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Evaluation of clinical and para-clinical parameters related to disease severity and mortality in patients with influenza in Isfahan, Iran; a cross sectional study

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Abstract

Introduction: Managing influenza (flu) due to its rapid transmission is a considerable challenge for the health system. Considering the variety of clinical symptoms in influenza and recognizing its symptoms in different conditions of patients can be effective in its management.
Objectives: In the present cross-sectional study, we evaluate the relationship between clinical and para-clinical findings and the treatment measures observed at the time of hospitalization of influenza patients and their conditions at the time of discharge from the hospital.
Patients and Methods: Our investigation was conducted from March 2019 to March 2021 in Alzahra hospital of Isfahan, Iran. The research population included influenza patients admitted to the infectious ward.
Results: A total of 122 hospitalized influenza patients (n=122) were included in this research. The number of patients with influenza A and B was 44 and 78, respectively. There was a significant relationship between the type of influenza and the patient's condition upon discharge ($P=0.001$). Influenza vaccination ($P<0.001$), diabetes ($P=0.038$), and cardiovascular disease ($P=0.004$) were significantly associated with the patient's condition at discharge. According to our investigation, among the drugs used, oseltamivir significantly reduced mortality in patients receiving it ($P<0.001$). There was a statistically significant difference between the variables of all chest radiology and the patient's condition at the time of discharge ($P<0.001$). Furthermore, there was a statistically significant difference between the length of hospital stay ($P=0.001$), the number of white blood cells ($P=0.001$), the number of platelets ($P=0.006$), and the amount of C-reactive protein (CRP) ($P<0.001$) with the patient's condition upon discharge.
Conclusion: Among the comorbidities studied, diabetes and cardiovascular disease were significantly associated with mortality in patients with influenza. Vaccination significantly reduces mortality from influenza in high-risk patients. The antiviral drug oseltamivir is recommended as a useful drug for patients with the influenza. However, a multi-center study with larger sample size is necessary for a more conclusive result.

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Introduction

Managing influenza (flu) is a serious challenge for the health system due to its rapid transmission. Severe influenza species affect 3-5 million people worldwide annually, leading to significant mortality in pandemic conditions (1). Some epidemiological studies have reported more than 600 000 deaths per year due to respiratory involvement (2). Influenza mortality is mainly seen in high-risk groups such as children, pregnant women, the elderly, patients undergoing chemotherapy and radiotherapy, and patients with comorbidities (3). Influenza viruses (IVs) are members of the Orthomyxoviridae family (4). There are four main types of IV, labeled IV A, B, C, and D. Birds are the main source of IV A, which can be transmitted to humans. Similarly, IV B and C first affect humans, and IV D first appears in pigs and cattle. Circulation of IV A and B in humans is associated with considerable seasonal epidemics or pandemics; IV C is usually associated with moderate infections in children; and IV D does not cause any considerable disease in humans (5,6). The most important feature of IV is its rapid evolution that leads to its

Key point

Lower respiratory infections due to influenza are the main cause of mortality in low-income countries annually. Some populations are more vulnerable to influenza, either because they have a greater risk of developing severe disease or they have a greater risk of exposure, such as pregnant women, health workers, people over the age of 65 years, children from 6-59 months, and people with chronic health conditions such as diabetes, HIV, asthma, heart or lung disease.

inordinate variability (7).

Influenza is associated with a number of signs and symptoms in patients, and about 90% of them have a fever (8). Other symptoms include cardiovascular, respiratory, and gastrointestinal involvement, myalgias, fatigue, and malaise (9). Elderly people with IV infection may show atypical signs and symptoms such as weakness, confusion, and pulmonary complications that are less common in children (10). In this respect, clinical, radiological, and serological knowledge of influenza patients plays an essential role in planning to equip hospitals and reduce hospitalization length and mortality.

Objectives

Considering the variety of clinical symptoms in influenza and recognizing the symptoms in different conditions of patients can be effective in its management. Accordingly, the present study investigates the relationship between clinical and para-clinical findings and the treatment measures performed at hospitalization time of influenza patients and their conditions upon discharge from the hospital.

