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Clinical and Epidemiological Characteristics of Seasonal *Influenza* Virus Infection in Hospitalized Patients in Mashhad, Iran, 2009-2017: A Retrospective Study

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ABSTRACT

Objective: Despite the availability of effective vaccines and antiviral treatments, influenza remains a significant cause of hospitalizations and mortality globally. This study aimed to evaluate the epidemiological characteristics, clinical manifestations, and outcomes of patients diagnosed with seasonal influenza in two referral centers in northeastern Iran.

Methods: This retrospective cross-sectional study analyzed data from 58 patients with a mean age of 45 who tested positive for seasonal influenza via PCR. These patients were hospitalized at Imam Reza and Qaem hospitals between 2009 and 2017. Data were collected using a standardized checklist and analyzed using SPSS software version 23. Non-normally distributed data were assessed using the Mann-Whitney test, while qualitative variables were compared using the Chi-square test, with Fisher's exact test applied when necessary.

Results: Among the 58 influenza-infected patients, 37 (67.2%) survived, 18 (32.7%) died, and 6 (10.9%) were discharged at their own request. Influenza A subtypes identified included H1N1 (15.7%) and H3N2 (23.6%), with 60.5% remaining untyped. Antiviral drug administration did not significantly correlate with hospital mortality. However, initiating antiviral treatment within the first 48 hours did influence mortality outcomes. Patient age, influenza virus type, and subtype showed no significant relationship with hospital mortality.

Conclusion: The study highlights concerning clinical outcomes and hospital mortality rates among patients diagnosed with seasonal influenza. Given the preventable nature of influenza and the challenges in managing these patients, there is an urgent need to enhance physician awareness, particularly among specialists. Emphasizing timely diagnostic and therapeutic interventions is critical, especially during peak influenza seasons.

Keywords:

Epidemiology, Influenza, Clinical outcome, Socio-economic burden.

1. Introduction

Influenza is a highly contagious respiratory infection caused by a virus belongs to the Orthomyxoviridae family. (1) Four types of influenza viruses, comprising types A, B, C and D have been identified based on their immunological and biological characteristics (2,3). Types A and B are responsible for seasonal epidemics, that can affect public health and the economic situation, while type C influenza virus exhibits much lower pathogenicity in humans (4). Among these, influenza type A is the most prevalent globally (5). Influenza type A viruses are further classified based on the presence of two surface proteins including hemagglutinin (H) and neuraminidase (N). The most notable subtypes associated with seasonal influenza are H1N1 and H3N2 (6).

The World Health Organization (WHO) has recommended 28 vaccine strain changes since the introduction of the H3N2 subtype in 1968, reflecting significant genetic and antigenic alteration of the virus, resulting in multiple seasonal epidemics. The H3N2 subtype is usually the dominant subtype of seasonal type A in seasonal outbreaks (7). Although there is limited information on the epidemiology and circulation patterns of influenza type B virus in various regions, the mortality rate of respiratory diseases associated with influenza type B virus in the United States has indicated a concerning mortality rate of 29% (8). The influenza virus has a significant impact on public health compared to other prevalent respiratory diseases due to its high transmissibility and associated mortality rate (9,10). Seasonal influenza is a major public health concern in Iran, with outbreaks occurring every year, particularly during the colder months when hospital admissions tend to rise. Research and surveillance reports show that Influenza A, particularly the H1N1 and H3N2 subtypes, along with Influenza B, are the most commonly circulating strains. These viruses significantly impact people of all ages, leading to a considerable number of illnesses and deaths each year (9).

During the 2022–2023 season, Iran experienced significant outbreaks of Influenza A, specifically the H3N2 and H1N1 subtypes. The low vaccination rates in the population contributed to a notable increase in mortality (11).

In Hormozgan province, located in southern Iran, a peak in influenza cases was recorded from August to December 2022, characterized primarily by the H3N2 subtype, although H1N1 also saw a considerable rise. Hospitalization rates for patients testing positive for influenza increased during this period (12).

A study in Iran employing the hemagglutination inhibition (HI) test revealed that the prevalence of influenza was significantly higher among groups with potential exposure, such as hospitalized individuals and healthcare staff, compared to healthy controls. Notably, slaughterhouse workers exhibited the highest pooled prevalence among those tested (13).

The economic impact and disease burden resulting from influenza are significant in both seasonal and pandemic cases (14,15).

This study aims to provide a clear and coherent overview of human influenza infection in hospitalized patients at Imam Reza and Qaem educational and therapeutic centers in Mashhad with emphasize on investigating the molecular epidemiology and clinical outcomes of patients during the years 2009 to 2017.

