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THE FIRST FLU SEASON AFTER THE COVID-19 PANDEMIC IN THE TUZLA CANTON AREA

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ABSTRACT

Background: Seasonal influenza viruses, in temperate climates predominantly spread during winter and early spring. Each year, the influenza virus affects approximately 10% of the world's population. The most vulnerable groups are individuals at the extremes of age and those with chronic illnesses.
Aim: To present the epidemiological, laboratory, and clinical characteristics of patients with influenza, to assess the presence of complications, and to evaluate the outcomes of patients with influenza.
Methods: A retrospective analysis was conducted on the clinical records of 49 patients treated for influenza at the Clinic for Infectious Diseases from January 1 to March 31, 2024. The study included all patients over the age of 18 years, with a confirmed diagnosis of influenza (positive PCR test for influenza).
Results: The overall mortality rate was 36.7%. Older patients, particularly those over 65 years, had a significantly higher likelihood of mortality compared to younger patients ($p<0.001$). Elevated D-dimer and troponin levels were significantly associated with poor outcomes ($p=0.005$, and $p=0.004$). The need for oxygen therapy was another significant predictor of mortality ($p=0.036$). The presence of comorbidities, especially diabetes mellitus, significantly increased the risk of mortality ($p=0.037$). No significant differences in mortality rates were observed between male and female patients.
Conclusion: The study highlights the severe impact of influenza on hospitalized patients, particularly those with advanced age and comorbidities. High mortality rates comparable to those in this study have been reported in various countries, underscoring the need for improved healthcare strategies, early intervention, and targeted vaccination programs.

Keywords: Influenza, clinical characteristics, laboratory, comorbidities, outcome

INTRODUCTION

Seasonal influenza viruses are influenza A and B viruses that are characterized by seasonal periodicity where, in temperate climates, they can spread across the population during the fall-to-winter and winter-to-spring months (the flu season) [1].
Influenza virus affects 2% to 10% of the global population, resulting in 250,000 to 500,000 deaths annually [2].
The incubation period of influenza is 2 days on average but may range from 1 to 4 days. Transmission is by droplets, aerosol, or through direct contact with respiratory secretions of someone with the infection [3].
The onset of symptoms is sudden, and initial symptoms are predominately non -specific, including fever, chills, headaches, muscle pain or aching, a feeling of discomfort, loss of appetite, lack of energy/fatigue, and confusion. These symptoms are usually accompanied by respiratory symptoms such as a dry cough, sore or dry throat, hoarse voice, and a stuffy or runny nose. Coughing is the most common symptom [4].
Of the common laboratory tests, nonspecific blood count analysis, C-reactive protein (CRP), and white blood cell count (WBC) are useful for differentiating a viral from a bacterial disease. Especially in the case of influenza, a decrease in the number of lymphocytes is common [5].
The major complication of influenza is pneumonia, which occurs most frequently in certain groups of patients with underlying chronic illnesses who are classified as high risk [6].
Chronic medical conditions, such as heart disease, lung disease, diabetes, renal disease, rheumatologic disease, dementia, and stroke, are all risk factors for influenza complications. Regardless of age,

those with high-risk conditions have increased rates of hospitalization and death [7].
Molecular diagnostics (rapid molecular assays, reverse transcription polymerase chain reaction, and other nucleic acid amplification tests) have become widely available and are currently considered the gold standard diagnostic strategies. Molecular assays generally have a high sensitivity (90% to 95%) and high specificity [8].
For seasonal influenza, antivirals are not usually recommended for otherwise healthy individuals. If influenza is circulating in the community and treatment can be started within 48 hours of symptom onset (36 hours for zanamivir in children), individuals at risk of complications or in an at-risk group should be prescribed oral oseltamivir (inhaled zanamivir if there is a risk of oseltamivir resistance, e.g. A(H1N1), or as second-line treatment) [9].
Vaccines have moderate effectiveness in preventing laboratory-confirmed influenza with effectiveness varying from year to year for a variety of reasons [10]. In healthy adults and children, influenza vaccine prevents 50% to 80% of influenza illness depending on the adequacy of match with circulating virus [11].
The aim of this study was to evaluate demographic, laboratory and clinical characteristics, as well outcomes of patients with seasonal flu admitted to Clinic for Infectious Diseases, University Clinical Centre (UCC) Tuzla, Tuzla Canton, Bosnia and Herzegovina. This is first study about flu in our region after end of COVID-19 pandemic.

