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Original Research

Investigation of Influenza Cases and Risk Factors Associated with Fatality in Türkiye

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Abstract

Objectives: Influenza is an infectious disease that primarily affects the respiratory system. It can cause high morbidity and mortality, especially in people with risk factors. This study aimed to epidemiologically analyze influenza PCR-positive patients in the 2014-2015 influenza season and to identify risk factors associated with disease severity and fatality.

Methods: Within the scope of national influenza surveillance program, clinical samples from patients with influenza-like illness (ILI) symptoms are sent to the Turkish Public Health Institution, National Influenza Center for testing, accompanied by case information forms. A retrospective analysis was conducted on the case information forms of patients who tested positive for influenza via PCR during the 2014-2015 influenza season. Demographic data were analyzed, and the presence of risk factors associated with fatality was investigated through further analysis.

Results: A total of 1330 patients were included in the study. 684 (51.4%) of the patients were female. The median age was 42.8 years (IQR: 23-61). Among the patients, 154 (11.9%) died. The median age of deceased patients was 60.2 years (IQR: 39.8-75). Being over 65 years old in deceased patients is 3.4 times more likely compared to survived patients [OR=3.4 (95% CI=2.4-4.9)]. Additionally, deceased patients were 4.8 times more likely to have Influenza A (H1N1) compared to survivors [OR=4.8 (95% CI=3.2-7.2)], and the presence of chronic diseases in deceased patients was also 3.4 times higher than in those who survived [OR=3.4 (95% CI=2.3-5.1)].

Conclusion: Infection with H1N1, being elderly and presence of chronic diseases were found to be associated with increased fatality. To mitigate morbidity and mortality, it is crucial to vaccinate individuals with chronic diseases and the elderly, educate them about contact precautions, and encourage prompt healthcare seeking when symptoms appear.

Keywords: Chronic disease, human, influenza, mortality, public health, risk factors

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Influenza is an infectious disease that primarily affects the respiratory system, caused by influenza viruses belonging to the Orthomyxoviridae family.[1] It can cause complications, leading to high morbidity and mortality, especially in people with underlying risk factors. Each year, approximately one-billion cases of influenza occur worldwide and there are 3–5 million cases of severe illness. According to the World Health Organization (WHO), influenza causes globally 290.000-650.000 respiratory deaths annually.[2]

Influenza viruses have four major antigenic types: A, B, C and D. Influenza A and B viruses cause seasonal epidemics and have public health importance. Influenza C virus usually causes mild infections and is detected less frequently. Influenza D viruses are not known to cause illness in people.

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Influenza viruses can show antigenic changes in virus surface proteins; either the virus subtype changes completely (antigenic shift) or the strain changes (antigenic drift) with minor changes within the same subtype. Influenza A has high antigenic diversity and, is particularly responsible for most epidemics and pandemics.[2,3]

Influenza viruses are transmitted from person to person mostly through droplets and also by contact.[4] The incubation period is 1-4 days (average 2 days).[2] Symptoms include sudden onset of high fever, shivering-chills, cough, weakness-fatigue, diffuse muscle aches, runny nose, sore throat and headache. The disease is usually self-limiting and uncomplicated in most healthy young adults. Although there is a benign course in most cases, it can lead to hospitalization, complications, and death, especially in the elderly, children, those with underlying chronic diseases, and patients with immune deficiency.[2,4,5]

Influenza has substantial socioeconomic impacts in terms of direct healthcare costs and indirect costs. Indirect costs are related to productivity loss and are the main contributor to the economic burden of influenza.[6] Overall, 20-75% of employees miss work because of influenza or influenza-like illness (ILI), with an average work absence of approximately 2-3 days. Average productivity loss due to influenza varies between 67-74%.[7,8] Additionally, the average school absence among children is 3.8 days and employees also miss work to care for household members affected by influenza.[7,9]

