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EPIDEMIJA INFLUENZE A H1N1 2019. GODINE U ZLATIBORSKOM OKRUGU

Abstract

Introduction: Influenza A H1N1 occurs worldwide sporadically or epidemically. There have been several epidemics of this disease in recent decades. Millions of people fell ill and hundreds of thousands died. The clinical picture varies from asymptomatic to lethal outcome. Older age, male gender and obesity are the most common risk factors for adverse disease.

The aim of the research was to examine the clinical course and outcome of the disease of patients with pneumonia during the epidemic of influenza A H1N1 in 2019 in the Zlatibor district.

Methods: Epidemiological, clinical, microbiological and radiographic data of patients with influenza A H1N1 treated at the Department of Infectious and Tropical Diseases and the Intensive Care Unit of the General Hospital of Užice were retrogradely collected and analyzed. Virological and serological analyzes were performed at the Institute of Immunology and Virology "Torlak" in Belgrade. The diagnosis of acute respiratory distress syndrome (ARDS) was made according to the Berlin definition. Statistical analysis was performed using the Statistical Package for Social Sciences SPSS (version 16.0).

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Results: Out of a total of 274 patients, women accounted for 52.9%. The most common age was 61 to 70 years. 55.4% of patients had comorbidities, 61.8% of that had cardiovascular disease. C reactive protein was elevated in 79.2% of patients. Pneumonia confirmed by radiographic findings was present in 82.8% of patients, 51.5% of that had bilateral pneumonia. 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. 10.2% of patients were treated in the intensive care unit. Complications occurred in 23.7% of patients, ARDS in 52.3% of that. 55.9% of patients with ARDS were aged 61 to 70 years, and 58.8% were male. Among patients with ARDS, 94.1% had associated diseases, most often CVD (85.3%). C reactive protein was elevated in 85.3% of patients with ARDS. In 8.4% of patients, the disease had an unfavorable course and ended in death. Among these patients, 65.2% were women, and 73.9% were over 65 years of age. Associated diseases were present in 95.6% of these patients, cardiovascular diseases was present in 87% of that.

Conclusion: During the influenza epidemic in 2019 in the Zlatibor district, pneumonia, most often bilateral, was most often in patients aged 61–70 with associated cardiovascular diseases. These were also the main risk factors for complications and adverse disease outcome. ARDS was the most common complication and risk factor for the lethal outcome of the diseases.

Key words: influenza A H1N1, epidemic 2019, Zlatibor district, clinical course, outcome of disease

Uvod

Influenza A H1N1 predstavlja ozbiljan problem u celom svetu. Osim sporadičnih slučajeva, poslednje decenije su obeležile i pandemije ove bolesti. U pandemiji 2009. u 208 zemalja od ove bolesti umrlo je skoro 400.000 ljudi. Pandemijom 2015/16. bilo je obuhvaćeno 17 zemalja sa oko 217.000 smrtnih ishoda. 2018/19. je zbog ove bolesti hospitalno lečeno više od 490.000 ljudi, a nepovoljan ishod bolesti imalo je oko 34.000 obolelih (1). Infekcija virusom influenze je u dijapazonu od asimptomatske do multiorganske uz respiratorne komplikacije (3). Upala pluća tokom gripa može biti primarna infekcija, ali i sekundarna bakterijska (3). Sepsa i akutni respiratorno distress sindrom (ARDS) moguće su komplikacije ove infekcije i važni faktori rizika za lošu prognozu. Osim njih, na nepovoljan ishod bolesti utiče stariji uzrast, muški pol i gojaznost, kao i kardiohirurške intervencije (4, 5).

Cilj ispitivanja

Cilj ispitivanja bio je da se analiziraju

- epidemiološki, klinički i biohemijski parametri bolesnika sa influenzom A H1N1,
- učestalost, vrste i tok komplikacija,
- epidemiološki, klinički i biohemijski podaci bolesnika sa ARDS-om i bolesnika sa letalnim ishodom bolesti.

Metodi

Retrogradno su ispitani bolesnici lečeni na Odeljenju za infektivne bolesti i Jedinici za intenzivnu negu Opšte bolnice Užice, u periodu od 15.01.2019. do 01.04.2019. godine.

Prikupljeni su epidemiološki, biohemijski i mikrobiološki podaci, prisustvo komorbiditeta i radiografski nalaz pluća.