PATIENTS AND METHODS

In this retrospective study, medical records and data from all patients aged 18 years and older treated for seasonal flu at the Clinic for Infectious Diseases, University Clinical Centre (UCC) Tuzla, from January 1 to March 31, 2024, were analyzed. The patients were divided into four age categories: 18-49, 50-64, 65-79, and 80+ years. They were also categorized into two groups based on outcomes. This study was approved by the Ethics Committee of the UCC Tuzla.
All patients exhibited some or all of the following flu symptoms: fever, cough, difficulty breathing, dyspnea, chest pain, sweating, tiredness, headache, sore throat, chills, nasal discharge, dizziness, myalgia, bone aches, fatigue, diarrhea, vomiting, and loss of appetite.
Laboratory analyses performed for all patients included: complete blood count (CBC), C-reactive protein (CRP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), ferritin, D-dimer, creatine kinase (CK), creatine kinase-MB (CK-MB), and troponin. Additionally, chest radiography was performed for all patients upon admission. For those with an elevated D-dimer value, CT angiography of the pulmonary artery was conducted.
Data on comorbidities (such as diabetes mellitus, chronic pulmonary diseases, heart conditions, kidney disease, obesity, cancer, and hematologic disorders), duration of symptoms before hospitalization, and length of hospitalization were also included.
For flu confirmation, the diagnostic real-time polymerase chain reaction (RT-PCR) method was used to detect the flu virus (A or B) from respiratory tract samples obtained via nasopharyngeal swabs.
Patients were treated with oseltamivir, oxygen (if blood gas analysis showed oxygen levels below 94%), corticosteroids, and, in most cases, antibiotics. In moderate to severe cases where patients required more than 15 L/min of oxygen, they were transferred to the Intensive Care Unit (ICU) and treated with high-flow oxygen therapy, non-invasive ventilation, or invasive ventilatory support.

Statistical analysis

Standard methods of descriptive statistics (measures of central tendency, dispersion measures) were used to summarize the basic characteristics of the sample. Data are presented as mean ± standard deviation (SD) for continuous variables and as frequencies (percentages) for categorical variables. To assess differences between groups of patients with different outcomes, the following statistical tests were used: T-test, used to compare mean values of continuous variables between groups (e.g., age, D-dimer, LDH). Chi-square test: used to assess differences in frequencies between groups for categorical variables (e.g., gender, comorbidities, symptoms). Logistic regression was used to evaluate the impact of multiple factors on the likelihood of poor outcomes (death). Variables included in the model were age, gender, presence of comorbidities, and laboratory findings (D-dimer, LDH). The $p< 0.05$ was considered statistically significant. SPSS 26.0 were used for all statistical tests.

RESULTS

From 1 January to 31 March 2024, 49 patients were treated at the Clinic for Infectious Diseases with a diagnosis of influenza. Thirty patients (61.2%) were male, and 19 patients (38.8%) were female. The mean age was 67.86 ± 14.29 years; the mean age of recovered patients was 63.00 ± 15.29 years, while the mean age of patients with poor outcomes was 76.22 ± 6.84 years. Most patients belonged to the age group of 65-79 years (24 patients, 49.0%), followed by the 80+ years group (11 patients, 22.4%). Influenza type A was confirmed in 32 patients (65.3%), while 17 patients (34.7%) had influenza without type identification.
Age had the greatest influence on poor outcomes, with patients over 65 years having a higher risk of death compared to younger patients ($p<0.001$) (Table 1).
The overall length of hospital stay was 10.76 ± 8.79 days. For survivors, the length of stay was 12.16 ± 9.23 days, while it was shorter for those who died, at 8.33 ± 7.62 days; however, this difference was not statistically significant ($p=0.143$) (Table 1).

The use of oxygen therapy was higher in deceased group (p=0.036), indicating that patients with worse outcomes were more likely to require oxygen therapy. Lung infiltration was present in 44 patients (89.8%) and in all patients with fatal outcomes (18/18, 100%), though this was not statistically significant (p=0.143) (Table 1). Three patients required mechanical ventilation; one survived, while two died.

Oseltamivir was used in the vast majority of patients (46/49, 93.9%), including all deceased patients (18/18, 100%). Antibiotics were administered to nearly all patients (45/49, 91.4%), and corticosteroids were given to all deceased patients (18/18, 100%) (Table 1).

The most common symptoms were fever (41 patients, 83.7%), followed by cough and difficulty breathing (38 patients, 77.6%). None of these symptoms had a significant association with fatal outcomes (Table 1).