Most cases of influenza are diagnosed based on clinical signs and symptoms. Definitive diagnosis of influenza is made by microbiological analysis. Isolation of the virus by cell culture, demonstration of virus antigens or demonstration of influenza-specific antibody response can be used for definitive diagnosis. Cell culture and nucleic acid-based tests (NAT) are considered the gold standard methods in demonstrating virus and detection of viral nucleic acids by polymerase chain reaction (PCR) is most commonly used test for diagnosis.[10]

Antiviral drugs for treatment of influenza include drugs that are active against both influenza A and B; the neuraminidase inhibitors (oseltamivir, zanamivir, and peramivir) and a selective inhibitor of influenza cap-dependent endonuclease (baloxavir), and drugs have only activity against influenza A; the adamantanes (amantadine and rimantadine). The use of adamantanes in the treatment of influenza is not recommended due to high resistance rates. For the treatment of influenza, oral oseltamivir, inhaled zanamivir, intravenous peramivir, or oral baloxavir can be used depending on disease severity.[11]

Influenza vaccine is most effective method known to protect against influenza epidemics. Influenza viruses and seasonal activity are continuously monitored globally, and vaccine components are periodically updated according to the influenza virus surveillance data from WHO Global Influenza Surveillance and Response System. Trivalent vaccines containing two influenza type A (H3N2 and H1N1) and one influenza type B (Victoria proposed for the 2023-2024 season) hemagglutinin antigens. There are tetravalent vaccines contain both seasonal influenza A(H3N2) and A(H1N1), and both influenza B lineages, B/Victoria and B/Yamagata. To maintain the high efficacy of vaccines, it is crucial to continuously monitor antigenic types of circulating influenza viruses and periodically assess the components of influenza vaccines.[2,12]

This study aimed to epidemiologically examine the patients who received a definitive influenza diagnosis due to positive Influenza PCR results from samples sent to the Turkish Public Health Institution within the scope of sentinel and non-sentinel influenza surveillance during the 2014-2015 influenza season and to determine the risk factors associated with disease severity and fatality.

Methods

In Türkiye, influenza surveillance has been conducted as 'Sentinel Influenza-Like Illness (ILI) Surveillance' since 2005. Within the scope of Sentinel ILI Surveillance, clinical samples are collected from patients who have ILI symptoms in designated health institutions across the country and are sent to the National Influenza Center Laboratory together with ILI case information forms. During our study period, sentinel influenza surveillance was conducted in 17 provinces in Türkiye. Non-sentinel surveillance was also conducted by health institutions other than the designated centers. In addition to sentinel ILI surveillance, 'Severe Acute Respiratory Infections (SARI) Surveillance' has been conducted in our country since December 2015 to follow up hospitalized severe influenza cases.[13] However, SARI surveillance was not carried out during our study period, so we analyzed data obtained from both sentinel and non-sentinel ILI surveillance in our research.

During the 2014-2015 influenza season within the scope of national influenza surveillance, samples such as nasal, nasopharyngeal and throat swabs, tracheal aspirates, throat rinse water and bronchoalveolar lavage samples were taken from patients who had ILI symptoms. The case information forms were filled out by the physicians and delivered to the laboratory together with the samples.

All samples received by the National Influenza Center Laboratory were first subjected to nucleic acid extraction. Qiagen EZ1 Virus Mini Kit v2.0 extraction kit and Qiagen EZ1 Advanced XL extraction device (Qiagen, Germany) was

used for virus RNA isolation. Following nucleic acid extraction, presence of Influenza A and Influenza B RNA was investigated using rRT-PCR technique by the recommendations of Centers for Disease Control and Prevention (CDC) in the National Influenza Center Laboratory.[14] CDC annually provides primers and probes containing updated sequences that detect Influenza A and Influenza B viruses as well as subtypes such as A(H1), A(H3), A(H1) pdm09 as per the agreement between WHO and the National Influenza Centers. Influenza rRT-PCR was performed on real-time PCR devices (Stratagene Mx3005P, Stratagene, ABI 7500, Applied Biosystems) using SuperScript™III Platinum® One-StepqRT-PCR Kit (Invitrogen, USA) or AgPath-ID™ One-Step RT-PCR Kit (Applied Biosystems, USA) according to the protocol recommended by the CDC.[15]