Patients and Methods

Patients

The present cross-sectional study was approved by the department of infectious diseases, school of medicine, medical university of Isfahan, Isfahan, Iran. This study aimed to evaluate the clinical characteristics of patients with types A and B viral infections hospitalized in Al-Zahra hospital of Isfahan. Our investigation was realized from March 2019 to March 2021. The research population included influenza patients admitted to the infectious ward. Inclusion criteria were definitive diagnosis of influenza based on the U.S. Centers for Disease Control and Prevention guidelines, hyperthermia (37.8℃ or higher), headache, tiredness, sore throat, cough, runny or stuffy nose, body aches, and gastrointestinal involvement. Patients who did not have molecular tests to diagnose the influenza type and without chest radiographs were excluded from the study. Patient-related information was recorded on separate forms, and they were assured that their information would be kept confidential.

Real-time reverse transcriptase polymerase chain reaction

- In all suspected cases, throat discharge samples were taken for the presence of specific viral antigen for IV A and IV B. Molecular real-time reverse transcriptase polymerase chain reaction (RT-PCR) technique was conducted to detect antigens associated with influenza A and B. For this purpose, a viral transport medium (Virocult, Medical Wire & Equipment, UK) was used with the following RT-PCR primers (sequence 5' to 3'): GGAATGGCTAAAGACAAGACCAAT (Forward primer for influenza A),
- GGGCATTTTGGACAAAGCGTCTAC (reverse primer for influenza A),
- CCAGGGATTGCAGACATTGA (Forward primer for influenza B), and
- ACAGGTGTTGCCATATTGTAAAGAG (reverse primer for influenza B) (11).

Imaging procedures

In the current study, chest computerized tomography (CT) scan without contrast was ordered to check for respiratory complications caused by the influenza. Provided chest scans were assessed for the presence or absence of lobular pneumonia, viral pneumonia, and bronchopneumonia. CT scan was not taken when patients were pregnant and diagnoses were made based on chest radiographic findings.

Serological and clinical examination

Monitored parameters related to influenza were vaccination history and comorbidities. Clinical presentations (e.g., fever, cough, myalgia and headache) were investigated by asking a 'Yes/No' question. Furthermore, we recorded information about patients' blood tests such as white blood cells (WBC), platelet (PLT), hemoglobin (Hb), C-reactive protein (CRP) levels, *erythrocyte sedimentation rate* (*ESR*), D-dimer, pH, patients' drug history, time since the onset of symptoms, length of hospital stay, and patient mortality in separate forms.

Evaluating the patient's condition at the time of discharge

In the present study, the patient's condition upon discharge was assessed based on three variables: complete recovery, the persistence of cough, and the need for respiratory aids. We evaluated patient mortality rate as a separate variable. All patient information (i.e., influenza type, radiological and serological findings, drug treatments, vaccinations, and comorbidities) was evaluated based on patients' condition upon discharge.

Statistical analysis

Statistical analysis was done by the SPSS statistical package version 18.0 (SPSS Inc., Chicago, IL, USA). Chi-square test was used for descriptive data analysis, and a t-test was employed for quantitative data. A P value less than 0.05 was accepted as a significant statistical difference.

Result

In this research, 12 hospitalized influenza patients (n = 122) were studied, of which 88 were male and 34 were female. The mean age of men and women was 59.8 ± 14.5 and 60.26 ± 15.6 years, respectively. The statistical analysis showed no statistically significant difference between the two groups regarding age (P = 0.87). The number of patients with influenza A was 44 and the number with influenza B was 78. A total of three patients died due to complications of influenza. Similarly, two of the patients

who died were infected with influenza B and one with influenza A. There was a significant relationship between the influenza type and the patient's condition upon discharge ($P=0.001$). Table 1 presents the association between influenza vaccination and comorbidities and the patient's condition at discharge. Among the studied variables, influenza vaccination ($P<0.001$), diabetes ($P=0.038$), and cardiovascular disease ($P=0.004$) were significantly associated with the patient's condition at discharge.

Based on the statistical analysis, there was no significant difference between the reduction of oxygen saturation and the patient's condition at the time of discharge ($P=0.11$). There was a statistically significant difference between oxygen therapy ($P<0.001$), the need for a respiratory aid ($P=0.001$), and intubation ($P < 0.001$) with the patient's condition upon discharge (Table 2).

According to the chi-square test, among the drugs administered, oseltamivir significantly reduced mortality in patients receiving it ($P<0.001$).

