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Original Article

Investigation of influenza and respiratory viruses in hospitalised patients with influenza-like illness in an emergency room

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Abstract

Introduction: Influenza-like illness (ILI) surveillance is usually performed using outpatient data, and information on the surveillance of patients hospitalised for ILI, which is critical for the complete assessment of the influenza burden, is lacking.

Methodology: In this prospective active surveillance study, patients with community-acquired ILI hospitalised for at least 24 hours in the Emergency Room (ER) of Gazi University Hospital were identified according to the ICD-10 codes at hospital admission through active surveillance of the 2013–2014 and 2014–2015 influenza seasons. The presence of influenza and other respiratory viruses was analysed in the nasopharyngeal or pharyngeal specimens by real-time polymerase chain reaction.

Results: 351 patients admitted to emergency room with certain ICD-10 codes were assessed, and 111 patients with ILI were included in the study. We detected 15 influenza and 23 other respiratory viruses in 33 of the 111 patients. More than one virus was detected in 5 patients. No virus was detected in a majority of the patients with ILI. The sensitivity of hospital admission/discharge ICD-10 codes used in the study to detect real influenza cases was low. Patients with influenza were admitted to the hospital more frequently with high fever symptoms compared with patients with influenza virus-negative and other respiratory virus-positive ($p < 0.05$).

Conclusions: This study revealed that non-influenza respiratory viruses were a major contributor to ILI. Patients admitted with fever during the influenza seasons should be evaluated for influenza virus infection, and the use of diagnostic codes in surveillance studies can lead to incorrect results.

Key words: Influenza; influenza-like illness; emergency room.

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Introduction

Acute respiratory infections, which are common infections found worldwide, are frequently caused by influenza and other respiratory viruses such as coronavirus, adenovirus, rhinovirus, parainfluenza virus, human metapneumovirus and respiratory syncytial virus (RSV) [1]. Among these, influenza is particularly important because of its ability to evolve into seasonal epidemics and pandemics and the availability of influenza vaccines and influenza-specific antiviral therapy. Influenza outbreaks are estimated to cause serious infections in 3–5 million individuals, accounting for 250,000–500,000 deaths per year globally according to World Health Organization (WHO) [2]. Annual influenza epidemics also result in substantial workplace absenteeism and significant economic loss. Therefore, active surveillance networks that assess influenza in all aspects are necessary to understand its epidemiology and to control its outbreaks. In several countries, including Turkey, influenza surveillance is performed via sentinel surveillance, which collects information on outpatient data and no in-patient data are included [3]. However, influenza can cause serious complications in elderly individuals, especially those with underlying diseases, and more than 200,000 hospitalisations per year are estimated to be associated with influenza in the Unites States [4]. Therefore, in-patient surveillance is crucial for the complete assessment of influenza burden and for the identification of causative strains in patients with a severe clinical course.

The main objective of the present study was to identify the types and subtypes of influenza leading to ILI and determine the contribution of other respiratory viruses to ILI using the International Statistical Classification of Diseases and Related Health Problems (ICD) code-based and laboratory-confirmed ILI surveillance in the emergency room (ER). The study setting was the ER, which are often the first admission

point where serious and complicated influenza cases can easily be identified before hospitalisation.

Methodology

This prospective, active surveillance study was performed as a part of the Hospital-Based Influenza Surveillance project conducted by the Global Influenza Hospital Surveillance Network (GIHSN) in two consecutive influenza seasons. The study was approved by the Ethics Committee of the Istanbul University Faculty of Medicine. The fieldwork for this study was initiated on 1 December, 2013, and ended on 1 May, 2014, for the first influenza season (2013–2014) and on 6 January, 2015, and 1 May, 2015, for the second influenza season (2014–2015). This study followed the core reference protocol of the GIHSN coordinating site in Spain.

The Global Influenza Hospital Surveillance Network

The GIHSN initiative was established in 2012 to contribute to hospital-based influenza surveillance by focusing on serious influenza cases. The main objectives of this initiative are to evaluate the burden of serious influenza cases and the distribution of influenza virus types and to detect the protective effects of seasonal influenza vaccines on patients during hospital admissions. The GIHSN was based on public–private partnerships constituted by Fundación para el Fomento de la Investigación Sanitaria y Biomédica de la Comunitat Valenciana (FISABIO), Sanofi Pasteur, Fondation Mérieux, and multiple country sites affiliated with health authorities. In Turkey, the GIHSN was supported by National Influenza Reference Laboratory at the Istanbul Faculty of Medicine during the study period. The GIHSN conducted studies at 24 hospitals located at several sites in Spain, Turkey, Russia, China, and Brazil in the 2013–2014 influenza season and in 27 hospitals located at several sites in Russia, Czech Republic, Turkey, China, Brazil, and Spain in the 2014–2015 influenza season [3,5].