Case Description

According to the Turkish Ministry of Health, Notification and Reporting System of Communicable Diseases, Standard Diagnosis, Surveillance and Laboratory Guide for Influenza: a clinical case is defined as a disease characterized by sudden onset of fever (>38°C) and cough and/or sore throat that cannot be explained by any other reason. Individuals who meet the clinical case definition are considered as suspected cases. Definitive diagnosis of influenza is made by microbiological examination and can be made by demonstrating the virus in samples using cell culture, molecular techniques (nucleic acid amplification tests) or antigen detection tests.[13]

A total of 6583 samples were sent to the National Influenza Center Laboratory between September 29, 2014, and May 10, 2015 (between the 40th week of 2014 and the 19th week of 2015) within the scope of sentinel and non-sentinel ILI surveillance. Influenza PCR results were detected positive in 1677 of these samples.

Study Method

In our study, the samples sent to the Turkish Public Health Institution National Influenza Center between September 29, 2014, and May 10, 2015, were retrospectively examined and data was obtained from ILI case information forms of patients with influenza PCR positivity. 347 patients were excluded from the study due to the absence of case information forms or insufficient information on forms. A total of 1330 patients were included in the study.

The information on the case information forms of the patients was reviewed retrospectively. Patients' age, gender, occupation, symptom onset dates, hospitalization, survival information, symptoms (fever, cough, myalgia, nasal discharge, headache, arthralgia, sore throat, respiratory distress, acute respiratory failure, etc), antiviral treatment, medical history (chronic diseases, immunosuppression, complications, pregnancy or obesity), vaccination status, contact and travel history were evaluated. Additionally, patients' chronic diseases and antiviral treatments were checked through pharmacy registration system.

In the study, the influenza virus types and seasonal influenza activity were examined based on the influenza PCR results. Risk factors associated with fatality was investigated and examined through further analysis.

Ethical approval was obtained from the Diskapi Yildirim Beyazit Training and Research Hospital Clinical Research Ethics Committee (decision date: 16.01.2017, decision number: 34/15). We declare that this study was conducted according to the Declaration of Helsinki.

Statistical Analysis

Descriptive statistics are given with n, percentage, median with interquartile range (IQR). Chi-square and Fisher's exact probability test were used for qualitative variables in intergroup comparisons. The distribution of quantitative data in the groups was evaluated by Shapiro-Wilk, Kolmogorov Smirnov normality tests and histograms. Mann Whitney U test was used to compare the distribution of quantitative data in two independent groups. Crude Odd Ratios were calculated using the OpenEpi program. Risk factors associated with fatality were examined by logistic regression. Presence of chronic diseases, age, influenza type, admission time and gender were included in the model. The statistical significance limit was accepted as $p<0.05$. The data were analyzed with SPSS Version 29 (IBM SPSS, Armonk, New York, USA).

Results

1330 patients were included in the study. 561 (42.2%) were obtained through sentinel surveillance and 769 (57.8%) were obtained through non-sentinel surveillance. 684 (51.4%) of the patients were female. The median age was 42.8 (interquartile range 23-61). 759 (57.1%) of the patients were monitored as inpatients, and 154 patients (11.9%) died.

The median age for deceased patients was 60.2 (39.8-75), and it was 41.1 (18.6-58.9) for those who survived ($p<0.001$). When the 18-64 age group is taken as the reference, being over 65 years old in deceased patients is 3.4 times more likely compared to survived patients [OR=3.4 (95% CI=2.4-4.9)].

The most frequently reported symptoms were cough (86.5%), fever (75.6%), myalgia (61.7%), headache (60.2%), sore throat (57.1%) and nasal discharge (52.1%). Table 1 shows the distribution of possible risk factors according to patients' survival.

