Original Article

Characteristics and Outcomes of Critically ill Patients with Influenza A (H1N1) in the Western Balkans during the 2019 Post-Pandemic Season

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Abstract

Background: This study looked at the characteristics and outcomes of critically ill patients with confirmed influenza A (H1N1) pdm09 infection in the Western Balkans in the post-pandemic period. **Materials and Methods:** This retrospective observational study of medical records and associated data collected during the post-pandemic period included all mechanically ventilated adult patients of two university-affiliated hospitals of the Western Balkans between 1 January and 31 March 2019 who had influenza A (H1N1) pdm09 infection confirmed by real-time reverse transcriptase-polymerase chain reaction from nasopharyngeal swab specimens and respiratory secretions. **Results:** The study included 89 patients, 49 males (55.1%), aged 56.09 ± 12.64 years. The median time from shift from hospital time to intensive care unit was 1 day (range: 1–2). In the post-pandemic period, cases observed in this study were found to have the following comorbidities: cardiovascular diseases in 44 (49.4%) patients and diabetes in 21 (23.6%) patients. Thirty-one patients (34.8%) in this study were obese. All 89 patients (100%) experienced some degree of acute respiratory distress syndrome, and 39 (44%) had multiorgan failure. Eighty-three patients (93%) were intubated and mechanically ventilated, 6 (7%) received non-invasive mechanical ventilation, 12 (13%) were treated with vvECMO and 36 (40%) received renal replacement therapy. Vasoactive support was needed by 56 (63%) patients. The median duration of mechanical ventilation was 9 (6–15.5) days. The hospital mortality rate was 44%. **Conclusion:** Critically ill patients with confirmed influenza A (H1N1) pdm09 infection in the post-pandemic season were older, required vasoactive drugs more often, and there was a trend of higher survival compared to H1N1 infection patients in the previous pandemic seasons.

Keywords: Acute respiratory distress syndrome, influenza A (H1N1) pdm09, mechanical ventilation, outcome

INTRODUCTION

The pandemic form of influenza A (H1N1) pdm09 represents a major health problem and treatment challenge worldwide, especially in low- and middle-income countries (e.g., Western Balkans).[1-3] Treatment of critically ill patients with influenza A (H1N1) pdm09 is accompanied with a high mortality rate, which is a big socio-economic problem even for high-income countries, especially when it is well known that this form of influenza usually attacks a previously healthy and relatively young population besides people with risk factors.[4-7] The most common complication in critically ill patients with confirmed influenza A (H1N1) pdm09 is pneumonia and other respiratory problems like acute respiratory distress syndrome (ARDS).[8] The highest mortality rate in medical intensive care units (MICUs) during the influenza season is seen in these patients.[9] The Western Balkans are often faced with economic, post-war and problems related to transition (and all challenges related to transition from communistic to capitalistic political system). In addition,

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slow development of intensive care medicine in developing countries (insufficient number of intensivists and a lack of official training in intensive care medicine) aggravates the issue of management of critically ill patients.[10,11] Post-pandemic periods of influenza A (H1N1) pdm09 are associated with a high mortality rate and a higher number of concomitant medical conditions (comorbidities) in patients. Hence, every new wave of influenza should be investigated in order to determine its characteristics. During the 2019 flu season, the Western Balkans experienced extremely high number of critically ill influenza A (H1N1) pdm09 patients. The incidence of influenza-like diseases in the 2018/2019 season was 135/100,000 inhabitants in the Western Balkan countries, and these data were published by the Institutes for Public Health of the Western Balkan countries. It is important to study the pattern of behaviour of influenza A (H1N1) pdm in the period from 2009 to 2019. Data from the Institutes for Public Health of the Western Balkan countries show just one wave in this period during the season 2014/2015 when the number of critically ill patients infected with influenza A (H1N1) pdm was similar to 2019.[12] Literature data describing characteristics and treatment outcomes of critically ill patients with influenza A (H1N1) pdm09 during the winter season of 2018/2019 are very scarce. Our objective in the present study was to determine the characteristics and outcomes of critically ill patients with influenza A (H1N1) pdm09 in the Western Balkans (Bosnia and Herzegovina and Serbia) during the 2019 post-pandemic period.

