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Original Article

Predictors of Hospitalization and Admission to Intensive Care Units of Influenza Patients in Serbia through Four Influenza Seasons from 2010/2011 to 2013/2014

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SUMMARY: A retrospective analysis of the surveillance data on laboratory confirmed cases of influenza in 4 post pandemic seasons in Serbia was performed to evaluate predictors of hospitalization and admission to intensive care units (ICU). The specimens, including nasal and throat swabs were tested for influenza. Univariate and multivariate logistic regression analyses were performed. Data of a total of 777 confirmed influenza cases were analyzed. Age > 65 years, the presence of any co-morbidity or the presence of ≥ 2 comorbidities, infection with influenza virus subtype A (H1) pdm09, and an interval greater than 3 days between symptom onset and the first physician visit, were independently associated with hospital admission. These variables, as well as infection with non-subtype influenza virus A, were predictors for ICU admission. Obesity and chronic neurological disease were independent predictors for ICU admission but not hospitalization. Overall, 41.7% of patients with influenza had at least one co-morbidity, but only 3% of all patients were vaccinated against influenza. Identification of high risk groups and education of these groups regarding their increased susceptibility to severe forms of influenza, and in particular regarding the importance of influenza vaccination, is essential.

INTRODUCTION

Influenza is a serious public health problem because it is associated with an increased number of physician visits, hospital admissions, and increased absence from work. In a temperate climate region, the epidemic of influenza commonly occurs during the autumn and winter months. The outbreak, duration, intensity, and geographical spread of influenza are unpredictable and depend on a number of factors, such as the characteristics of the virus, the sensitivity of the population, climate, and environmental factors (1–3). Patients requiring hospitalization for severe forms of influenza usually suffer from chronic respiratory disease, asthma, diabetes mellitus, chronic heart disease, chronic kidney disease, or are immunocompromised patients undergoing immunosuppressive therapy or chemotherapy (4,5). There is limited information from Central and Southeastern Europe on the predictors of hospitalization of patients with influenza in the post-pandemic influenza seasons, when the influenza virus A (H1) pdm09 becomes a seasonal influenza virus (6). We focused on the characteristics of laboratory confirmed cases, particularly regarding treatment site.

The aim of this study was to identify predictors of hospitalization and admission to the intensive care unit (ICU) of patients with influenza over 4 seasons (2010/2011, 2011/2012, 2012/2013, 2013/2014) in the Republic of Serbia.

MATERIALS AND METHODS

The Serbian influenza surveillance system: The health care system in Serbia is based on universal health coverage. Health care of the population is directly provided through a network of health care institutions and is categorized into 3 levels: primary, secondary, and tertiary health care. All citizens have access to health care in Serbia, irrespective of social status.

In Serbia, influenza is seasonally monitored through different surveillance systems: universal, sentinel, and

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non-sentinel. The universal surveillance system for influenza-like-illness (ILI)-outpatients was implemented in 2006 and includes approximately 158 health facilities, and general and pediatric practices (according to the season). This system provides data for the joint European Center for Disease Prevention and Control (ECDC)-World Health Organization (WHO) Regional Office for Europe influenza bulletin, Flu News Europe, and for The European Surveillance System (TESSy).

Sentinel surveillance of ILI, acute respiratory infection (ARI) and sentinel severe acute respiratory infection (SARI), in Serbia first started in the 2009/10 season, during a pandemic, following WHO recommendations. Sentinel surveillance of ILI and ARI are functional and include 359 sentinel doctors, general practitioners, and pediatricians (depending on the season), with coverage of 6% of the population. A SARI sentinel surveillance system was implemented in 10 hospitals. Hospitals specializing in infectious diseases, pulmonology, and pediatrics were included. All age groups were represented in the surveillance system.

The National Institute of Public Health uploads all data regarding laboratory confirmed cases, obtained from all types of surveillance systems in the country, to the same database. Respiratory specimens were collected from a selection of ILI and SARI cases, meeting the case definition and in consultation with an epidemiologist. However, the number of collected and tested samples varied, according to the epidemiological situation of influenza in the country. Hospitalized patients were routinely monitored, particularly those admitted to ICUs. With an increasing number of cases developing as the influenza season progressed, specimens were taken from the majority of SARI patients.

Laboratory testing for influenza was ordered at the discretion of doctors at primary health care centers and clinicians in hospitals, in consultation with epidemiologists from the District Institutes of Public Health who organized the taking of samples. Laboratory confirmed cases were analyzed over 4 seasons, within the period of surveillance of the 40th week of one year to the 20th week of the following year.