Virus influenze A dokazivan je na Institutu za imunologiju i virusologiju „Torlak“ u Beogradu iz brisa ždrela reakcijom umnožavanja polimeraze (PCR) i određivanjem IgM titra antitela iz seruma.

Dijagnoza akutnog respiratornog distress sindroma (ARDS) postavljena je prema berlinskoj definiciji koja podrazumeva:

- akutno kliničko stanje,
- kliničku sliku respiratornog oštećenja (tahipneja > 20 min),
- $PaO_2 < 6,6$ kPa (50 mmHg),
- bilateralni plućni infiltrati na rendgenogramu (6).

Hematološke i biohemijske analize iz krvi rađene su standardnim metodama koji se primenjuju u Republici Srbiji. Etiološka dijagnoza udruženih bakterijskih infekcija postavljena je identifikacijom uzročnika iz kulture sputuma/bronhijalnog lavata ili krvi. Ispitivanje minimalne inhibitorne koncentracije vršeno je E testom, prema CLSI smernicama (7).

Za statističku analizu korišćen je Statistički paket za društvene nauke SPSS (verzija 16.0). Značajnu razliku predstavljao je $P < 0.05$.

Rezultati

Ispitano je ukupno 274 bolesnika, 145 (52,9%) žena, 129 (47,1%) muškaraca, što nije ukazalo na statistički značajnu razliku u polu ($p > 0.05$).

Uzrast bolesnika bio je od 42 do 93 godine, prosečno $59,9 \pm 16,3$. Najveći broj bolesnika bio je uzrasta od 61 do 70 godina. Uzrast bolesnika prikazan je na grafikonu 1.

Grafikon 1. Uzrast bolesnika sa influenzom A H1N1

Komorbidityte je imalo 152 bolesnika (55.4%), od čega najčešće kardiovaskularne bolesti (KVB), (61.8%) ($p < 0.01$) (grafikon 2).

Grafikon 2. Komorbiditeti bolesnika sa influenzom A H1N1

Četvrtina pacijenata je imala leukocitozu, dok je leukopenija uočena kod 14,2%. C reaktivni protein (CRP) bio je povišen kod 217 (79,2%) bolesnika ($p < 0,01$). Vrednosti CRP bile su od 0,2 do 499 mg/L. Upalu pluća potvrđenu radiografskim nalazom imalo je 227 (82,8%) bolesnika ($p < 0.01$), najčešće obostranu (51,5%). Laboratorijski parametri i radiografski nalaz pluća prikazani su u tabeli 1.

Tabela 1. Laboratorijski parametri i radiografski nalaz pluća bolesnika sa influenzom A H1N1

Parametri	Broj bolesnika No (%)	P
WBC > 11×10^9 /L	70 (25.5)	0.00
WBC < 4.0×10^9 /L	39 (14.2)	0.00
Hb < 120 g/L	80 (30.3)	<0.01
RBC < 4.0×10^{12} /L	63 (23)	0.00
PLT < 150×10^9 /L	69 (25.2)	0.00
CRP > 10 mg/L	217 (79.2)	<0.01
Rtg pneumonia levostrano	34 (12.4)	<0.01
Rtg pneumonia desnostrano	76 (27.7)	
Rtg pneumonia obostrano	117 (42.7)	

Komplikacije su nastale kod 65 (23,7%) bolesnika, pri čemu je signifikantno najčešći bio ARDS, kod 34 (52,3%) ($p < 0.01$) (grafikon 3).

Grafikon 3. Komplikacije kod bolesnika sa influenzom A H1N1

Dužina hospitalizacije bila je u proseku 8.5 ± 5.2 dana (1–51 dan).

Od ukupnog broja, u jedinici intenzivne nege lečeno je 28 (10,2%) bolesnika.

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.

Dalji rezultati se odnose na bolesnike sa ARDS-om.

Najčešći uzrast bolesnika sa ARDS-om bio je od 61 do 70 godina ($p < 0.01$). Od svih bolesnika sa ARDS-om, 32 (94,1%) je imalo udružene bolesti, najčešće KVB (85,3%) ($p < 0.01$). Nije bilo značajne razlike u učestalosti leukopenije i leukocitoze. Značajna većina ovih bolesnika (85.3%) u fazi nastanka ARDS-a imala je povišen CRP ($p < 0.01$). Parametri bolesnika sa ARDS-om prikazani su u tabeli 2.