MATERIALS AND METHODS

Study design and population

A retrospective observational study was conducted in the MICUs of two university-affiliated, tertiary care hospitals of the Western Balkans: University Clinical Center of Republika Srpska (UCC RS), Banja Luka (20 beds, medical intensive care unit [ICU]) (Bosnia and Herzegovina), and the Institute for Pulmonary Diseases of Vojvodina, Sremska Kamenica (9 beds, medical ICU) (Serbia) between 1 January and 31 March 2019. Both MICUs were established during the last 15 years (UCC RS, Banja Luka, in 2008 and Sremska Kamenica in 2003) with support of critical care specialists trained in the United States and Europe, members of the European Society of Intensive Care Medicine and the Society of Critical Care Medicine.[11,13] As the study was epidemiological without any interventions, the requirement for informed consent was waived.

The study included all critically ill and mechanically ventilated patients with influenza A (H1N1) pdm09 virus infection and confirmed ARDS. Influenza A (H1N1) pdm09 infection was confirmed in all patients using real-time reverse transcriptase-polymerase chain reaction from nasopharyngeal swab specimens and respiratory secretions at the time of hospital admission.[14]

Study parameters

Severity of illness was assessed according to the Acute Physiology and Chronic Health Evaluation (APACHE) II score and Sequential Organ Failure Assessment (SOFA).[15,16] Information regarding the need for vasopressor treatment, mechanical ventilation, renal replacement therapy (RRT) or extracorporeal membrane oxygenation (ECMO) was also recorded. The presence of ARDS was classified according to Berlin ARDS criteria: no, mild, moderate and severe ARDS.[17] The mortality rate and length of MICU stay were also determined.

Statistical analysis and data registration

Data are expressed as the mean and standard deviation for normally distributed or as a median and interquartile range for not normally distributed continuous variables and counts with percentages for categorical variables. A comparison of measures for continuous variables was done using Mann–Whitney U and Student's *t*-test. A comparison of proportion was done using Chi-square test and Fisher's exact test as appropriate. The analyses were performed with IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21. *P*=0. Armonk, NY: IBM Corp.

RESULTS

Basic clinical characteristics in post-pandemic 2018/2019 period

The study population comprised 89 patients treated in medical ICUs of two tertiary care hospitals in the Western Balkans (56 in UCC RS, Banja Luka, and 33 in Sremska Kamenica) with confirmed influenza A (H1N1) pdm09 infection and confirmed ARDS [Table 1]. The median time from hospital admission to ICU admission was 1 day (1–2 days). Antiviral treatment was initiated on average 7 days after symptom onset. A total of 89 patients, 49 men (55.1%) with a mean age of 56.09 ± 12.64 years, were included in the study. The mean APACHE II score was 21.21 ± 9.493. The most frequent comorbidities were obesity, smoking, diabetes and congestive heart failure [Table 1]. There were 3 (3.4%) pregnant women amongst H1N1 patients treated during 2019.

All patients with confirmed influenza A infection (H1N1) pdm09 in the post-pandemic season 2019 were admitted

Table 1: Characteristics of mechanically ventilated patients with influenza A (H1N1) pdm09-confirmed infection

Characteristics	Value
Age, median (range)	60 (27-83)
Male sex, *n* (%)	49 (55.1)
APACHE II (mean±SD)	21.21±9.493
SOFA on day 1 (mean±SD)	7.55±3.662
Obesity (BMI >30), *n* (%)	31 (34.8)
Ever smoker, *n* (%)	30 (33.7)
Chronic respiratory disease, *n* (%)	18 (20.2)
Congestive heart failure, *n* (%)	44 (49.4)
Diabetes, *n* (%)	21 (23.6)
Pregnancy, *n* (%)	3 (3.4)

APACHE: Acute Physiology and Chronic Health Evaluation, SOFA: Sequential Organ Failure Assessment, BMI: Body mass index, SD: Standard deviation

to MICU due to respiratory dysfunction accompanied by subjective tachypnoea. All 89 patients in 2019 had bilateral infiltrates seen on chest x-ray along with certain degree of ARDS.