For influenza surveillance, the WHO case definition for ILI (2011) was used: an acute respiratory illness with onset over the preceding 7 days, with a measured temperature ≥ 38˚C and a cough (7). The SARI WHO case definition was also used: an acute respiratory illness with onset of the following symptoms ≤ 7 days prior to hospital admission and requiring overnight hospitalization: history of fever or measured temperature of ≥ 38°C, cough and shortness of breath or difficulty breathing.

A retrospective study of predictors of hospitalization in patients with laboratory confirmation of influenza infection over 4 post pandemic seasons (2010/2011, 2011/2012, 2012/2013, 2013/2014) in the Republic of Serbia was conducted, based on the surveillance of laboratory confirmed cases of influenza, by the National Institute of Public Health of Serbia and 22 District Institutes of Public Health throughout the country.

This study was conducted in accordance with professional and methodological guidance for epidemiological surveillance of influenza for the current season, issued by the Institute of Public Health of Serbia, in compliance with WHO recommendations (7). The questionnaires for laboratory confirmed cases of influenza were filled in manually by epidemiologists or technicians from the District Institutes of Public Health, or clinicians from hospitals. These were then submitted to the Institute of Public Health of Serbia. The questionnaire response rate was approximately 85%. For laboratory diagnosis, nasal and throat swabs were collected into a suitable transport medium. For laboratory confirmation of influenza, real time polymerase chain reaction was used, using the WHO CDC reagent kit for influenza diagnostics (7). Testing was performed in the National Reference Laboratory for influenza and other respiratory viruses, at the Institute of Virology, Vaccines and Sera "Torlak" and at the Center for Virology of the Institute of Public Health of Vojvodina.

Study design: This study included only laboratory confirmed influenza cases reported during the 4 influenza seasons to Institute of Public Health of Serbia. All cases were divided into 3 groups, according to the site where treatment was administered: patients treated in the ICU (individuals with serious forms of the disease), hospitalized patients not admitted to the ICU, and patients treated at the primary health care (PHC) center.

During the period of observation, we collected the following data from all subjects: age; sex; date of symptom onset; symptoms; comorbidities, including chronic respiratory disease, asthma, diabetes mellitus, chronic heart disease, chronic kidney disease, chronic liver disease, chronic neurological disease, immunodeficiency condition, morbid obesity (body mass index ≥ 40); pregnancy, number of comorbidities (≤1 and >2); date of first physician visit; number of days between the onset of symptoms and first physician visit (over than 3 days); antiviral treatment; number of days between the onset of symptoms and influenza antiviral therapy (> 2 days); complications, such as pneumonia; virus type and subtype; and vaccination status.

We defined a variable of the existence of any comorbidity, which referred to chronic respiratory disease, asthma, diabetes mellitus, chronic heart disease, chronic kidney disease, chronic liver disease, chronic neurological disease, immunodeficiency condition, and obesity.

We compared cases treated at PHC centers with hospitalized cases without those treated in ICU. We also compared patients treated in the ICU with patients treated at PHC as well as the patients treated in the ICU plus those who were hospitalized, with patients treated at PHC.

The Institute of Public Health of Serbia determined that data collection through influenza surveillance was for routine public health surveillance and therefore, was not subject to institutional review board approval for the

protection of human subjects of research.

Data analysis: Descriptive analyses were used to summarize patient demographics and clinical characteristics, including age, sex, symptoms, interval of > 3 days from the onset of symptoms to the first physician visit, presence of underlying chronic medical conditions, type and sub-types of influenza virus, antiviral use, hospital admission, ICU admission.

For statistical analysis we used Pearson's chi-square test, Pearson's correlation coefficient and univariate and multivariate logistic regression analysis. All test variables with statistical significance in the univariate model ($p \leq 0.10$) were included in the multivariate model. Statistical testing was performed at the level of statistical significance of 0.05. Statistical analysis was performed using the statistical package SPSS 20.

RESULTS

Over the 4 seasons, 777 confirmed influenza cases were notified. Distribution of the laboratory-confirmed influenza cases by month during the 4 seasons (2010/2011, 2011/2012, 2012/2013, and 2013/2014) are shown in Fig. 1.