Tabela 2. Karakteristike bolesnika sa influenzom A H1N1 i ARDS-om

Karakteristike		No (%) (34)	*p
Uzrast	41-50	1	< 0.01
	51-60	4	
	61-70	19 (55.9)	
	71-80	4	
	81 -90	5 (14.7)	
	> 90	1	
Pol	Muškarci	20 (58.8)	0.078
	Žene	14 (41.2)	
Komorbiditeti	Astma/HOBP	11 (32.3)	0.00
	KVB	29 (85.3)	
	Gojaznost	12 (35.3)	
	Diabetes mellitus	13 (38.2)	
	Psijijatrijska ob.	2	
	Onkološke bolesti	2	
	Alkoholizam	3	
	Ukupno	32 (94.1)	0.00
Laboratorijski parametri	WBC > 11×10^9 /L	16 (47.1)	0.016
	WBC < 4.0×10^9 /L	9 (26.4)	
	Hb < 120 g/L	15 (44.1)	0.238
	RBC < 4.0×10^{12} /L	17 (50)	1.0
	PLT < 150×10^9 /L	11 (32.4)	< 0.01
	CRP > 10mg/L	29 (85.3)	0.00

*P - statistička značajnost za uzorke ≥ 5

Kod 23 (8,4%) bolesnika bolest je imala nepovoljan tok i završila se letalnim ishodom. Analizom parametara bolesnika sa nepovoljnim tokom bolesti uočena je značajno veća učestalost žena. Ovi bolesnici su češće bili stariji od 65 godina (73,9%). Većina je imala komorbiditete (95,6%), najčešće KVB ($p < 0.01$).

Parametri bolesnika sa nepovoljnim tokom bolesti prikazani su u tabeli 3.

Tabela 3. Karakteristike bolesnika sa influencom A H1N1 i letalnim ishodom

Karakteristike		No (%) (23)	*P
Uzrast	41-50	1	<0.01
	51-60	2	
	61-70	11 (47.8)	
	71-80	3	
	81 -90	5 (21.7)	
	> 90	1	
Pol	Muškarci	7 (34.8)	0.002
	Žene	15 (65.2)	
Komorbiditeti	Astma/HOBP	8 (34.8)	0.00
	KVB	20 (87)	
	Gojaznost	9 (39.1)	
	Diabetes mellitus	10 (43.4)	
	Psihijatrijske bolesti	1	
	Onkološke bolesti	1	
	Alkoholizam	2	
	Ukupno	22 (95.7)	0.00

*P - statisticka značajnost za uzorke ≥ 5

Diskusija

Klinička slika i ishod influenze variraju u zavisnosti od mnogo faktora, među kojima su pol i uzras bolesnika, dužina trajanja simptoma, udružene bolesti, vakcinalni status obolelog i mnogi drugi (8). Naši pacijenti su bili prosečne starosti 59,9 godina, što je starije od opisane pakistanske, ili tajvanske populacije gde je prosečna starost bila 36,9, odnosno 52,4 godine (9, 10). Takođe, prosečna starost naših pacijenata sa letalnim ishodom bila je viša od pacijenata sa istim ishodom bolesti u pomenutim istraživanjima. Međutim, uzrast obolelih i preminulih pacijenata u Evropi i Americi najčešće je preko 60 godina što, očekivano, odgovara našim rezultatima (1, 11). Svakako da na ovakvu geografsku starosnu distribuciju utiču kulturološke razlike i način života, ali i vakcinalni status obolelih osoba (12).

U našem istraživanju nije uočena značajna razlika u polu, što je u skladu sa drugim rezultatima (11). Razliku u polu smo uočili među bolesnicima sa nepovoljnim ishodom bolesti gde su u većini bile žene. U literaturi su to češće osobe muškog pola (13). Treba uzeti u obzir da je naš uzorak ispitanika sa nepovoljnim ishodom bolesti mnogo manji od uzorka u pomenutom istraživanju.

Najčešći komorbiditeti naših bolesnika bile su kardiovaskularne bolesti, što je u skladu sa starosnom strukturom. Prisustvo drugih udruženih bolesti bilo je od zna-

čaja i kod bolesnika sa ARDS-om i nepovoljnim ishodom bolesti. I kod njih su bile najčešće udružene kardiovaskularne bolesti. Poznato je da virus influenze podstiče proupalne citokine koji dovode do endotelne disfunkcije, povećanog viskoziteta plazme i oslobađanja endogenih kateholamina.