The median P/F ratio (arterial oxygen concentration to the fraction of inspired oxygen) on day 1 post-pandemic season 2019 was 108 mmHg (interquartile range, 71–162.5). In the post-pandemic season, 83 (93%) patients were intubated and mechanically ventilated and 6 (7%) patients were treated using non-invasive mechanical ventilation.

During 2019, 12 (13%) patients were subjected to ECMO and RRT was used in 36 (40%) patients. Severity of patient's conditions and haemodynamical instability in the post-pandemic season (2019) was obvious because 56 (63%) of patients required vasoactive support immediately after admission (day 1/first of hospitalisation). Multiple organ dysfunction syndrome developed in 39 (44%) patients and corticosteroids were administered to 56 (63%) patients. Corticosteroid treatment included methylprednisolone 1 mg/kg BW/day or hydrocortisone 300 mg/day divided into 3 single doses. Ventilator-acquired pneumonia was diagnosed in 56 (60%) patients.

Prone positioning was performed in 51 (57%) in the post-pandemic period. Recruitment manoeuvre was attempted in all patients with signs of very severe respiratory failure. We did not treat any patients with inhalation of nitric oxide.

Other clinical characteristics of patients in post-pandemic period of 2019

Some parameters of inflammation and perfusion (C-reactive protein and lactate) in critically ill patients infected with influenza A (H1N1) 09 pdm were monitored and data are presented in Table 2. Literature sources show a lack of monitoring of these parameters in similar patients during the pandemic season (2009/2010) in the observed area (Western Balkans).

Tracheotomy was performed in 18 out of 89 (20%) patients, whereas pneumothorax developed in 7 (14%) patients. Some authors state that the incidence of *Aspergillus* infection in critically ill patients infected with influenza A (H1N1) 09 pdm can reach 20%; in our observed group of patients, only one patient with fungal (*Aspergillus*) superinfection was detected. Muscle relaxants were administered to 66 (74%) patients, mostly pancuronium, atracurium and rocuronium. Only one patient out of 89 critically ill patients admitted and treated in MICU received an influenza vaccine at the beginning of the influenza season.

Outcomes

Overall, hospital mortality in season 2019 was 44% (39). The median duration of mechanical ventilation was 9 (6–15.5) days and the median ICU length of stay was 9 (1–49 days), as shown in Table 2. Higher severity of illness scores on admission was strongly associated with increased mortality [Table 3].

DISCUSSION

Our study revealed that during the post-pandemic season 2019, a high number of critically ill patients (89 patients) with confirmed influenza A (H1N1) pdm09 were admitted to the MICU. The authors from the Western Balkan countries reported that during the 2009/2010 season, 50 patients were admitted to newly establish MICU.[6]

Characteristics of patients admitted to the newly established MICU in the post-pandemic season (2019) were different than in the pandemic period, patients had higher illness severity scores (APACHE II and SOFA scores), statistically significantly lower P/F ratio, higher Le as well as temperature on admission to the MICU and they required more vasoactive support, i.e., they had circulatory failure more often.[6] Similar results are reported by other authors who followed the second and third waves of post-pandemic influenza (2011–2016).[18-20] Influenza A (H1N1) pdm09 virus circulating in Finland in the 2013/2014 season was different in terms of viral genome (mutation of genetic material).[21,22] This genetic mutation may at least partially explain the reasons why the profile of patients with post-pandemic influenza A (H1N1) pdm09 is different from the 2009/2010 season. It has also been found that the post-pandemic influenza A (H1N1) pdm09 virus replicates more rapidly in the respiratory epithelium than