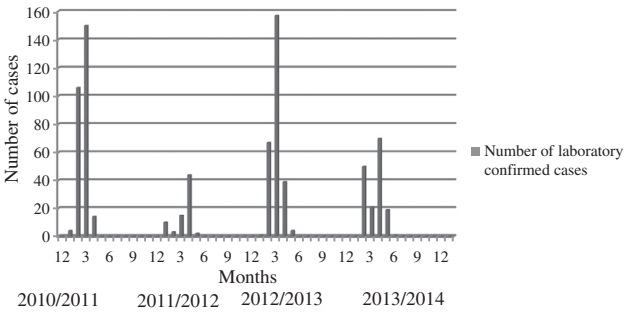

Fig. 1. Laboratory-confirmed influenza cases by month during 4 seasons -2010/2011, 2011/2012, 2012/2013, and 2013/2014 in Serbia (n = 777)

Overall, 322 (41.44%) patients were treated in PHC centers, 329 (42.34%) were hospitalized, but not treated in the ICU, and 126 (16.22%) patients were treated in the ICU. There was no significant difference among patients treated in PHC centers, hospital, and ICU according to sex. The percentage of older patients (≥ 18 years and ≥ 65 years) was significantly higher among hospitalized patients and patients in the ICU than among patients in PHC centers. Influenza virus sub-type A (H1) pdm09 was significantly more frequent among patients in hospital (54.1%) and in the ICU (67.5%) than among patients in PHC centers (28.9%), reflecting the greater disease severity associated with this subtype compared with subtypes A (H3) or with influenza B viruses (Table 1).

Table 1. Basic characteristics of patients with laboratory confirmed influenza virus by the site of their treatment, 2010/2011, 2011/2012, 2013/2013, and 2013/2014 influenza seasons, Serbia

Characteristic	Primary health care (n = 322) No (%)	Hospital (n = 329) No (%)	ICU (n = 126) No (%)	P value[1)]
Sex (female)	157 (48.8)	164 (49.8)	54 (42.9)	0.399
Age groups (yr)				
0-4	44 (13.7)	18 (5.5)	7 (5.6)	
5-14	136 (42.2)	21 (6.4)	3 (2.4)	
15-29	49 (15.2)	69 (21.0)	12 (9.5)	
30-64	86 (26.7)	179 (54.4)	87 (69.0)	
≥ 65	7 (2.2)	42 (12.8)	17 (13.5)	< 0.001
The type and sub-typed of the virus				
A	4 (1.2)	14 (4.3)	8 (6.3)	
A (H1) pdm09	93 (28.9)	178 (54.1)	85 (67.5)	
A (H3)	158 (49.1)	77 (23.4)	17 (13.5)	
B	67 (20.8)	60 (18.2)	16 (12.7)	< 0.001
Symptoms				
Fever	318 (98.8)	324 (98.5)	125 (99.2)	0.824
Sore throat	201 (62.4)	168 (51.1)	52 (41.3)	< 0.001
Runny nose	183 (56.8)	120 (36.5)	34 (27.0)	< 0.001
Sneezing	156 (48.4)	89 (27.1)	29 (23.0)	< 0.001
Cough	301 (93.5)	306 (93.0)	100 (79.4)	< 0.001
Conjunctivitis	20 (6.2)	17 (5.23)	8 (6.3)	0.814
Change of states of consciousness	2 (0.6)	4 (1.2)	21 (16.7)	< 0.001
Headache	186 (57.8)	205 (62.3)	64 (50.8)	0.077
Gastrointestinal[2)]	55 (17.1)	73 (22.2)	18 (14.3)	0.092
Myalgia	195 (60.6)	255 (77.5)	81 (64.3)	< 0.001
Joint pains	115 (35.7)	194 (59.0)	58 (46.0)	< 0.001
Shortness of breath	32 (9.9)	198 (60.2)	121 (96.0)	< 0.001
Nosebleeds	6 (1.9)	7 (2.1)	7 (5.6)	0.068
Viral pneumonia	11 (3.4)	218 (66.3)	125 (99.2)	< 0.001
Vaccine history	11 (3.4)	8 (2.4)	4 (3.2)	0.751
Pregnancy[3)]	4 (2.5)	11 (6.7)	1 (1.9)	0.117

[1)] : P value for χ^2 test.
[2)] : Nausea, vomiting, diarrhea.
[3)] : Percentage of pregnancies shown represents proportion in women aged 16 to 45.
ICU, intensive care unit.

As expected, symptoms correlated with disease severity (Table 1). Specifically, shortness of breath was significantly more frequent among patients treated in ICU and hospitalized patients compared to patients who were treated in PHC centers. Viral pneumonia was documented in 218 (66.3%) patients in hospital and 125 (99.2%) in the ICU.