Table 3 presents the association between the chest radiological findings and the patient's condition upon discharge from the hospital. As can be seen, there is a significant difference between the variables of chest radiology and the patient's condition upon discharge ($P<0.001$).

The quantitative variables studied, including the time from the onset of symptoms to hospitalization, the duration of hospitalization, and serological factors, are listed in Table 4. There was a statistically significant difference between the length of hospital stay ($P=0.001$), the number of WBCs ($P=0.001$), the number of PLTs ($P=0.006$), and the amount of CRP ($P<0.001$) and the patient's condition upon discharge from hospital.

Discussion

Influenza can cause clinical presentations that are indistinguishable from some severe seasonal colds (1). However, due to its rapid transmission and the risks it poses to high-risk patients, it is among the major challenges of the health system. The present study examined the clinical and para-clinical findings of patients with influenza admitted

Table 1. The association between the influenza vaccination and comorbidities and the patient's condition upon discharge

Variable	Total	Number	Survival, No. (%)			Mortality, No. (%)	*P* value[a]
			Recovery	Cough	Respiratory aid	Death	
Influenza vaccination	No	102	39 (38.2)	31 (30.4)	29 (28.4)	3 (2.9)	< 0.001*
	Yes	20	18 (90)	2 (10)	0 (0)	0 (0)	
Chronic kidney disease	No	108	53 (49.1)	28 (25.9)	24 (22.2)	3 (2.8)	0.40
	Yes	14	4 (28.6)	5 (35.7)	5 (35.7)	0 (0)	
Diabetes	No	84	43 (51.2)	23 (27.4)	18 (21.4)	0 (0)	0.038*
	Yes	38	14 (36.8)	10 (26.3)	11 (28.9)	3 (7.9)	
Cardiovascular disease	No	87	47 (54)	23 (26.4)	17 (19.5)	0 (0)	0.004*
	Yes	35	10 (28.6)	10 (28.6)	12 (34.3)	3 (8.6)	
Hypertension	No	73	39 (53.4)	20 (27.4)	13 (17.8)	1 (1.4)	0.14
	Yes	49	18 (36.7)	13 (26.5)	16 (32.7)	2 (4.1)	
Neurological disease	No	104	47 (45.2)	30 (28.8)	24 (23.1)	3 (2.9)	0.60
	Yes	18	10 (55.6)	3 (16.7)	5 (27.8)	0 (0)	
Mental disease	No	105	51 (48.6)	28 (26.7)	23 (21.9)	3 (2.9)	0.53
	Yes	17	6 (35.3)	5 (29.4)	6 (35.3)	0 (0)	
Respiratory disease	No	94	39 (41.5)	29 (30.9)	23 (24.5)	3 (3.2)	0.13
	Yes	28	18 (64.3)	4 (14.3)	6 (21.4)	0 (0)	
Malignancies	No	100	43 (43)	28 (28)	26 (26)	3 (3)	0.30
	Yes	22	14 (63.6)	5 (22.7)	3 (13.6)	0 (0)	
Stroke	No	115	55 (47.8)	29 (25.2)	28 (24.3)	3 (2.6)	0.32
	Yes	7	2 (28.6)	4 (57.1)	1 (14.3)	0 (0)	

[a] Chi square test, *Significant.

Table 2. The association between respiratory complications and the patient's condition upon discharge

Variable	Total	Number	Survival, No. (%)			Mortality, No. (%)	*P* value[a]
			Recovery	Cough	Respiratory aid	Death	
Oxygen therapy	No	89	48 (53.9)	26 (29.2)	15 (16.9)	0 (0)	< 0.001*
	Yes	33	9 (27.3)	7 (21.2)	14 (42.4)	3 (9.1%)	
Respiratory aids	No	100	51 (51)	27 (27)	22 (22)	0 (0)	0.001*
	Yes	22	6 (27.3)	6 (27.3)	7 (31.8)	3 (13.6%)	
Intubation	No	117	57 (48.7)	33 (28.2)	27 (23.1)	0 (0)	< 0.001*
	Yes	5	0 (0)	0 (0)	2 (40)	3 (60%)	

[a] Chi square test, *Significant.