Table 2: Interventions and outcomes amongst survivors and non-survivors			
	Survivors (*n*=50)	Non-survivors (*n*=39)	*P*
Interventions, investigations and complications			
MODS, *n* (%)	10 (20)	29 (74.4)	<0.01[††]
Dialysis, *n* (%)	11 (22)	25 (64.1)	<0.01[††]
Ventilator-associated pneumonia, *n* (%)	26 (52)	26 (66.7)	0.164[††]
Lactate (median IQR)	1.49 (1.11-2.48)	2.07 (1.48-3.52)	<0.01[†]
CRP (median IQR)	136.2 (69.85-261.20)	175.9 (109.7-257)	0.312[†]
Outcomes			
Mechanical ventilation, days, (median IQR)	9 (5.5-13)	9 (6-22.75)	0.172[†]
ICU length of stay, days (median IQR)	10 (5.5-14)	8.5 (4.25-17)	0.658[†]
Vasoactive drugs, *n* (%)	19 (38)	37 (94.9)	<0.01[††]

[†]Mann-Whitney U-test, [††]Pearson Chi-square test. MODS: Multiple organ dysfunction syndrome, CRP: C-reactive protein, ICU: Intensive care unit, IQR: Interquartile range

Table 3: Characteristics of survivors and non-survivors on intensive care unit admission

	Survivors (*n*=50)	Non-survivors (*n*=39)	*P*
Baseline characteristics			
Age, median (IQR)	56.5 (47-63.25)	61 (49-68)	0.141[†]
Male sex, *n* (%)	26 (52)	23 (58.97)	0.659[‡]
Cigarette smoker, *n* (%)	13 (26)	17 (43.59)	0.209[‡]
BMI >30, *n* (%)	18 (36)	13 (33.33)	0.970[‡]
Any comorbidity, *n* (%)	11 (22)	15 (38.46)	0.144[‡]
Chronic pulmonary disease, *n* (%)	9 (18)	9 (23.08)	0.745[‡]
Diabetes mellitus, *n* (%)	7 (14)	14 (38.9)	0.031[‡]
Pregnancy, *n* (%)	3 (6)	0 (0)	0.253[§]
ICU admission characteristics			
APACHE II, median (IQR)	18 (12-22)	22 (17-31)	0.001[†]
SOFA day 1, median (IQR)*	6 (4.75-7.25)	8 (6-11)	0.000[†]
GCS[a], median (IQR)	15 (6-15)	15 (8-15)	0.345[†]
Temperature (°C), median (IQR)	36.7 (36-37.10)	37.05 (36.48-37.85)	0.007[†]
Heart rate, mean (SD)	95.72 (19.627)	100.94 (22.320)	0.252[††]
Systolic blood pressure (mmHg), mean (SD)	118.97 (26.808)	125.28 (25.486)	0.261[††]
Respiratory rate (/min), median (IQR)	30 (26-30)	30 (30)	0.618[†]
PaO_2/FiO_2 day 1, median (IQR)*	87 (62-110)	128.50 (94-178.75)	0.000[†]
WBC count 10^9/L, median (IQR)	5.44 (3.71-10.04)	8.11 (6.29-13.26)	0.024[†]
Urea mmol/L, median (IQR)	12.3 (6.50-23.30)	7.50 (4.25-13.60)	0.008[†]
Creatinine mg/dL, median (IQR)	131 (84-208)	96 (57.50-137)	0.006[†]
Bilateral lung infiltrates, *n* (%)	50 (100)	39 (100)	

*Significance: < 0,01, [†]Mann-Whitney U-test, [††]Independent-samples *t*-test, [‡]Chi-square test with correction according to Yates-u, [§]Fisher's exact test. BMI: Body mass index, CHF: Congestive heart failure, APACHE: Acute Physiology and Chronic Health Evaluation, SOFA: Sequential Organ Failure Assessment, IQR: Interquartile range, WBC: White blood cell, SD: Standard deviation, GCS: Glasgow Coma Scale, ICU: Intensive care unit

the original influenza A (H1N1) pdm09 virus had during the 2009/2010 season.[22]