A significantly higher proportion of people with comorbidities (chronic respiratory disease, asthma, diabetes mellitus, chronic heart disease, chronic kidney disease, chronic neurological disease, immunodeficiency condition, and obesity) was found among patients treated in hospital and in the ICU than among patients treated in PHC centers. The percentage of patients with at least one comorbidity was significantly higher among patients treated in hospital (38.6%) and in the ICU (53.2%) than among those treated in PHC centers (11.5%). There was a significantly higher percentage of patients with 2 or more comorbidities among ICU (29.4%) and non-ICU hospital (15.5%) patients than among patients treated in PHC centers (1.6%) (Table 2).

The interval (over 3 days) from the onset of symptoms to the first physician visit was significantly longer for patients treated in the ICU (31%) and hospital (21.6%) than for patients admitted to PHC centers (10.9%).

Of the 126 patients admitted to the ICU, 103 (81.7%) received antiviral treatment. Of the 329 patients admitted to hospital without ICU, 153 (46.5%) received antiviral treatment. Of 103 patients in the ICU, 25 (24.3%) received antiviral treatment within 48 hours of symptom onset (Table 3).

The interval between the onset of symptoms and undertaking antiviral therapy was significantly longer (over 3 days) in patients treated in the ICU (75.7%) and in hospital (66%) than in patients admitted to PHC centers (33.3%). Therefore, the severity of illness increased with the increasing interval from symptom onset to the start of antiviral therapy (Table 3).

Table 2. Distribution of comorbidities i.e. underlying medical conditions in influenza patients and interval from symptom onset to first visiting a physician, 2010/2011, 2011/2012, 2013/2013, and 2013/2014 influenza seasons, Serbia

Comorbidity	Primary health care (n = 322) No (%)	Hospital (n = 329) No (%)	ICU (n = 126) No (%)	P value[1)]
Chronic respiratory disease	6 (1.9)	27 (8.2)	29 (23.0)	< 0.001
Asthma	3 (0.9)	14 (4.3)	13 (10.3)	< 0.001
Diabetes mellitus	4 (1.2)	21 (6.4)	21 (16.7)	< 0.001
Chronic heart disease	10 (3.1)	49 (14.9)	33 (26.2)	< 0.001
Chronic kidney disease	4 (1.2)	29 (8.8)	14 (11.1)	< 0.001
Chronic liver disease	1 (0.3)	4 (1.2)	2 (1.6)	0.319
Chronic neurological disease	13 (4.0)	15 (4.6)	14 (11.1)	0.008
Immune Compromised status	8 (2.5)	47 (14.3)	15 (11.9)	< 0.001
Obesity	6 (1.9)	12 (3.6)	15 (11.9)	< 0.001
Any comorbidity[2)]	42 (13.0)	178 (54.10)	104 (82.5)	< 0.001
Number of comorbidities				
0	280 (87.0)	151 (45.9)	22 (17.5)	
1	37 (11.5)	127 (38.6)	67 (53.2)	
2+	5 (1.6)	51 (15.5)	37 (29.4)	< 0.001
Interval from symptom onset to first visiting a physician **(≤ 3 d v. > 3 d)**				
≤ 3	287 (89.1)	258 (78.4)	87 (69.0)	
> 3	35 (10.9)	71 (21.6)	39 (31.0)	< 0.001

[1)] : P value for χ^2 test.
[2)] : Chronic respiratory disease, asthma, diabetes mellitus, chronic cardiac disease, chronic renal disease, chronic liver disease, chronic neurological disease, immune compromised status and obesity.
ICU, inteusive care unit.

Table 3. Patients with laboratory confirmed influenza virus by the site of their treatment, 2010/2011, 2011/2012, 2013/2013, and 2013/2014 influenza seasons regarding antiviral therapy, Serbia

	Primary health care (n = 322) No (%)	Hospital (n = 329) No (%)	ICU (n = 126) No (%)	P value[1)]
No of patients with given antiviral therapy	6 (1.9)	153 (46.5)	103 (81.7)	< 0.001
No of days between the onset of symptoms and given antiviral therapy				
≤ 2	4 (66.7)	52 (34.0)	25 (24.3)	
3+	2 (33.3)	101 (66.0)	78 (75.7)	0.041

[1)] : P value for χ^2 test.
ICU, inteusive care unit.

There were 7 pregnant women in the first trimester of pregnancy and 7 in the third trimester. A total of 11 (6.7%) pregnant women required admission to hospital and one (1.9%) to ICU.