Table 1. Influenza surveillance data by survival status of participants

	Survival	Mortality	OR (%95 GA)	p
Age[a]				
Median (IQR)	41.1 (18.6-58.9)	60.2 (39.8-75)	p<0.001[c]	
Age distribution n (%)[b]				
<5 years old	96 (8.2)	4 (2.6)	0.4 (0.1-1.1)	<0.001[d]
5-17 years old	189 (16.2)	3 (1.9)	0.1 (0.1-0.5)	
18-64 years old	689 (59.2)	76 (49.4)	Ref	
≥65 years old	190 (16.3)	71 (46.1)	3.4 (2.4-4.9)	
Total	1164 (100.0)	154 (100.0)		
Gender n (%)[b]				0.080[d]
Female	615 (52.3)	69 (44.8)	0.7 (0.5-1.0)	
Male	561 (47.7)	85 (55.2)	Ref	
Total	1176 (100.0)	154 (100.0)		
Employment status n (%)[b,e]				0.043[g]
Healthcare worker	60 (7.5)	-	-	
Instructor/teacher	20 (2.5)	-	-	
Student	163 (20.3)	1 (3.6)	Ref	
Other	228 (28.5)	9 (32.1)	6.4 (0.8-51.3)	
Unemployedf	330 (41.2)	18 (64.3)	8.9 (1.2-67.1)	
Total	801 (100.0)	28 (100)		
No chronic disease n (%)[b]	589 (50.1)	35 (22.7)	Ref	<0.001[d]
Has chronic disease n (%)[b]	587 (49.9)	119 (77.3)	3.4 (2.3-5.1)	
Total	1176 (100.0)	154 (100.0)		
Chronic diseases n (%)[b]				
Diabetes mellitus (DM)	150 (12.8)	26 (16.9)	1.4 (0.8-2.2)	0.155[d]
Hypertension	275 (23.4)	38 (24.7)	1.1 (0.7-1.6)	0.723[d]
Chronic Obstructive Pulmonary Disease	122 (10.4)	36 (23.4)	2.6 (1.7-4.0)	<0.001[d]
Asthma	162 (13.8)	14 (9.1)	0.6 (0.4-1.1)	0.107[d]
Chronic Heart Disease	94 (8.0)	25 (16.2)	2.2 (1.3-3.6)	<0.001[d]
Chronic Renal Failure	21 (1.8)	13 (8.4)	5.1 (2.5-10.3)	<0.001[g]
Malignancy	31 (2.6)	8 (5.2)	2.0 (0.9-4.5)	0.120[g]
Neuropsychiatric disease[g]	35 (3.0)	7 (4.5)	1.6 (0.7-3.6)	0.322[g]
Other[h]	173 (14.7)	23(14.9)	1.0 (0.6-1.6)	0.941[d]
Total[i] (n)	1063	190		1253
Pregnancy n (%)[b]	35 (3.0)	5(3.2)	1.1 (0.4-2.8)	1.000[g]
Contact history n (%)[b]				0.005[g]
Yes	389 (38.7)	9 (14.3)	0.3 (0.1-0.5)	
No	613 (60.9)	54 (85.7)	Ref	
Not known	4±0.4	-		
Totalk	1006 (100.0)	63 (100)		
Travel history (Last 7 days) n (%)[b]				0.337[g]
Yes	31 (3.1)	-	-	
No	967 (96.7)	62 (100.0)	Ref	
Not known	2 (0.2)	-		
Total[l]	1000	62		

IQR: Interquartile range; [a] 12 missing; [b] Column percentage; [c] Mann Whitney U; [d] Pearson's chisquare; [e] 501 missing; fChild, unemployed and housewife; [g]Fisher's exact test; [h] Cerebrovascular disease, epilepsy, migraine, cerebral palsy, muscular dystrophy, schizophrenia, depression; [i] Non-DM endocrine disorders, liver disease, osteoporosis, psoriasis, tuberculosis, pick wick syndrome; [j]Multiple responses have been given; [k]261 missing, those whose symptoms started at admission have been excluded; [l] 268 missing.