2. Methods

This was a retrospective cross-sectional study in which the medical records of patients diagnosed with influenza in Ghaem and Imam Reza educational hospitals in Mashhad during 2009-2017 were reviewed. To start gathering the data, PCR positive patients with influenza were selected from the provincial health center and was completed by information obtained from Hospital information system (HIS) in order to assemble the list of influenza cases. The main data collected was demographic information, underlying diseases, influenza vaccine history, influenza complications, hospital mortality and molecular

epidemiology of influenza virus.

Statistical Analysis:

The data was collected using a checklist and was analyzed using SPSS software version 23. Mean values were expressed as mean ± standard error of the mean (SEM). Descriptive statistics were used to describe the frequency and characteristics of patients using central measures, dispersion and frequency distribution and presented in tables. Quantitative variables between groups were compared using independent t test in normal distribution and Mann-Whitney test in non-normal distribution. Qualitative variables such as gender were compared using the Chi-square test and Fisher's exact test in case of need. All tests were statistically significant at the level of $P<0.05$.

The inclusion criteria included all patients hospitalized in Imam Reza and Qaem hospitals in Mashhad, with a definitive diagnosis of influenza, during the years 2009 to 2017. Exclusion criteria included incomplete hospital records, negative PCR results, and cases where the patient samples were not submitted for influenza testing. It is notable that, to maintain ethical standards, patient records were collected without documenting any identifiable information, such as first and last names, addresses, or other personal details. The data were coded sequentially to ensure complete confidentiality and protect the identities of the individuals involved.

3. Results

A total of 58 patients diagnosed with seasonal influenza and positive PCR were included in the study. Among these, 38 cases (65.5%) were diagnosed with influenza A and 20 cases (34.5%) diagnosed with influenza B, within the type A influenza group, there were 6 cases (15.7%) of H1N1 influenza, 9 cases (23.6%) of H3N2 influenza, and 23 cases (60.5%) that were not subtyped.

The mean age of the patients was 45.0 ± 3.81 years (Mean ± SEM), ranging from 1 to 90 years with equal gender distribution. All demographic data of patients are summarized in table 1.

Table 1: Demographic data of influenza infected patients included in the study

Demographic Characteristic	Value
Total Patients	58
Mean Age	45.0 ± 3.81 Years
Gender Distribution	29 Males (50%)/ 29 Females (50%)
Pregnant Patients	5 (8.6%)
Geographic Distribution	48 Urban (88.8%)/ 6 Rural (11.1%)
Occupational Distribution	19 Housewives (47.5%) 11 Self-employed (27.5%) 1 Employee (2.5%) 4 Retirees (10%) 5 Unemployed (12.5%)

The majority of hospitalizations occurred in winter, with 46 patients (79.3%) followed by 9 patients (15.5%) in autumn, and 3 patients (5.1%) in spring. Notably, there were no recorded cases of seasonal influenza hospitalization during the summer.

The mean length of hospital stay was 12.40 ± 2.41 days (Mean ± SEM), with a range from 1 to 120 days.

Comorbidities among the patients included hypertension in 19 individuals (33.9%), diabetes in 11 (19.6%), cardiovascular disease in10 (17.8%) chronic obstructive pulmonary disease (COPD) in 9 (16%), rheumatoid arthritis in 2 (3.5%), cancer in 1 (1.7%) cerebrovascular accident (CVA) in 2 (3.5%) HIV in 1 (1.7%) and tuberculosis in (1.7%).

A family history of contact with an influenza-infected individual was reported by 13 patients (36.1%) whereas 23 patients (63.8%) had no known contact with an infected person.

Out of the 58 patients, the timing of hospitalization varied considerably: 8 patients (14.5%) were admitted on the first day, 5 patients (9%) on the second day, 11 patients (20%) on the third day, 9 patients (16.3%) on the fourth day, 2 patients (3.6%) on the fifth day, 10 patients (18.1%) on the seventh day, 1 patient (1.8%) on the ninth day, 2 patients (3.6%) on the tenth day, 1 patient (1.8%) on the twelfth day, 3 patients (5.8%) two weeks later, 2 patients

(3.6%) on the fifteenth day, and 1 patient (1.8%) three weeks following the onset of symptoms. The mean duration between onset of symptoms and hospital admission was 5.47 ± 0.60 days (Mean ± SEM), ranging from 1 to 21 days.