Patients in the post-pandemic period (2019) developed severe forms of pneumonia compared to the 2009/2010 season.[6] Similar results are reported by other authors.[20,23]

We noticed that the trend of overall ICU mortality in the critically ill influenza A (H1N1) pdm09 patients was lower in the post-pandemic period 2019, compared to the pandemic season 2009/2010, although we have not performed a statistical calculation on these data.[6] These results are in contradiction with the findings of other authors who reported that ICU and hospital mortality in post-pandemic influenza A (H1N1) pdm09 is significantly higher.[18,20,24]

There are more reasons that may contribute to the reduction of ICU mortality in the study group in the post-pandemic season. One of the reasons may be in the fact that both observed MICUs were just opened during the 2009/2010 flu season. At that moment, there was a lack of officially trained healthcare providers (doctors and nurses) for treating critically ill patients, and the capacity of the MICUs was significantly less, and all these were contributing to increase mortality.[11] For a period of 10 years, there has been a significant breakthrough in the development of intensive care medicine in the Western Balkans, both in terms of infrastructure and education and also in terms of the creation of the first officially trained intensive care doctors. All of the above are clearly illustrated by the results of the study. There are many procedures that

were performed only in the post-pandemic period, e.g., prone positioning, recruitment manoeuvres, use of neuromuscular blocking agents and vvECMO. One of the tools for education in critical care was tele-education. This model of education was performed in the Western Balkans through the implementation of the CERTAIN project. The influence of all these projects was the overall improvement of intensive care medicine in the Western Balkans.[13,25] The state of vaccination of patients in the Western Balkans is of extreme importance because the number of people who undergo influenza vaccination during the winter season is very low. This may be another reason why, in the 2019 season, we noted a higher number of critically ill influenza A (H1N1) pdm09 patients. In developed countries, one-fifth of vaccinated patients can develop the most severe forms of viral infection, mainly in elderly population (older than 65 years).[26-30] The fact that only one patient received an influenza vaccine out of all critically ill patients in season 2019 clearly signals a public health issue that needs improvement in the Western Balkans. Lack of vaccination is an independent risk factor for the development of the most severe forms of influenza in hospitalised patients.

Antiviral treatment was not started in the pre-hospital setting in any patient, and it was administered to all patients admitted to MICU immediately. The problem, which was revealed by analysis of patients' histories, is that the admission of patients in both MICUs (tertiary university hospitals) was up to 7 days after the onset of symptoms. Although the use of

antiviral drugs (oseltamivir) in critically ill influenza A (H1N1) pdm09 patients is controversial, the fact that antiviral therapy in the observed group of patients was started 5–7 days after the onset of the first symptoms further diminishes the effect of antiviral therapy.[31]

Strength and limitation

The strength of this study lies in the fact that this is the first report on the characteristics and outcomes of treatment of mechanically ventilated critically ill patients with confirmed influenza A (H1N1) pdm09 infection in the post-pandemic 2019 season in the Western Balkans. The strength is also reflected in the fact that in this way, an evaluation of the work of newly established and scarce MICUs in the Western Balkans was made. The multidisciplinary teams of physicians working at these MICUs have been the same for the past 10 years.

The major limitations of this study include a relatively small patient size from limited centres (two). The study included critically ill patients from two tertiary care centres who required mechanical ventilation and ICU admission. This may not necessarily be representative of the region of the Western Balkans, and the total burden of pandemic in the region is likely to be higher.

CONCLUSION

It can be pointed out that in the post-pandemic season of 2019, there were a high number of critically ill patients with confirmed influenza A (H1N1) pdm09 infection admitted to the MICUs of the Western Balkan countries. Most of the clinical features described in our study are consistent with the findings of other studies. Survival rates seem to be higher in the post-pandemic period, which is the only difference from all other studies. The reason for these findings might be found in the fact that the recently established Western Balkan MICUs have shown significant progress in all aspects of intensive care medicine.

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Conflicts of interest

There are no conflicts of interest.

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