The majority of patients (42 patients, 85.7%) had comorbidities, with 33 patients (67.3%) having two or more comorbidities. All patients who died had comorbidities (18/18, 100%), indicating that comorbidities were associated with poor outcomes (p=0.038). Additionally, diabetes mellitus as an individual comorbidity also influenced poor outcomes (p=0.037) (Table 1).

Table 1. Demographic and clinical characteristics for all patients according to the outcome

Demographic and clinical characteristics	All patients (N=49)	Recovered patients (N=31)	Deceased patients (N=18)	p-value
Age	67.86 ± 14.29	63.00 ± 15.29	76.22 ± 6.84	< 0.001
18-49	5 (10.2%)	5 (16.1%)	0 (0.0%)	
50-64	9 (18.4%)	9 (29.0%)	0 (0.0%)	
65-79	24 (49.0%)	13 (41.9%)	11 (61.1%)	< 0.001
80+	11 (22.4%)	4 (12.9%)	7 (38.9%)	< 0.001
Length of stay in hospital	10.76 ± 8.79	12.16 ± 9.23	8.33 ± 7.62	0.143
Days from illness onset to admission	5.63 ± 3.68	5.84 ± 3.94	5.28 ± 3.25	0.612
Gender				0.229
Male	30 (61.2%)	17 (54.8%)	13 (72.2%)	
Female	19 (38.8%)	14 (45.2%)	5 (27.8%)	
Tretament				
Oxygen	37 (75.5%)	20 (64.5%)	17 (94.4%)	0.036
Antibiotics	45 (91.8%)	28 (90.3%)	17 (94.4%)	1
Corticosteroids	45 (91.8%)	27 (87.1%)	18 (100%)	0.282
Oseltamivir	46 (93.9%)	28 (90.3%)	18 (100%)	0.288
Symptoms and radiologic features				
Fever	41 (83.7%)	26 (83.9%)	15 (83.3%)	1
Cough	38 (77.6%)	25 (80.6%)	13 (72.2%)	0.503
Weakness	23 (46.9%)	15 (48.4%)	8 (44.4%)	0.790
Malaise	22 (44.9%)	16 (51.6%)	6 (33.3%)	0.215
Muscle pain	6 (12.2%)	4 (12.9%)	2 (11.1%)	1
Bone pain	5 (10.2%)	3 (9.7%)	2 (11.1%)	1
Chest pain	8 (16.3%)	6 (19.4%)	2 (11.1%)	0.693
Difficulty breathing	38 (77.6%)	24 (77.4%)	14 (77.8%)	1

Demographic and clinical characteristics	All patients (N=49)	Recovered patients (N=31)	Deceased patients (N=18)	p-value
Poor appetite	9 (18.4%)	6 (19.4%)	3 (16.7%)	1
Vomiting	8 (16.3%)	7 (22.6%)	1 (5.6%)	0.229
Diarrhea	9 (18.4%)	5 (16.1%)	4 (22.2%)	0.708
Sweating	2 (4.1%)	2 (6.5%)	0 (0.0%)	0.526
Headache	2 (4.1%)	2 (6.5%)	0 (0.0%)	0.526
Sore throat	5 (10.2%)	4 (12.9%)	1 (5.6%)	0.639
Chills	8 (16.3%)	6 (19.4%)	2 (11.1%)	0.693
Runny nose	3 (6.1%)	3 (9.7%)	0 (0%)	0.288
Pulmonary infiltration	44 (89.8%)	26 (83.9%)	18 (100.0%)	0.143
Comorbidities	42 (85.7%)	24 (77.4)	18 (100.0%)	0.038
0	7 (14.3%)	7 (22.6%)	0 (0.0%)	
1	8 (16.3%)	5 (16.1%)	3 (16.7%)	
2+	34 (69.4%)	19 (61.3%)	15 (83.3%)	
Diabetes mellitus	18 (36.7%)	8 (25.8%)	10 (55.6%)	0.037
Hypertension	34 (69.4%)	21 (67.7%)	14 (77.8%)	0.453
Atrial fibrillation	12 (24.5%)	6 (19.4%)	6 (33.3%)	0.314
Obesity	5 (10.2%)	2 (6.5%)	3 (16.7%)	0.342
COPD	9 (18.4%)	5 (16.1%)	4 (22.2%)	0.708
Heart failure	5 (10.2%)	3 (9.7%)	2 (11.1%)	1
Hematological disease	2 (4.1%)	0 (0.0%)	2 (11.1%)	0.130
Leukemia	1 (2.0%)	0 (0.0%)	1 (5.6%)	0.367
Malignant disease	2 (4.1%)	1 (3.2%)	1 (5.6%)	1
Neurological disease	1 (2.0%)	1 (3.2%)	0 (0.0%)	1
Thyroid disease	1 (2.0%)	1 (3.2%)	0 (0.0%)	1

The total mortality rate was 18/49 (36.7%); for men, it was 13/30 (43.3%), and for women, it was 5/19 (26.3%). There was no statistically significant difference in fatal outcomes based on gender.