There were no statistically significant differences in vaccination status between the 3 groups. Overall, 41.7% of patients with influenza had at least one comorbidity, but only 3% of all patients were vaccinated against influenza (Table 1). Morbid obesity was present in 15/126 (11.9%) ICU cases and in 12/329 (3.6%) hospital admissions not requiring ICU (Table 2).

Patients treated in ICU compared to those treated in PHC: Univariate logistic regression analysis showed that the following variables were significantly associated with disease severity (defined by ICU admission): age ≥ 65 years, not sub-type influenza virus A, influenza virus sub-type A (H1) pdm09, chronic respiratory disease, asthma, diabetes mellitus, chronic heart disease, chronic kidney disease, chronic neurological disease, immune suppression, obesity (Table 4, Model I,II,III).

The presence of any comorbidity significantly increased the odds of severe disease (OR, 31.52; 95% CI, 17.95–55.33). The odds for severe disease were greater among patients with more than 3 days from the onset of the symptoms to first physician visiting (OR, 3.68; 95% CI, 2.20–6.16) and among those with ≥ 2 comorbidities (OR, 26.36; 95% CI, 10.06–69.04). The univariable odds ratio associated with obesity was (OR, 7.12; 95% CI, 2.70–18.80).

All variables showing a significant association with ICU admission ($p \leq 0.10$) on univariate regression analysis were entered into the multivariate regression model. A significant ($p \leq 0.001$, r = 0.77) correlation was found between 2 or more comorbidities and any number of comorbidities, 3 models of multivariate regression analyses (MRA) were used for the identification of independent variables. In the first MRA model, the following factors were examined: type of comorbidity (chronic respiratory disease, asthma, diabetes mellitus, chronic heart disease, chronic kidney disease, chronic neurological disease, immunocompromised status, and obesity), age > 65 years, virus type and sub-type, and an interval greater than 3 days between symptom onset and the first physician visit; however a number of comorbidities and the existence of any comorbidity were excluded from the analysis (Table 4). In the second MRA model, the number of comorbidities was analyzed (≥ 2 vs. ≤ 1); age ≥ 65 years, virus type and sub-type, interval greater than

Table 4. Results of univariate and multivariate logistic regression analysis: predictors of hospitalization and admission to intensive care units (ICU) in patients with influenza for ICU v. PHC

Characteristic	Univariate OR (95% CI)	Multivariate (Model I) OR (95% CI)	Multivariate (Model II) OR (95% CI)	Multivariate (Model III) OR (95% CI)
Sex (female)	0.79 (0.52-1.19)			
Adults≥65	**7.02 (2.83-17.38)**	/	/	3.19 (1.00-10.14)
The type and sub-typed of the virus				
A	**5.39 (1.59-18.23)**	9.67 (2.06-45.39)	14.25 (3.54-57.29)	8.76 (1.81-42.45)
A (H1) pdm09	**5.11 (3.28-7.96)**	7.79 (4.04-15.02)	8.29 (4.70-14.61)	6.25 (3.28-11.91)
A (H3)	**0.16 (0.09-0.28)**	/	/	/
B	0.55 (0.31-1.00)			
Comorbidity				
Chronic respiratory diseases	**15.75 (6.35-39.04)**	17.94 (6.17-52.15)		
Asthma	**12.23 (3.42-43.72)**	16.75 (3.55-79.05)		
Diabetes mellitus	**15.90 (5.34-47.38)**	20.63 (5.48-77.67)		
Chronic heart diseases	**11.07 (5.26-23.31)**	9.82 (3.86-25.02)		
Chronic liver diseases	5.18 (0.47-57.61)			
Chronic kidney diseases	**9.94 (3.20-30.82)**	10.96 (2.63-45.63)		
Chronic neurological diseases	**9.94 (3.20-30.82)**	6.43 (2.27-18.21)		
Immune compromised status	**5.30 (2.19-12.85)**	3.86 (1.68-8.56)		
Obesity	**7.12 (2.70-18.80)**	9.80 (3.01-31.93)		
Any comorbidity[1)]	**31.52 (17.95-55.33)**			27.68 (14.60-52.48)
≥ 2 comorbidities[2)]	**26.36 (10.06-69.04)**		37.61 (12.92-109.52)	
More than 3 days[3)]	**3.68 (2.20-6.16)**	4.01 (1.90-8.48)	3.65 (1.92- 6.95)	4.18 (1.94-9.04)
Vaccine history	1.08 (0.38-3.45)			

In bold, in the univariate model $p \leq 0.10$

[1)] : For this variable, a separate model was constructed (multivariable for age 65 and more, influenza virus type A, influenza virus sub-typed A(H1)pdm09, A(H3), the interval of more than 3 days from the onset of symptoms to the first visit to a physician).

