76 (27.7)	
X-ray pneumonia bilateral	117 (42.7)	

Complications occurred in 65 (23.7%) patients. ARDS was the most common, in 34 (52.3%) ($p < 0.01$) (Graph 3).

Graph 3. Complications in patients with influenza A H1N1

The length of hospitalization was on average 8.5 +/- 5.2 days (1 - 51 days).

Out of the total number, 28 (10.2%) patients were treated in the Intensive care unit.

Four patients were pregnant, GML 5 - 9. Two of them had a mild clinical course of infection, one moderate with unilateral pneumonia. All three had a favorable disease outcome. A fourth pregnant woman was admitted in a severe clinical condition and was immediately referred to a tertiary health institution where the disease ended in death.

Further results relate to patients with ARDS.

The most common age of patients with ARDS was 61 to 70 years ($p < 0.01$). Of all patients with ARDS, 32 (94.1%) had associated diseases, most often CVD (85.3%) ($p < 0.01$). There was no significant difference in the incidence of leukopenia and leukocytosis. A significant majority of these patients (85.3%) in the stage of ARDS development had elevated CRP ($p < 0.01$). The parameters of patients with ARDS are shown in Table 2.

Table 2. Characteristics of patients with influenza A H1N1 and ARDS

Characteristics	No (%) (34)	*P
Age	41-50	1
	51-60	4
	61-70	19 (55.9)
	71-80	4
	81 -90	5 (14.7)
	> 90	1
Gender	Male	20 (58.8)
	Female	14 (41.2)
Comorbidities	Asthma/COPD	11 (32.3)
	CVD	29 (85.3)
	Obesity	12 (35.3)
	Diabetes mellitus	13 (38.2)
	Psychiatric diseases	2
	Oncological diseases	2
	Alcoholism	3
	Total	32 (94.1)
Laboratory parameters	WBC $> 11 \times 10^9/L$	16 (47.1)
	WBC $< 4.0 \times 10^9/L$	9 (26.4)
	Hb $< 120 \text{ g/L}$	15 (44.1)
	RBC $< 4.0 \times 10^{12}/L$	17 (50)
	PLT $< 150 \times 10^9/L$	11 (32.4)
	CRP $> 10 \text{ mg/L}$	29 (85.3)

*P - statistical significance for samples ≥ 5

In 23 (8.4%) patients the disease had an unfavorable course and ended in death. The analysis of the parameters of patients with an unfavorable course of the disease showed a significantly higher frequency of women. These patients were more often older than 65 years (73.9%). Most had comorbidities (95.6%), most often CVD ($p < 0.01$).

The parameters of patients with an unfavorable course of the disease are shown in Table 3.

Table 3. Characteristics of patients with influenza A H1N1 and lethal outcome

Characteristics	No (%) (23)	*P	
Age	41-50	1	<0.01
	51-60	2	
	61-70	11 (47.8)	
	71-80	3	
	81 -90	5 (21.7)	
	> 90	1	
Gender	Male	7 (34.8)	0.002
	Female	15 (65.2)	
Comorbidities	Asthma/COPD	8 (34.8)	0.00
	CVD	20 (87)	
	Obesity	9 (39.1)	
	Diabetes mellitus	10 (43.4)	
	Psychiatric diseases	1	
	Oncological diseases	1	
	Alcoholism	2	
	Total	22 (95.7)	0.00

*P - statistical significance for samples ≥ 5

Discussion

The clinical course and outcome of influenza depend on many factors including the sex and age of the patient, the duration of symptoms, associated diseases, the vaccine status of the patient, and many others (8). Our patients had an average age of 59.9 years. They were older than the described Pakistani or Taiwanese population where the average age was 36.9 and 52.4 years, respectively (9, 10). The average age of our patients with lethal outcome was higher than patients with the same disease outcome in the mentioned studies, also. However, the age of sick and dead patients in Europe and America was usually over 60 years. This correlates with our data as expected. (1, 11). Geographical age distribution is influenced by cultural differences and lifestyle, as well as the vaccine status of infected persons (12).

In our study, there were no significant gender difference which is consistent with the results of other studies (11). We observed a gender difference among patients with an unfavorable disease outcome where the majority were women. In the literature, these are more common males (13). This finding may be affected by sample size. Our sample of subjects with an unfavorable disease outcome is much smaller than the sample in the mentioned research.

The most common comorbidities of our patients were cardiovascular diseases, which is in line with the age structure. The presence of other associated diseases was also important in patients with ARDS and an unfavorable disease outcome. Cardiovascular diseases were also most often associated with them. It is known that the influenza virus stimulates proinflammatory cytokines that lead to endothelial dysfunction, increased plasma viscosity and the release of endogenous catecholamines.

In addition, the clinical picture of influenza implies dehydration, which leads to hypotension and hypoxemia. This virus also has profound procoagulant effects (14). It is logical that people with chronic CVD will find it much harder to tolerate these effects of the virus and develop complications more often.

Influenza A H1N1 virus replication was detected in alveolar cells. The high virulence of this virus induces an aberrant immune response and severe lung damage. This process affects the progression of respiratory symptoms and the development of ARDS (15). Patients with chronic lung disease have an expectedly more severe clinical picture.

However, our patients with associated diabetes, more than patients with chronic lung disease, had ARDS and lethal outcome of influenza. A similar result was reported by Mata-Marin et al. (16). The “cytokine storm” caused by the influenza virus in diabetics can be expected to cause greater deregulation of the immune system (17).

Obesity has also been described as an important factor in the development of complications in patients with influenza A. The impact of obesity is explained by the altered cellular immune response that exists in these individuals, and is reflected in reduced T lymphocyte counts. Dysfunction of the cellular immune response to the influenza virus is a consequence of this process (18).

Pneumonia caused by influenza A virus is common in younger people as well as in people without comorbidities (19). Our results confirm the high percentage of pneumonia in patients with influenza described by other researchers (20).

The lethal outcome in our patients was higher than expected for patients with seasonal influenza pneumonia (21). Higher lethality, similar to our result, has been described in the case of associated bacterial pneumonia (22). The frequency of proven bacterial infections in our subjects was low. The reason may be the use of broad-spectrum antibiotics from the very beginning of the disease. In support of this is the finding of a significant frequency of elevated C reactive protein in our patients.

Pregnancy as a risk factor for the development of ARDs in influenza has already been observed by other researchers (20). This is confirmed by the example of a pregnant woman with an unfavorable clinical course in our study.

Conclusion

During the influenza epidemic in 2019 in the Zlatibor district, the risk factor for pneumonia was the age of 61 to 70. Pneumonia was usually bilateral. The major risk factor for complications and unfavorable disease outcomes were associated cardiovascular diseases. ARDS was the most common complication. This complication was also the most common cause of unfavorable disease outcome. The onset of ARDS was accompanied by elevated C reactive protein values which may indicate secondary bacterial pneumonia. Females and age over 65 years were risk factors for death.

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