Among 58 patients, 47 patients (81%) reported fever and chills and 47 patients (81%) exhibited a non-productive coughs. Also Lung auscultation revealed crackles and shortness of breath were reported from 35 (60%) and 36 (62%) patients respectively. Other common symptoms are listed in Table 2.

Out of 58 hospitalized patients diagnosed with seasonal influenza, Oseltamivir was administered to 51 patients (87.9%), whereas 7 patients (12%) did not receive antiviral medication. Among the patients with a definitive diagnosis of influenza who received antiviral therapy, 41 patients (77.3%) received their treatment within the first 48 hours of hospitalization, while 12 patients (22.6%) were treated after this period. Additionally, Out of 58 patients, 50 patients (86.2%) received antibiotics during their hospitalization, with 8 patients (13.7%) not receiving such treatment. Thirteen patients (22.8%) were transferred to the intensive care unit.

Outcomes revealed that out of 58 patients with a definitive diagnosis of influenza, 37 patients (67.2%) survived and 18 patients (32.7%) died during hospitalization. Six patients (10.9%) were discharged at their own request.

To evaluate the relationship between antiviral administration and hospital mortality in patients with a confirmed influenza, we used the Cox regression and Chi-Square Tests.

Our analysis indicated no a significant association between antiviral treatment and hospital mortality (P=0.388). Similarly, the timing of antiviral initiation within the first 48 hours did not significantly affect hospital mortality (P=0.459). Age of patients also did not show a significant correlation with hospital mortality (P=0.204). Moreover, the molecular type and subtype of the influenza virus did not demonstrate a significant relationship with hospital mortality (P=0.840 and 0.329, respectively).

4. Discussion

In this study, we analyzed 58 hospitalized patients with a definitive diagnosis of seasonal influenza. Our findings indicated that 66.5% (n=38) of the cases were type A influenza, while 34.5% (n=20) were classified as type B. Among the type A cases, 15.7% (n=6) were identified as H1N1, 23.6% (n=9) as H3N2, and 60.5% (n=23) were of undetermined subtype. The average age of the patients was 45 years, with a balanced gender distribution, including five pregnant women. These results are consistent with other studies, such as that conducted by Javid et al., which reported 68 confirmed influenza cases, with 36.7% (n=25) as

Table 2: Common symptoms/conditions in influenza infected patients included in the study

Symptom/ Condition	Number of Patients	Percentage
Fever and chills	47	81%
Non-productive cough	47	81%
Pneumonia	46	39.6%
Shortness of breath	36	62%
Vomiting	22	37.9%
Myalgia	16	27.5%
Productive cough	16	27.5%
Decreased consciousness	18	31%
Loss of appetite	13	22.4%
Headaches	7	12%
Sepsis/septic shock	7	6%
Exacerbations of chronic obstructive pulmonary disease (COPD)	9	7.7%
Abdominal pain	4	6.8%
Chest pain	4	6.8%
Acute respiratory distress syndrome (ARDS)	6	5.1%
Weakness	6	10.3%
Sore throat	3	5.1%
Hemoptysis	3	2.5%
Gastroenteritis	3	2.5%
Meningitis	3	2.5%
Rhabdomyolysis	1	1.7%
Pulmonary embolism	1	1.7%
Endocarditis	1	1.7%
Pleurisy	7	6%

H1N1 and 30.8% (n=21) as H3N2 (16). Notably, our study exclusively focused on hospitalized patients, whereas many previous studies have included both hospitalized and outpatient populations. This distinction may account for variations in the observed epidemiological patterns.

Similar to our findings, Elsherif et al. reported that 72.4% of influenza cases were type A, with H3N2 and H1N1 comprising 58.7% and 41.3%, respectively (17). Similarly, Caini et al. found that 76.5% of their 70,532 confirmed cases were type A. Notably, the circulation rates of type B influenza in our study (34.5%) were comparable to those reported in Bahrain, Jordan, and Pakistan, where rates were 45.2%, 42%, and 29.3%, respectively (18). In contrast, Moasser et al. reported a significantly lower prevalence of type B influenza (18%), suggesting that type B cases represent a substantial portion of hospitalizations that should not be overlooked (19). Importantly, our findings indicate that the mortality rates associated with type B influenza should be regarded with equal concern as those for type A influenza, given the lack of a significant relationship between influenza type and hospital mortality.

Among the five pregnant patients in our cohort, all survived, and we found no significant association between pregnancy and increased risk of death or ICU admission. This contrasts with findings from Mazagatos et al., who reported a hospital mortality rate of 4.4% among hospitalized pregnant women with influenza in Italy, predominantly infected with H1N1 (20). However, the differences in sample size and population characteristics warrant caution in direct comparisons.