Patient groups

Patients with community-acquired ILI who were hospitalised for at least 24 hours in the Emergency Room of Gazi University Hospital were screened according to certain influenza predicting ICD-10 codes at the time of hospital admission. Patients aged > 18 years who met the following European Centre for Disease Prevention and Control (ECDC) ILI criteria were included in the study: acute onset of at least one of the systemic symptoms, including fever, malaise, headache and myalgia; at least one of the respiratory symptoms, including cough, sore throat and dyspnoea in the last 7 days before admission. Patients who refused to provide consent, those who were institutionalised and those with a history of hospitalisation in the last 30 days were excluded from the study. Written informed consent was obtained from all the patients included in the study.

Data collection

The enrolled patients were assessed, and a GIHSN form that includes ILI symptoms, patient demographic characteristics, comorbidities and vaccination status was filled. Data on hospital admission and discharge ICD-10 codes, intensive care unit admission and mechanical ventilation status were obtained from the patient records. In addition to the study protocol, initial laboratory results and chest X-rays were also assessed. Nasopharyngeal or oropharyngeal swab specimens were collected in the Virocult transport medium (Medical Wire & Equipment, Wiltshire, UK) from all the study patients and transported to the Virology Laboratory of Istanbul Faculty of Medicine on the day of collection. The specimens that could not be sent to the laboratory on the day of collection were stored at 4°–8°C and delivered to the laboratory within 2 days of collection.

Confirmation of influenza virus infection

Virological examination was performed for the clinical samples at the Virology Laboratory of Istanbul University Medical School. The samples in the Virocult transport medium were transferred into cryotubes and stored at -80 °C if they were not assessed on the same day. An EZ1 Virus Mini Kit v2.0 (catalogue number: 955134; Qiagen, Hilden, Germany) was used for total nucleic acid extraction. A real-time polymerase chain reaction-based multiplex FTD® Respiratory Pathogens 21 kit (Fast-track Diagnostics Ltd. Malta) was used to detect respiratory pathogens on the RotorGene Q platform (Qiagen, Hilden, Germany). The kit can detect influenza A (H1N1), influenza B, rhinovirus, coronavirus NL63, 229E, OC43, HKU1; parainfluenza 1, 2, 3, 4; human metapneumovirus A/B, bocavirus, *Mycoplasma pneumoniae*, RSV A/B, adenovirus, enterovirus, parechovirus and internal control. Real-time RT-polymerase chain reaction was performed according to the Centers for Disease Control and Prevention (CDC) protocol using the ABI 7500 platform with CDC primers and probes for the detection of influenza H3 subtype and influenza B Yamagata and Victoria lineages [6].

Statistical analysis

Statistical analysis was performed using the SPSS statistical software package version 20. Qualitative variables were expressed as percentages, and quantitative variables were expressed as means (± standard deviation) and medians (range). The normality of data was tested using the Kolmogorov–Smirnov test, and non-parametric tests were used for non-normal distributions. Comparisons between groups were achieved using the chi-square test for categorical variables and the Mann–Whitney *U* test for numeric variables. A p value of < 0.05 was considered statistically significant.

Results

Virological analysis of the enrolled patients

A total of 351 patients with hospital admission ICD-10 codes included in the present study were screened during the 2013–2014 and 2014–2015 influenza seasons, and 177 patients were excluded from the study for the following reasons: < 24 hours of follow-up in the ER (n = 73), inability to communicate (n = 7), non-residence status (n = 3), institutionalised patients (n = 7), hospitalisation in the last 30 days (n = 71) and no consent (n = 16). The remaining 174 patients were evaluated for the clinical and time-related criteria of ILI, and 63 patients who did not meet the ILI criteria were excluded from the study. Finally, respiratory specimens were collected from the remaining 111 patients.

During the 2013–2014 influenza season, the positivity rates for all and influenza viruses were 52.7% and 19.4%, respectively, in a total of 36 patients with ILI who provided respiratory swab specimens. One viral agent was detected in 14 of the 36 patients, and more than one viral agent was detected in 5 (1 patient with influenza H3N2 and adenovirus, 1 patient with coronavirus 229E and adenovirus, 2 patients with coronavirus 229E and human metapneumovirus and 1 patient with coronavirus 229E and RSV) patients. During the 2014–2015 influenza season, the positivity rates for all and influenza viruses were 18.6% and 10.6%, respectively, among a total of 75 patients with ILI who provided respiratory swab specimens. None of the patients in this period had more than one virus isolated from the respiratory specimens. The distribution of the detected viruses is presented in Table 1. The total positivity rates in the two influenza seasons for all viruses, influenza virus and other respiratory viruses were 29.7%, 13.5% and 17.1%, respectively.

Patient characteristics and comorbidities

The patient characteristics of the study patient group are summarised in Table 2. The underlying chronic diseases, including cardiovascular diseases, chronic obstructive pulmonary diseases (COPD), asthma, diabetes mellitus, chronic kidney diseases, rheumatological diseases, neurological diseases, malignancy, chronic liver diseases, and chronic metabolic diseases, were present in 87.3% of all the patients with ILI (n = 111). The most prevalent comorbid diseases were cardiovascular diseases, followed by COPD. Comorbid diseases were also present in 13 of the 15 patients with influenza; the remaining 2 patients who were positive for influenza virus were below 35 years of age and presented with viral encephalitis.