Table 3. The association between the chest radiological findings and the patient's condition at discharge

Radiologic finding	Total	Survival, No. (%)			Mortality, No. (%)	*P* value[a]
		Recovery	Cough	Respiratory aid	Death	
Lobar pneumonia	34	34 (100)	0 (0)	0 (0)	0 (0)	< 0.001*
Viral pneumonia	58	3 (5.2)	28 (48.3)	24 (41.4)	3 (5.2)	
Bronchopneumonia	9	3 (33.3)	3 (33.3)	3 (33.3)	0 (0)	
Bronchitis	5	3 (60)	0 (0)	2 (40)	0 (0)	
Bronchiectasis	2	0 (0)	2 (100)	0 (0)	0 (0)	
Normal	14	14 (100)	0 (0)	0 (0)	0 (0)	

[a] Chi square test, *Significant.

Table 4. The association between the quantitative variables studied and the patient's condition upon discharge from the hospital

Variable	Survival			Mortality	*P* value
	Recovery	Cough	Respiratory aid	Death	
The onset of symptoms to hospitalization (day)	2.42 ± 0.8	2.12 ± 0.99	2.55 ± 1.2	2.67 ± 0.57	0.31
Duration of hospitalization (day)	2.91 ± 0.78	2.7 ± 8.4	3.21 ± 0.81	6 ± 1.73	<0.001*
WBC (mm^3)	8712.28 ± 3313.9	7954.5 ± 2336.9	8337.9 ± 2596.7	15100 ± 1039.2	0.001*
PLT (mm^3)	267859.6 ± 80046.5	266878.7 ± 76324	219862.07 ± 104402.2	131000 ± 19052.5	0.006
Hemoglobin (g/dL)	11.32 ± 1.98	12.26 ± 1.75	11.27 ± 1.9	11.23 ± 0.98	0.2
CRP (mg/L)	15.12 ± 8.39	19.7 ± 10.57	25.45 ± 14.81	31.67 ± 2.30	<0.001*
ESR (mm/h)	38.26 ± 19.05	28.73 ± 12.83	39.48 ± 21.16	36.43 ± 17.89	0.06
D-dimer(ng/L)	987.0 ± 363.3	998.5 ± 287.7	911.43 ± 192.6	979 ± 156.38	0.68
pH	7.19 ± 0.98	7.22 ± 0.18	7.30 ± 0.095	7.26 ± 0.57	0.91

WBC; White blood cells, PLT; Platelet, CRP; C-reactive protein, ESR; Erythrocyte sedimentation rate.
[a] Independent *t* test, *Significant.

to university hospital in Isfahan. One of the important points in our research, which was less considered in previous studies, was studying the factors related to the death or survival of patients. In surviving these patients, their conditions (i.e., complete recovery, cough, and need for respiratory aids) were evaluated as three important variables and correlated with their medical history, serological, and radiological findings. We found, diabetes was identified as important comorbidity that significantly affects the mortality rate due to influenza. Therefore, the death rate was higher in diabetic patients with influenza. So far, the underlying mechanisms associated with the severity of influenza and the presence of diabetes mellitus are unclear. However, hyperglycemia seems to weaken the immune response to pathogens by increasing free radicals and inflammatory factors (12,13). Marshall et al examined changes in blood glucose levels in patients with influenza (14). According to their results, blood glucose fluctuations are among the important causes that weaken the immune system and lead to the occurrence of severe influenza in diabetic patients (14). The results of the present study were in line with those of Marshall et al, reporting that the severity of influenza was higher in diabetic patients than in nondiabetic patients. Another comorbidity significantly associated with the severity of influenza in the present study was cardiovascular disease, which had a higher mortality rate than those without cardiovascular disease. In a recent cross-sectional study, Chow et al examined cardiovascular events in hospitalized influenza patients. Their results indicated that about 12% of patients with influenza have acute cardiovascular events (15).

Another point studied in the present research was the relationship between influenza vaccination and death rate and severity of symptoms. Our results showed that the mortality rate in vaccinated influenza patients was significantly lower than in the unvaccinated group, and the incidence of respiratory problems in vaccinated patients was such that they did not need respiratory aids. This finding is consistent with most cross-sectional studies on the role of vaccination in reducing the severity of symptoms in influenza patients. Moreover, Gutiérrez-González et al, in a cross-sectional study, investigated the effect of vaccination and comorbidities on mortality and symptom severity in patients with influenza in Spain (16). These studies showed that the influenza vaccination in high-risk patients reduces the severity of influenza and the mortality rate in patients. In another study conducted in the Netherlands between 2003 and 2015, Backer et al examined the role of influenza vaccination in inflammation, hospitalization, and mortality in influenza patients (17). Their outcomes showed that the influenza vaccine effectively reduced the mortality rate from the

flu, reduced its transmission, and reduced hospitalization. The results of our study were in line with the results of the above two studies.