[2)] : For this variable, a separate model was constructed (multivariable for age 65 and more, influenza virus type A, influenza virus sub-typed A(H1)pdm09, A(H3), the interval of more than 3 days from the onset of symptoms to the first visit to a physician).

[3)] : More than 3 days from the onset of the symptoms to visiting a physician.

ICU, inteusive care unit; PHC, public health care.

3 days between symptom onset and the first physician visit, comorbidity type, and the existence of any comorbidity, were not included in the analysis. The third MRA model analyzed the existence of any comorbidity, age ≥ 65, virus type and sub-type, and interval greater than 3 days between the symptom onset and the first physician visit; it did not include comorbidity type or the number of comorbidities.

In our multivariable model, the presence of "any comorbidity" was significantly associated with admission to the ICU (OR, 27.68; 95% CI, 14.60–52.48) and with hospital admission (OR, 6.38; 95% CI, 4.23–9.62).

The presence of chronic respiratory disease was associated with a higher risk of admission to hospital, particularly to an ICU (OR, 17.94; 95% CI, 6.17–52.15). Asthma, diabetes mellitus, chronic heart disease, chronic renal disease, immunosuppression, and obesity significantly increased the risk of hospital and ICU admission. Non-subtype influenza virus A was the significant independent predictor for admission to the ICU (OR, 14.25; 95% CI, 3.54–57.29) and for hospital admission (OR, 3.94; 95% CI, 1.22–12.77). Subtype influenza A (H1) pdm09 was the significant independent predictor in all 3 groups. In a separate multivariable analysis of hospital controls without ICU admission and of community controls, we observed consistent associations.

Patients treated in ICU plus hospitalized patients compared to those treated in PHC: Univariate logistic regression identified the following predictors of the occurrence of the severe form of disease, defined by admission to hospital: chronic respiratory disease, asthma, diabetes mellitus, chronic heart disease, chronic kidney disease, immune suppression, and obesity (Table 5). An interval > 3 days between symptom onset and the first physician visit correlated with severe disease (OR, 2.61; 95% CI, 1.73–3.95).

Based on MRA, the independent positive predictors for admission to the hospital were: an interval of > 3 days between the onset of symptoms and the first physician visit, any comorbidity and the presence of at least 2 comorbidities. Among individual comorbidities, significant independent predictors for hospital admission were: chronic respiratory disease, asthma, diabetes mellitus, chronic heart disease, chronic kidney disease, and immunosuppression. Obesity was not a significant independent predictor for hospital and ICU admission. We

Table 5. Results of univariate and multivariate logistic regression analysis: predictors of hospitalization and admission to intensive care units (ICU) in patients with influenza for ICU + hospital v. PHC

Characteristic	Univariate OR (95% CI)	Multivariate (Model I) OR (95% CI)	Multivariate (Model II) OR (95% CI)	Multivariate (Model III) OR (95% CI)
Sex (female)	0.97 (0.73- 1.29)			
Adults ≥65	**6.71 (3.02-11.88)**	3.85 (1.57- 9.45)	5.54 (2.35-13.05)	3.73 (1.51-9.22)
The type and sub-typed of the virus				
A	**3.37 (2.49- 4.57)**	/	3.94 (1.22-12.77)	/
A (H1) pdm09	**4.04 (1.38-11.84)**	2.26 (1.47- 3.48)	2.77 (1.79- 4.28)	2.04 (1.31-3.19)
A (H3)	**0.27 (0.20- 0.37)**	0.46 (0.29- 0.73)	0.52 (0.33- 0.82)	0.47 (0.30-0.76)
B	0.85 (0.58- 1.25)			
Comorbidity				
Chronic respiratory diseases	**7.39 (3.14-17.38)**	6.68 (2.68-16.65)		
Asthma	**6.71 (2.02-22.31)**	6.82 (1.94-23.95)		
Diabetes mellitus	**8.09 (2.87-22.78)**	4.75 (1.53-14.72)		
Chronic heart diseases	**6.86 (3.50-13.45)**	4.29 (2.02- 9.08)		
Chronic liver diseases	4.29 (0.51-35.80)			
Chronic kidney diseases	**8.30 (2.95-23.36)**	4.23 (1.35-13.28)		
Chronic neurological diseases	1.62 (0.83- 3.17)			
Immune compromised status	**6.19 (2.92-13.12)**	4.31 (1.90- 9.74)		
Obesity	**3.32 (1.36- 8.14)**	/		
Any comorbidity[1)]	**7.23 (5.16-10.12)**			6.00 (4.23-8.50)
≥ 2 comorbidities[2)]	**15.20 (6.10-37.90)**		12.46 (4.85-31.96)	
More than 3 days[3)]	**2.61 (1.73- 3.95)**	2.69 (1.68- 4.31)	2.59 (1.64- 4.10)	2.70 (1.72-4.54)
Vaccine history	0.77 (0.33- 1.76)			