Contact information was available for 1065 patients (80.1%). Among these, 398 patients (37.4%) reported having contact with a person with ILI, and the source of infection was identified in 249 patients (62.6%). Among the patients with a known source of infection, 177 (71.1%) had contact history at home, 35 (14.1%) at work, 29 (11.6%) at

school, 7 (2.8%) both at home and at work, and 1 (0.4%) in hospital. Contact history was higher in the surviving group than in deceased patients (p=0.005).

Presence of chronic disease in deceased patients is 3.4 times that of surviving patients [OR=3.4 (95% CI= 2.3-5.1)]. The most common diseases in this group were determined as chronic obstructive pulmonary disease, chronic heart disease, and chronic renal failure.

No difference was observed between the deceased and surviving patients in terms of gender, pregnancy status and travel history.

In analysed samples, Influenza B positivity was found in 667 cases (50.2%), Influenza A H1N1 positivity in 535 cases (40.2%), and Influenza A H3N2 positivity in 128 cases (9.6%). The distribution of virus subtypes according to patients' survival is shown in Table 2. Taking influenza B infection as a reference, being infected with influenza A (H1N1) in deceased patients is 4.8 times more likely compared to those who survived [OR=4.8 (95% CI=3.2-7.2)]. Table 3 shows the distribution of influenza types and survival rates according to patients' hospitalization status. Taking influenza B infection as a reference, being infected with influenza A (H1N1) in hospitalized patients is 2.11 times more likely compared to outpatients [OR=2.11 (95% CI=1.67-2.68)].

Vaccination rates was low in both deceased and survived patients. Although the vaccination rate was higher in surviving patients than in those who died, the difference was not statistically significant [OR=2.5 (95% CI=0.3-18.3), p=0.615].

Table 2. Influenza surveillance data by survival status of participants

	Survival	Mortality	OR (%95 GA)	p
Influenza type n (%)[a]				<0.001[b]
Influenza A (H1N1)	422 (35.9)	113 (73.4)	4.8 (3.2-7.2)	
Influenza A (H3N2)	122 (10.4)	6 (3.9)	0.9 (0.3-2.2)	
Influenza B	632 (53.7)	35 (22.7)	Ref	
Total	1176 (100.0)	154 (100.0)		
Vaccination status n (%)[a]				0.002[b]
Yes	49 (4.2)	1 (1.4)	Ref	
No	910 (77.4)	46 (63.9)	2.5 (0.3-18.3)	
Not known	217 (18.5)	25 (34.7)		
Total[c]	1176 (100.0)	72 (100.0)		
Time elapsed between symptom-application[e]				
Median (IQR)	2 (1-4)	3 (0-6)		0.678[d]
Symptoms n (%)[a]				
Fever	906 (77.0)	100 (64.9)	0.6 (0.4-0.8)	<0.001[b]
Cough	1050 (89.3)	100 (64.9)	0.2 (0.2-0.3)	<0.001[b]
Muscle pain	772 (65.6)	48 (31.2)	0.2 (0.2-0.3)	<0.001[b]
Joint pain	473 (40.2)	22 (14.3)	0.2 (0.2-0.4)	<0.001[b]
Headache	771 (65.6)	29 (18.8)	0.1 (0.1-0.2)	<0.001[b]
Sore throat	731 (62.2)	29 (18.8)	0.1 (0.1-0.2)	<0.001[b]
Nasal discharge	669 (56.9)	24 (15.6)	0.1 (0.1-0.2)	<0.001[b]
Respiratory distress	370 (31.5)	128 (83.1)	10.7 (6.9-16.6)	<0.001[b]
Other[f]	89 (7.6)	30 (19.5)	3.0 (1.9-4.7)	<0.001[b]
Antiviral therapy				<0.001[b]
Yes	460 (39.1)	102 (66.2)	Ref	
No	265 (22.5)	29 (18.8)	0.5 (0.3-0.8)	
Not known	451 (38.4)	23 (14.9)		
Admitted to				<0.001[b]
Ward	530 (87.6)	21 (13.6)	Ref	
ICU	75 (12.4)	133 (86.4)	44.8 (26.6-75.3)	
Total	605 (100.0)	154 (100.0)		

IQR: Interquartile range; [a] Column percentage; [b] Pearson's chi-square; [c] 82 missing; [d] Mann Whitney U; [e] 268 missing; [f] Nausea, vomiting, dizziness, abdominal pain, loss of appetite, diarrhoea, nasal congestion.