The predominant symptoms leading to hospitalization in our study were respiratory in nature, with fever and chills reported in 81% of cases, cough in 81%, and shortness of breath in 62%. These findings align with previous studies, including Javid et al., where similar symptoms were observed (16). Specifically, fever, cough, and respiratory symptoms, along with myalgia, emerged as the most common clinical presentations in influenza patients (21). Our study also highlighted that 39.6% of patients were hospitalized with pneumonia, 10.3% with respiratory failure, and 7.7% with exacerbated respiratory symptoms, underscoring the severity of influenza-related complications.

Regarding demographic factors, we found no significant differences in hospitalization and mortality rates between genders, consistent with findings from Caini et al. and Cao et al (22,23). The average age of hospitalized patients was 45 years, suggesting that increased social interactions among individuals in this age group may elevate their risk of influenza infection, particularly during peak seasons (24).

Our data indicated a higher incidence of influenza during the winter and autumn months, consistent with the seasonal patterns observed in Iran and other regions (22) (24,25). The most common comorbidities associated with influenza infection were hypertension (33.9%), diabetes (19.6%), COPD (16%), and cardiovascular diseases (17.8%). These findings align with Mehdipour et al., who reported that a history of lung disease and diabetes significantly increased hospitalization likelihood (26). Similarly, Minkoul et al. identified immune deficiency, diabetes, cardiovascular diseases, and COPD as prevalent comorbidities in influenza patients, emphasizing the critical role of underlying health conditions in exacerbating influenza severity and complications (26)(27).

In our cohort, 37 patients (67.2%) survived, while 18 patients (32.7%) succumbed to their illness. Notably, 10.9% of patients were discharged at their own request. Our analysis revealed no significant correlation between the type or subtype of influenza virus and hospital mortality, suggesting that factors beyond the viral type may influence patient outcomes, a finding corroborated by Teale et al (28).

In our study, all five pregnant patients diagnosed with influenza survived, and we found no significant relationship between pregnancy and an increased risk of death or ICU admission. This contrasts with findings from Mazagatos et al., who reported that among hospitalized pregnant women in Italy from 2010 to 2016, 83% had H1N1, 53% had H3N2, and 11.3% had influenza B, with a hospital mortality rate of 4.4% (20). However, the differences in sample size and population characteristics between their study and ours—where only five pregnant women were included—limit direct comparisons and highlight the need for further investigation into the outcomes of pregnant patients with influenza.

In our cohort, Oseltamivir was administered to 51 patients (87.9%), while seven patients (12%) did not receive antiviral treatment. Notably, 41 patients (77.3%) received antiviral therapy within the first 48 hours of hospitalization, whereas 12 patients (22.6%) did not. Our analysis indicated that the timing of antiviral treatment did not significantly impact hospital mortality rates. This finding contrasts with the study by Mazagatos et al., which identified delays in antiviral treatment beyond 48 hours as a risk factor for ICU admission and mortality (20). Their results suggest that initiating antiviral treatment, even after the first 48 hours, can still reduce mortality, underscoring the importance of timely intervention in managing influenza.

Given the high transmissibility of influenza and its potential complications in high-risk populations, this study emphasizes the need for vigilant monitoring of influenza cases and effective treatment protocols. Understanding the molecular epidemiology and clinical outcomes of hospitalized influenza patients can inform community-level vaccination strategies and enhance awareness among healthcare providers. Timely diagnostic and therapeutic measures are crucial, particularly during the colder months when influenza activity typically peaks.

5. Conclusion

In conclusion, this study demonstrates that hospital mortality rate among patients diagnosed with seasonal influenza is approximately 32.7%, a concerning statistic given the preventable nature of this viral infection. The finding that 12% of hospitalized patients did not receive antiviral treatment within the critical first 48 hours underscores significant gaps in clinical management that must be addressed. Additionally, suboptimal sampling practices for influenza at both provincial and healthcare center levels likely contribute to the under diagnosis of acute respiratory infections, including influenza. This study emphasizes the urgent need for enhanced awareness and education among healthcare providers, regarding the timely diagnosis and management of acute respiratory infections during peak influenza seasons. Furthermore, the implementation of influenza vaccination programs for high-risk populations is essential to reduce complications, hospitalization rates, mortality, and overall healthcare costs associated with influenza. By addressing these challenges, we can improve patient outcomes and mitigate the impact of influenza within the community.

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Declaration

The authors declare no conflict of interest.

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