In bold, in the univariate model $p \leq 0.10$

[1)] : For this variable, a separate model was constructed (multivariable for age 65 and more, influenza virus type A, influenza virus sub-typed A(H1)pdm09, A(H3), the interval of more than 3 days from the onset of symptoms to the first visit to a physician).

[2)] : For this variable, a separate model was constructed (multivariable for age 65 and more, influenza virus type A, influenza virus sub-typed A(H1)pdm09, A(H3), the interval of more than 3 days from the onset of symptoms to the first visit to a physician).

[3)] : More than 3 days from the onset of the symptoms to visiting a physician.

PHC, public health care.

found that among specific comorbidities, asthma (OR, 6.82; 95% CI, 1.94–23.95) was most strongly associated with disease severity.

Hospitalized patients compared to patients treated in PHC: Univariate logistic regression showed that the following factors were significantly associated with hospital admission: age ≥ 65 years, influenza virus type A, influenza virus sub-typed A (H1) pdm09, an interval of > 3 days between the onset of symptoms to the first physician visit, and the presence of ≥ 2 comorbidities (Table 6). Among specific comorbidities, significant independent predictors of hospital admission were: chronic respiratory disease, asthma, diabetes mellitus, chronic heart disease, chronic renal disease, and immunosuppression. In all 3 models, infection with influenza virus A (H3) was a protective factor, independently associated with admission to hospital not requiring ICU (Table 6).

DISCUSSION

This is the first study to address independent predictors of hospitalization and admission to the ICU of influenza patients in Serbia. Our study showed that the following factors were independent risk factors for hospitalization, i.e. admission to ICU and the appearance of severe forms of the disease: age > 65 years, the existence of any comorbidity, the number of comorbidities (2 and more than less of 2), infection with influenza A (H1) pdm09 subtype and non-sub-type influenza virus A, an interval greater than 3 days between symptom onset and the first physician visit. Similar results were described in previous studies assessing the risk factors for severe forms of the disease. Patient age was significantly associated with clinical severity, as defined by ICU admission (6,8). The presence of chronic respiratory disease, asthma, chronic heart disease, diabetes mellitus, chronic kidney disease, chronic neurological disease, and immunodeficiency condition, was associated with a higher risk for admission to hospital and to the ICU.

A study conducted in Greece in the first post pandemic season showed that metabolic diseases (including diabetes) and chronic respiratory disease were the most common comorbidities in patients treated in ICU (9). A study conducted in Spain, in the first season after the pandemic, indicated that chronic obstructive pulmonary disease, obesity, and diabetes were the most fre-

Table 6. Results of univariate and multivariate logistic regression analysis: predictors of hospitalization and admission to intensive care units (ICU) in patients with influenza for Hospital v. PHC

Characteristic	Univariate OR (95% CI)	Multivariate (Model I) OR (95% CI)	Multivariate (Model II) OR (95% CI)	Multivariate (Model III) OR (95% CI)
Sex (female)	1.04 (0.77- 1.42)			
Adults ≥ 65	**6.59 (2.91-14.89)**	4.29 (1.72-10.68)	5.59 (2.33-13.39)	4.12 (1.68-10.14)
The type and sub-typed of the virus				
A	**3.53 (1.15-10.85)**	/	/	/
A (H1) pdm09	**2.90 (2.10-4.01)**	2.11 (1.34-3.31)	2.04 (1.32-3.17)	1.78 (1.12-2.82)
A (H3)	**0.32 (0.23-0.44)**	0.51 (0.32-0.81)	0.48 (0.30-0.76)	0.49 (0.30-0.79)
B	0.85 (0.58-1.25)			
Comorbidity				
Chronic respiratory diseases	**4.71 (1.92-11.56)**	3.91 (1.46-10.45)		
Asthma	**4.72 (1.35-16.60)**	5.56 (1.50-20.62)		
Diabetes mellitus	**5.42 (1.84-15.97)**	3.30 (0.97-11.21)		
Chronic heart diseases	**5.46 (2.71-10.98)**	2.76 (1.25-6.17)		
Chronic liver diseases	3.95 (0.44-35.54)			
Chronic kidney diseases	**7.69 (2.67-22.12)**	3.60 (1.01-11.81)		
Chronic neurological diseases	1.14 (0.53-2.43)			
Immune compromised status	**6.54 (3.03-14.08)**	3.86 (1.68-8.56)		
Obesity	1.99 (0.74-5.38)			
Any comorbidity[1)]	**7.86 (5.32-11.60)**			6.38 (4.23-9.62)
≥ 2 comorbidities[2)]	**11.63 (4.58-29.55)**		8.89 (3.38-23.39)	
More than 3 days[3)]	**2.26 (1.46-3.50)**	2.39 (1.46-3.90)	2.47 (1.53-3.99)	2.56 (1.56-4.23)
Vaccine history	1.42 (0.56-3.58)			