Table 3. Mortality rates and influenza types of patients according to hospitalization status

	Outpatient	Inpatient	OR (%95 GA)	p
Survival status n (%)[a]				
Survival	571 (100)	605 (79.7)	-	<0.001[b]
Mortality	0 (0)	154 (20.3)		
Total	571 (100.0)	759 (100.0)		
Influenza type n (%)[a]				
Influenza A (H1N1)	170 (29.8)	365 (48.1)	2.11 (1.67-2.68)	<0.001[b]
Influenza A (H3N2)	70 (12.3)	58 (7.6)	0.82 (0.56-1.19)	
Influenza B	331 (57.9)	336 (44.3)	Ref	
Total	571 (100)	759 (100)		
Antiviral therapy				
Yes	136 (23.8)	426 (56.1)	Ref	<0.001[b]
No	167 (29.3)	125 (16.5)	0.24 (0.17-0.32)	
Not known	268 (46.9)	208 (27.4)		

[a]Column percentage; [b]Pearson's chi-square.

In surviving patients, symptoms such as fever, cough, muscle pain, sore throat, and nasal discharge were more frequent, while respiratory distress was more prevalent in deceased patients. Respiratory distress is 10.7 times more prevalent in deceased patients compared to survivors [OR=10.7 (95% CI=6.9-16.6)].

Risk factors associated with influenza-related fatality were evaluated by multivariate analysis. Influenza type, age, gender, chronic illness, and time of admission were evaluated together and being infected with Influenza A (H1N1), being over 65 years old, and having chronic illness were found to be associated with fatality (Table 4). There was no interaction between age, gender, presence of chronic disease, duration of admission and influenza type; they were included in the model to control for confounding factors. Vaccination status could not be included in the model due to missing data.

Table 4. Investigation of risk factors associated with influenza-related fatalities (multivariate analysis)

	OR	%95 GA	p
Influenza A (H1N1)	3.9	2.2-6.9	<0.001
Influenza A (H3N2)	1.2	0.4-3.6	0.794
Influenza B (ref)			
<5 years old (ref)			
5-17 years old	0.3	0.03-3.24	0.337
18-64 years old	1.7	0.5-5.8	0.402
≥65 years old	5.9	1.7-20.1	0.005
Female	0.9	0.6-1.6	0.786
Chronic disease	2.6	1.3-5.0	0.006
Application period≥48 hours	1.2	0.7-2.0	0.515

Discussion

Influenza viruses can affect people all over the world and cause epidemics and pandemics. In healthy young adults, the disease is usually self-limiting and uncomplicated. Although usually having a benign course, influenza can lead to hospitalization, complications, and death, especially in elderly, children, individuals with underlying chronic illnesses, or immunocompromised patients.[4]

Although seasonal influenza affects all age groups, high attack rate is mostly seen in young people and the mortality rate is higher in the elderly population.[16,17] In a study, it was reported that influenza-related mortality increased with age and the estimated mean annual influenza-related respiratory mortality per 100,000 individuals was 2.9–44.0 in people aged 65–74 years and 17.9–223.5 in people aged ≥75 years; while it was 0.1–6.4 in people aged <65 years.[18] In our study, 46.1% of the deceased patients were ≥65 years old. Being over 65 years old in deceased patients is 3.4 times more likely compared to those survived. Factors such as decreased cellular and humoral immune response, reduced lung compliance and respiratory muscle strength, decreased cough reflex, presence of multiple comorbidities and nutritional deficiencies can contribute to increased susceptibility to influenza in the elderly.[19]

The samples in our study were collected from individuals who visited healthcare facilities with influenza symptoms. It is possible that young individuals applied to health care facilities less frequently due to a milder disease course, while admission to healthcare facilities may be higher in the elderly due to a more serious course of illness. Therefore, conducting community-based studies would be ben-

eficial to determine the age groups with the highest influenza activity and mortality.