D-dimer was significantly higher in the deceased group (p=0.015), associating elevated D-dimer levels with poor outcomes, also troponin levels was significantly elevated in deceased patients (p=0.004), indicating a strong link between higher troponin levels and mortality. Although ferritin levels were higher in those who died compared to those who recovered, this difference was not statistically significant (p=0.098). (p=0.098). (Table 2).

Logistic regression analysis demonstrated that age significantly predicted the outcomes of influenza patients, with each additional year increasing the odds of adverse outcomes by 11.8% (OR = 1.118, 95% CI = 1.037 to 1.205, p = 0.004), achieving an overall predictive accuracy of 75.5%.

Table 2: Laboratory findings for all patients according to the outcome of influenza

Laboratory parameter	All Patients (N=49)	Recovered patients (N=31)	Deceased Patients (N=18)	p-value
Leucocyte median (IRQ)	7.5 (5.4-11.2)	9.45 (5.55-13.125)	6.50 (4.0-9.2)	0.507
Platelet median (IRQ)	194 (156.0-260)	198.50 (164.25-272.25)	169.0 (128-227)	0.541
AST median (IRQ)	39 (25.0-71)	35.0 (27.75-63.25)	39.0 (23.5-98)	0.678
ALT median (IRQ)	25 (19.0-48)	23.0 (17-55.5)	35.0 (22.5-43.5)	0.740
LDH median (IRQ)	293 (226-338)	293.5 (223.75-339)	293.0 (232-675)	0.273
CRP median (IRQ)	131.6 (32.9-240.9)	111.45 (30.7-241.05)	224.0 (64.85-255.45)	0.290
Ferritin median (IRQ)	478 (144-1137)	400.4 (122.3-904.5)	884.0 (243.65-3205.5)	0.098
D-dimer median (IRQ)	1.2 (0.6-2.3)	1.0 (0.5-1.4)	2.3 (1.35-4.4)	0.005
Troponin median (IRQ)	16.7 (4.7-79.3)	7.4 (3.7-101.725)	33.5 (15.5-205.6)	0.004
CK median (IRQ)	112 (70-317)	112 (66.75-280.25)	121 (69.5-464)	0.276

DISCUSSION

On 5 May 2023, the World Health Organization (WHO) announced that the coronavirus disease 2019 (COVID-19) epidemic would no longer be listed as a public health emergency of international concern (PHEIC), 3 years after the first PHEIC alert on 30 January 2020 [12]. During these three years, there were almost no cases of influenza registered in our region, likely due to the dominance of the SARS-CoV-2 virus. Only this year (2024) did we experience the first wave of influenza, requiring hospitalization for a larger number of patients who had moderate to severe clinical presentations.

In our study, we had 49 patients treated for influenza in the first three months of 2024. The majority of patients were men, 30 (61.2%). In the Christmas 2017 edition of the BMJ, a review of existing research highlighted significant differences in immune response and outcomes of influenza between men and women. Epidemiological data indicated that men may have a higher risk of hospital admission and mortality from influenza compared to women [13].

Age is widely recognized as a risk factor for influenza complications, with one observational study estimating that 73%–85% of deaths and 54%–70% of hospitalizations secondary to influenza in the USA from 2010 to 2013 occurred in patients over 65 [14]. The vast majority of patients in our study were over 65 years old, 71.4%, and those over 80 years old made up 22.4%.

Mean age in our study was 67.86 ± 14.29 years. In similar studies, the mean age of patients was comparable [15]. This shows that in most countries around the world, older patients usually make up the majority of hospitalized influenza patients.

According to the literature, the largest numbers of influenza-related cases and fatalities should be expected in more susceptible populations: among young children, the elderly, chronically ill patients suffering from cardiovascular or respiratory disease, and immunosuppressed patients [16]. Thus, in our study, age had the greatest impact on disease outcome, with patients over 65 years old having the highest likelihood of a fatal outcome. This finding is consistent with previous studies that have shown older patients are at higher risk of complications and mortality due to influenza due to weakened immune systems and the presence of comorbidities. For instance, Thompson et al. (2003) found that approximately 90% of influenza-related deaths occurred in individuals aged 65 and older [17].