Uz to, klinička slika gripa podrazumeva dehidraciju koja dovodi do hipotenzije i hipoksemije. Ovaj virus ima i duboke prokoagulantne efekte (14). Logično je da će osobe sa hroničnim KVB mnogo teže podneti navedene efekte virusa i češće razviti komplikacije.

Otkrivena je replikacija virusa influenze A H1N1 u alveolarnim ćelijama. Visoka virulencija ovog virusa indukuje aberantni imuni odgovor i veliko oštećenje pluća. Ovaj proces utiče na progresiju respiratornih simptoma i nastanak ARDS-a (15). S obzirom na to, bilo je očekivano da bolesnici sa hroničnim bolestima pluća imaju težu kliničku sliku.

Međutim, naši bolesnici sa udruženom šećernom bolešću, više od bolesnika sa hroničnim plućnim bolestima, imali su ARDS i letalni ishod influenze. Sličan rezultat su objavili Mata-Marín i saradnici (16). Može se očekivati da „citokinska oluja” uzrokovana virusom influenze kod dijabetičara izazove veću deregulaciju imunološkog sistema (17).

Gojaznost je, takođe, opisana kao važan faktor za nastanak komplikacija kod bolesnika sa influenzom A. Uticaj gojaznosti se objašnjava izmenom celularnog imunog odgovora koji postoji kod ovih osoba, a ogleda se u smanjenom broju T limfocita. Posledica toga je disfunkcija celularnog imunog odgovora na virus influenze (18).

Upala pluća uzrokovana virusom A influenze česta je i kod mlađih osoba, kao i kod osoba bez komorbiditeta (19). Naši rezultati potvrđuju visok procenat upale pluća kod bolesnika sa influenzom koji je već uočen od strane drugih istraživača (20).

Letalni ishod kod naših bolesnika bio je veći od očekivanog za bolesnike sa pneumonijom kod sezonskog gripa (21). Veći letalitet, sličan našem rezultatu, opisan je u slučaju udružene bakterijske pneumonije (22). Učestalost dokazanih bakterijskih infekcija kod naših ispitanika bila je mala. Razlog može biti primena antibiotika širokog spektra od samog početka bolesti. U prilog tome je i nalaz značajne učestalosti povišenog C reaktivnog proteina kod naših bolesnika.

Trudnoću kao faktor rizika za nastanak ARDs-a kod influenze već su uočili drugi istraživači (20). To potvrđuje primer trudnice sa nepovoljnim kliničkim tokom u našem istraživanju.

Zaključak

Tokom epidemije influenze 2019. godine u Zlatiborskom okrugu faktor rizika za nastanak pneumonije bio je uzrast od 61 do 70 godina. Pneumonija je najčešće bila obostrana. Udružene kardiovaskularne bolesti bile su glavni faktor rizika za nastanak

komplikacija i nepovoljnog ishoda bolesti. Najčešća komplikacija je bio ARDS. Ova komplikacija je bila i najčešći uzrok nepovoljnog ishoda bolesti. Nastanak ARDS-a je bio praćen povišenim vrednostima C reaktivnog proteina, što može ukazati na sekundarnu bakterijsku pneumoniju. Ženski pol i uzrast preko 65 godina bili su faktori rizika za letalni ishod.

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EPIDEMIC OF INFLUENZA 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),
- $\text{PaO}_2 < 6.6 \text{ kPa}$ (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 > 11×10^9 /L	70 (25.5)	0.00
WBC < 4.0×10^9 /L	39 (14.2)	0.00
Hb < 120 g/L	80 (30.3)	<0.01
RBC < 4.0×10^{12} /L	63 (23)	0.00
PLT < 150×10^9 /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	< 0.01
	51-60	4	
	61-70	19 (55.9)	
	71-80	4	
	81 -90	5 (14.7)	
	> 90	1	
Gender	Male	20 (58.8)	0.078
	Female	14 (41.2)	
Comorbidities	Asthma/COPD	11 (32.3)	0.00
	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)	0.00
Laboratory parameters	WBC > 11×10^9 /L	16 (47.1)	0.016
	WBC < 4.0×10^9 /L	9 (26.4)	
	Hb < 120 g/L	15 (44.1)	0.238
	RBC < 4.0×10^{12} /L	17 (50)	1.0
	PLT < 150×10^9 /L	11 (32.4)	< 0.01
	CRP > 10mg/L	29 (85.3)	0.00

*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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