Chronic respiratory diseases, cardiovascular diseases, diabetes, and immunosuppression have been identified as the most prevalent underlying diseases among hospitalized patients with influenza.[17] Studies have also noted that pregnancy and obesity are significant underlying clinical conditions associated with disease severity.[20] Due to limited number of pregnant participants in our study, no significant difference was found related to hospitalization in pregnant patients. However, the effect of obesity could not be investigated because the patients' body mass index information was not available.

Children have high attack rates of influenza in the community and play a pivotal role in transmission of influenza to households and other close contacts. Due to being together in crowded environments, especially school-aged children have a high influenza disease burden.[21] In our study, according to employment status of patients, the highest percentage (42.0%) was found in non-working groups (children at home, unemployed and housewives) and 19.8% of influenza-positive cases were students. Given that the unemployed group with less contact with society was the predominant group, it was suggested that there are individuals responsible for transmitting the disease to these unemployed populations and children may play a role in this transmission. This situation may also be due to the possibility that the unemployed group may have applied to health institutions and may have been diagnosed more frequently than employed persons.

The importance of household contact has been demonstrated in studies investigating the transmission routes of influenza. If a member of the household is infected with influenza, the risk of infection in a person in contact with the household can be up to 38%, and younger people are at higher risk.[22] In a study conducted in 2021-2022, it was found that 50% of household contacts of influenza patients were infected.[23] Influenza transmission in the workplace is also important. In modeling studies an average of 16% (9-33%) of influenza transmission occurs in the workplace.[24] In our study, among those with contact information, the most frequent contact was found to be at home but contact at work and school was also evident.

The distribution of virus subtypes changes over time during the influenza seasons. According to the sentinel ILI surveillance in our country, between the 40th week of 2023 and the 33rd week of 2024, 62.8% of influenza viruses were Influenza A (53.5% H1N1, 15.9% H3N2, and 30.5% were not subtyped) and 37.2% were Influenza B. Between the same weeks, according to SARI surveillance, 71.1% of influenza viruses were Influenza A (63.7% H1N1, 17.6% H3N2 and 18.7% were not subtyped) and 28.9% were Influenza B.[13] When the virus distribution in 2014-2015 influenza season, in which our study was conducted, was compared with the virus distribution in 2023-2024 season, it was seen that the circulating virus subtypes were quite different. In our study, the most common virus type in all patients was Influenza B. Although influenza A (H1N1) was the most frequently reported virus type in hospitalized patients, influenza B virus was also common in inpatients. Continuous monitoring of viral circulation is essential to adapt influenza-prevention policies, especially those regarding vaccine formulation and composition, to the current epidemiological situation.

The relationship between influenza types and mortality may differ between studies depending on characteristic of epidemic and vaccination strategies. Influenza B is known to be associated with milder disease than Influenza A. Also, there are studies indicating that Influenza B may be associated with mortality.[25,26] In our study, although the dominant virus was Influenza B; Influenza A (H1N1) was found to be a risk factor associated with fatality.

The goal of the "Healthy People 2030" project, conducted by "CDC-National Center for Health Statistics", is to reach a 70% vaccination proportion in population to prevent influenza. According to the latest data the vaccination rate against seasonal influenza for people aged 6 months and over in 2020-2021 season was 49.8% in US.[27] In our study, it was determined that only 50 (4.97%) of 1006 patients with vaccination information had been vaccinated against influenza within the last year. The vaccination rates in our study were well below the targeted vaccination rates. On the other hand, the group included in the study is only influenza cases, and since non-influenza cases are not included in this study, the low vaccination percentage in this group does not reflect the society. In general population, those who were vaccinated may have experienced milder symptoms due to the protective effect of the vaccine and therefore may have sought medical attention less frequently or may not have had the influenza at all.