According to the statistical analysis performed in the present study, oxygen therapy and using respiratory aids improved the condition in influenza patients. In intubated patients, the mortality rate was higher than in non-intubated ones, and the length of hospital stay in patients who died was longer than those who survived. Certainly, prolonged hospital stays are associated with an increased risk of nosocomial infections, and intubated patients are more likely to develop bacterial respiratory infections (18). Our study was consistent with the results of the study by Mata-Marín et al (19), who conducted a cross-sectional study on risk factors for mortality in influenza patients in Mexico. Their results showed that the mortality rate and severity of influenza symptoms were higher in patients admitted to the intensive care unit and intubated. They noted the vital role of nosocomial infections and ventilator-associated pneumonia in increasing influenza-related mortality (19).

We found, among the drugs used, oseltamivir significantly reduced mortality in patients receiving it. It is known that oseltamivir, is an antiviral drug used to manage IV A and IV B (20). To date, several studies have examined oseltamivir's therapeutic role in reducing influenza symptoms and mortality. Our results were consistent with the study Hanshaoworakul et al too (21). They investigated the therapeutic role of oseltamivir in influenza mortality in Thailand. This study showed that treatment with oseltamivir reduced the mortality rate in influenza patients. A noteworthy point in our study was that using the antibiotic tazocin did not significantly lower influenza-related mortality. This issue can be examined from different aspects. Perhaps this drug did not have its optimal effect due to antibiotic resistance in patients receiving piperacillin-tazobactam. However, since we did not have accurate information about the level of antibiotic resistance to the drug in the study population, we could not comment definitively. Therefore, we have no clear decision about prescribing this drug and make it a subject of more detailed studies.

The present study faced some limitations. The first limitation was the small sample size. Due to the coincidence of this study with the COVID-19 pandemic and the priority of hospitalization of patients with COVID-19, the number of influenza patients in our hospital was low. Therefore, a similar study with a larger sample size must be conducted to make a definitive statement. The present study was performed at a single center; therefore, it is recommended to conduct a similar study at multiple health centers. In addition, we did not have accurate information on the antibiotic resistance of the patients under study, which resulted in an unintended bias. Furthermore, we did not have information about the histopathological condition of the patients' lungs. Nevertheless, it is certain that the correlation between clinical and histopathological findings adds to the accuracy of the results.

Conclusion

Among the comorbidities studied, diabetes and cardiovascular disease were significantly associated with mortality in patients with influenza. Vaccination significantly reduced mortality from influenza in high-risk patients. In this respect, the antiviral drug oseltamivir is recommended as a useful drug for patients with the flu. However, a multi-center study with a larger sample size seems necessary for more accurate results.

Limitations of the study

The small sample of patients and single-center study were the main limitations of the present trial study.

Authors' contribution

Conceptualization: Kiana Shirani.
Data curation: Manijeh Shams.
Formal analysis: Sodabeh Rostami.
Funding Acquisition: Kiana Shirani and Elham Honarjou.
Investigation: Elham Honarjou.
Methodology: Elham Honarjou.
Resources: Elham Honarjou.
Supervision: Kiana Shirani and Behrooz Ataei.
Validation: Sodabeh Rostami and Zary Nokhodian.
Visualization: Elham Honarjou.
Writing-original draft preparation: Elham Honarjou.
Writing-review and editing: Kiana Shirani and Behrooz Ataei.

Conflicts of interest

The authors of the present manuscript declare that there are no conflicts of interest.

Ethical issues

The research followed the tenets of the Declaration of Helsinki. The Ethics Committee of Isfahan University of Medical Sciences approved this study (IR.MUI.MED.REC.1399.882). Accordingly, written informed consent was taken from all participants before any intervention. This study was extracted from infectious disease residency thesis of Elham Honarjou at this university (Thesis#399783). The authors also completely observed ethical issues (including plagiarism, data fabrication, and double publication).

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