In bold, in the univariate model $p \leq 0.10$

[1)] : For this variable, a separate model was constructed (multivariable for age 65 and more, influenza virus type A, influenza virus sub-typed A (H1) pdm09, A (H3), the interval of more than 3 days from the onset of symptoms to the first visit to a physician).

[2)] : For this variable, a separate model was constructed (multivariable for age 65 and more, influenza virus type A, influenza virus sub-typed A (H1) pdm09, A (H3), the interval of more than 3 days from the onset of symptoms to the first visit to a physician).

[3)]: More than 3 days from the onset of the symptoms to visiting a physician.

PHC, public health care.

quent pre-existing conditions in patients with influenza (10). Research conducted in Canada during the season 2013/2014 indicated that the majority of patients treated in the ICU, had pulmonary disease, heart disease, and diabetes mellitus (11).

Our findings were consistent with the WHO recommendations for immunization against influenza, concerning patients at an increased risk of developing severe disease, defined as disease resulting in hospitalization (12). These results indicate that the probability of complications among patients with influenza increased with the number of comorbidities. In our study, 82.5% of patients with severe disease and treated in the ICU, had at least one comorbidity. In Canada, research conducted in the season 2013/2014, showed that 84.7% of patients treated in ICU had at least one comorbidity (11).

The link between obesity and influenza was first recorded in the early stage of the pandemic in 2009, when the data from numerous countries indicated that obese people were at higher risk of hospitalization, ICU admission, and developing more severe forms of the disease (13,14). Obese patients with and without chronic diseases were at increased risk of respiratory complications during the influenza season. Preventative measures, particularly immunization and antiviral treatment, should prioritize these patients.

In our study, 11.9% of patients in ICU were excessively obese. Based on multivariate regression analysis, obesity was independently associated with ICU admission and therefore the occurrence of severe disease. These findings were consistent with the results of previous studies (15,16).

In Serbia, during the reported period, patients with laboratory confirmed influenza A (H1) pdm09 were more likely to be hospitalized and treated in the ICU than patients with confirmed influenza virus A(H3), A or B. Furthermore, infection with virus influenza A (H3) was a protective factor, independently associated with admission to hospital without ICU. A French study reported similar findings for infection with A (H3N2) (17).

The results of studies conducted in the United States, indicated that hospitalized patients with virus influenza A (H1) pdm09 were more likely to have severe forms of the disease than those infected with A (H3) or B virus. Our results were consistent with those of previous studies (18).

The quality of routine surveillance data involving systems which rely on doctors and clinicians to detect cases may be limited in comparison with data collected in research programs. As well, as for most population based surveillance systems, a certain degree of underreporting probably occurred.

Some form of bias selection cannot be completely excluded; however, the same methodology for conducting influenza surveillance was used for all 4 seasons and in accordance with professional and methodological guidance. Also, laboratory testing of influenza did not change among seasons.

Although limited to laboratory confirmed cases, these data provide valid information about predictors of hospitalization or severe outcome and have an impact on clinical treatment. Also, these findings are important for the improvement of treatment at the PHC level and for developing adequate prevention strategies.

These findings are consistent with findings of other studies on risk factors for hospitalization, representing the severe forms of the disease and for admission to the ICU. Knowledge of predictors for the occurrence of severe forms of the disease caused by influenza viruses, as well as the implementation of adequate preventive measures, can help to reduce the number of influenza cases, or at least to reduce the occurrence of complications, representing severe forms of the disease.

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Conflict of interest None to declare.

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