It is known that in very mild or asymptomatic influenza cases, the disease is self-limiting and these people mostly recover spontaneously without medical support and no samples were taken from these people.[16] As highlighted in this study, surveillance studies that include only individuals with clinical findings tend to underestimate the prevalence of influenza in the community; additionally, because mild and asymptomatic cases are not included, the morbidity and mortality caused by influenza may be overestimated.

In treatment of influenza, clinical benefit is greatest when antiviral treatment is administered early, especially within

48 hours of influenza symptoms onset.[11] In our study, 65.6% of the patients whose treatment information is accessible received antiviral treatment (all oseltamivir) and most of these were inpatients. More than half of the inpatients and two-thirds of the deceased patients received antiviral treatment; this is thought to be related to severe course of the disease in these patients. It is known that the appropriate and early use of neuraminidase inhibitors in influenza patients reduces the complications and the risk of mortality.[28] In our study, this relationship could not be demonstrated due to lack of information regarding the interval between disease onset and initiation of antiviral therapy.

There are some limitations in our study. In order for the study results to be reliable, the data must be complete and of high quality. However, obtaining accurate and high-confidence epidemiological data is difficult, even in most advanced epidemiological surveillance systems.[29] Although standardized forms are used, since the forms are filled out by personnel with different knowledge and training levels regarding the approach to the disease, there may be quality differences in the data. In addition, data in some forms are incomplete and there were patients who did not have any case information form in our study. The forms with incomplete data were excluded from the analysis and the results were tried to be obtained as accurately as possible.

Additionally, since our study was a retrospective study analyzing surveillance data available in the forms, statistically significant results could not be obtained due to the small number of patients in some diseases (endocrine diseases, metabolic diseases, rheumatological diseases and liver diseases). In addition, since the details of antiviral treatment (dose, duration, initiation time of treatment, etc.) were not available, the effectiveness of antiviral treatment could not be evaluated. Fatality may be overestimated due to possibility that asymptomatic/mildly symptomatic patients did not seek medical care and underestimated due to possibility that severe cases diagnosed in tertiary care centers, which are outside the scope of the surveillance, were not detected and included.

Our study is a comprehensive study that evaluating patients from all regions of the country according to national influenza surveillance data, but the time period of the study is 2014-2015 and surveillance data for circulating viruses have become outdated. However, although our study was conducted in 2014-2015 season and the surveillance data for circulating viruses have become outdated, the data we obtained from our study are valuable and significant for identifying risk factors associated with disease severity and mortality. Furthermore, our study is also important in terms of emphasizing the critical importance of vaccination in high-risk groups, such as those with underlying diseases and the elderly, who are more likely to experience higher mortality rates.

Conclusion

In our study, influenza surveillance data and risk factors thought to be associated with fatality were examined.

When the risk factors that may be associated with fatality are examined, being infected with H1N1, being over 65 years of age and presence of chronic diseases were found to be associated with increased fatality. Analytical studies are needed to evaluate the relationship between influenza type and hospitalization and fatality. Potential confounding and effect-modifying factors should be evaluated in further studies. It is recommended that those identified as risk groups by the CDC such as those under the age of 5, those over the age of 65, and those with chronic diseases should be given priority for vaccination.

In our study, being over 65 years of age and the presence of chronic disease was found to be associated with fatality, consistent with the literature. Vaccination of people with chronic diseases and elderly people in influenza seasons, informing them about contact precautions, and encouraging them early healthcare seeking when symptoms arise are important for reducing morbidity and mortality.

Disclosures

Ethics Committee Approval: This study was approved by the Diskapi Yildirim Beyazit Training and Research Hospital Clinical Research Ethics Committee (16.01.2017, no: 34/15).

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