Many conditions are associated with the continuous activity of the hemostatic system such as malignancy, pregnancy, trauma, heart disease, liver disease (reduced clearance), inflammation, sepsis resulting from hemodialysis, recent surgery, or CPR, and they increase D-dimer levels [18]. Among laboratory findings in our study, D-dimer was most strongly associated with poor outcomes. In a study conducted by Wang et al., patients with respiratory insufficiency had lower lymphocytes, elevated LDH, and D-dimer [19]. Also in our study, elevated troponin values were associated with higher mortality. Troponin elevations may occur as the result of several inflammatory inducing insults to the heart, one of which is viral illness, including influenza [20].

The use of oxygen therapy in our study was associated with poor outcomes, with a total of 75.5% of patients receiving it, and 94.4% in the deceased group. In a study by Michael G, 60% of patients required oxygen therapy [21]. This data from our study aligns with the view that early recognition and treatment of respiratory complications are crucial for improving outcomes, as indicated by Phua et al. (2020) in their study on critical care management of respiratory infections [22].

In our patients, the use of antibiotics was very high, at 91.8%. Similar data can be found in other studies. Antibiotic therapy was given to almost 80% of patients, which corresponds well with previous studies on hospitalized influenza patients [23, 24]. Most patients

likely receive antibiotics more as a prophylaxis or due to possible suspicion that they already have developed bacterial pneumonia at the time of hospitalization.
International guidelines recommend antiviral treatment for all hospitalized patients with suspected or proven influenza disease [25]. In our study, all patients received antiviral therapy, yet we still had quite high mortality rates. This could possibly be explained by the fact that most patients presented to the hospital later during the illness, so antiviral therapy was not initiated within the first 48 hours of symptom onset.
The use of corticosteroids in our study was relatively high. This may be because we had a good response to corticosteroid therapy in patients with COVID-19, so we treated patients with influenza on the same principle, as this is also a viral disease that primarily affects the respiratory tract. The role of corticosteroids for the treatment of influenza is highly controversial. While some case series have reported improved outcomes with corticosteroid treatment of severe influenza [26], other cohort studies have suggested the opposite [27].
The common complication in influenza patients reported by studies in Japan, China, and the United States was pneumonia [28-30]. This complication was also the most common among our patients, with 89.8% having pneumonia, and 100% in the deceased group.
The most common symptoms among patients in our study were fever, cough, and shortness of breath. In the study conducted by Phetcharakupt, the most common symptoms were fever, cough, and runny nose [31]. Thus, in most studies, the dominant symptoms are similar, which was expected.
Underlying conditions such as diabetes mellitus, smoking, COPD, cystic fibrosis, coronary diseases, overweight, hypertension, renal insufficiency, history of cancer, immunosuppression status, pregnancy, and age over 65 years are considered recognized risk factors for developing severe influenza disease. The literature is consistent and emphasizes that the presence of one of these factors is related to an increased risk of hospitalization [32]. The presence of comorbidities in our study was a sign of poor outcomes, especially the presence of 2 or more comorbidities, as well as the presence of diabetes mellitus as a separate comorbidity. The study conducted by Dicembrini et al. also showed that influenza is associated with more severe complications in diabetic versus non-diabetic individuals [33].
The length of hospital stay in our study was 10.76 ± 8.79 days, with similar data found in the study by Rossler et al., where the average length of hospital stay was 11.4 ± 13.4 days [34]. In our study, patients in the deceased group had shorter hospital stays, likely due to the greater severity of their illness, which led to more complications and required transfer to the ICU.
The overall mortality rate in our study was as high as 36.7%, with no statistical difference between genders, although the rate was higher for men at 43.3% compared to 26.3% for women. In a study conducted in Pakistan, men also had a higher mortality rate compared to women (19.02% vs. 10%) [35]. In the study by Beumer et al., mortality was in 17/45 (38%) patients [36]. One possible reason for the very high mortality rate in our study could be that patients from our clinic were transferred to the ICU only in cases of need for mechanical ventilation, as well as due to a lack of ICU beds.

CONCLUSION

Our research highlights several key factors influencing the outcome of treatment in patients with influenza. Age, elevated D-dimer levels, elevated troponin levels, and the need for oxygen are significant predictors of poor outcomes. The presence of comorbidities, particularly diabetes mellitus, further increases the risk. Gender was not a significant risk factor for mortality. These findings emphasize the importance of timely identification and aggressive treatment of high-risk patients to reduce mortality. Future research should focus on strategies to improve outcomes in these patients, including optimizing therapy and managing comorbidities.

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