During the 2014–2015 influenza season, influenza positivity was detected in 2 influenza-vaccinated patients aged > 85 years. The influenza B/Yamagata lineage, which was covered by the trivalent vaccine, was detected in 1 of these 2 patients, and the other patient who was vaccinated within the last 14 days was positive for influenza (H1N1).

Oseltamivir was the only antiviral therapy used in patients for 5 days after the first assessment in the emergency room.

Table 1. The distribution of detected viruses according to the influenza season.

	2013-2014	2014-2015
Influenza A (H3N2)	7	0
Influenza A (H1N1)	0	3
Influenza B/Yamagata lineage	0	5
Adenovirus	3	2
Coronavirus 229E	8	0
Coronavirus OC43	0	3
Parainfluenza 4	2	0
Rhinovirus	0	1
RSV	1	0
HMPV	3	0
Total	**24**	**14**

Comparison of influenza virus-positive patients with influenza virus-negative patients and other respiratory virus-positive patients

When influenza virus-positive patients were compared with influenza virus-negative patients, fever was significantly more frequent in the influenza virus-positive group (p = 0.03), whereas dyspnoea was more frequent in the influenza virus-negative group (p = 0.007). Additionally, the incidence of pneumonia was lower in the influenza virus-positive group than in the influenza virus-negative group (p = 0.03). Comparison of the influenza virus-positive group with the other respiratory virus-positive group revealed that fever was significantly more frequent in the influenza virus-positive group (p = 0.019). No significant differences were observed in the remaining parameters among the groups (Table 2).

Evaluation of hospital admission and discharge ICD-10 codes

The ICD-10 code J11 for influenza was used for hospital admission and discharge in 2 and 4 patients, respectively; however, only 1 of these patients had laboratory-confirmed influenza virus positivity. According to this, the sensitivity and specificity of the hospital admission ICD 10 codes were 6.6% and 98.9% and the sensitivity and specificity of the hospital discharge ICD 10 codes were 6.6% and 94.7%, respectively. The most frequently encountered hospital admission and discharge ICD-10 codes in the influenza virus-positive patients were R06 (respiratory abnormalities) and J18 (pneumonia), respectively. Furthermore, 14 of the 15 patients with influenza did not have an influenza-specific ICD-10 code. Among these 14 patients, 5 were discharged before the influenza test results were available, whereas the ICD-

Table 2. Characteristics of ILI patients and comparison of influenza-positive patients with influenza-negative patients and those positive for other respiratory viruses.

	ILI (+) (n = 111, %)	**Influenza (+) (n = 15, %)**	**Influenza (-) (n = 96, %)**	**p**	**Other respiratory virus (+) (n = 19, %)**	**p**
Mean age (± SD*)	67.9 (± 16.2)	58.8 (± 23.5)	69.3 (± 14.4)	0.133	71.5 (± 11.6)	0.473
Gender (male)	62 (55.9)	8 (53.3)	54 (56.2)	0.832	12 (63.2)	0.721
Comorbid disease	97 (87.3)	13 (86.6)	84 (87.5)	0.923	19 (100)	0.183
Smoking status				0.539		0.655
Never smoked	55 (49.5)	9 (60.0)	46 (47.9)		9 (47.4)	
Ex-smoker	41 (37.0)	5 (33.3)	36 (37.5)		9 (47.4)	
Current smoker	15 (13.5)	1 (6.7)	14 (12.6)		1 (5.2)	
***Corticosteroid* usage**						
Systemic	4 (3.6)	0 (0)	4 (4.2)	0.421	1 (5.2)	1.000
Inhaled	33 (29.7)	4 (26.6)	29 (30.2)	0.780	3 (15.7)	0.699
Vaccination status**				0.549		0.559
Vaccinated	22 (19.8)	2 (13.3)	20 (20.8)		1 (5.3)	
Unvaccinated	79 (71.1)	11 (73.3)	68 (70.8)		13 (68.4)	
Unknown	10 (9.0)	2 (13.39)	8 (8.3)		5 (26.3)	
ILI symptoms						
Fever	68 (61.2)	13 (86.6)	55(57.3)	**0.03**	9 (47.3)	**0.019**
Malaise	89 (80.1)	11 (73.3)	78 (81.2)	0.474	17 (89.4)	0.209
Headache	26 (23.4)	4 (26.6)	22 (22.9)	0.750	2 (10.5)	0.209
Myalgia	34 (30.6)	2 (13.3)	32 (33.3)	0.118	6 (31.5)	0.217
Cough	95 (85.5)	13 (86.6)	82(85.4)	0.898	17 (89.4)	0.788
Sore throat	25 (22.5)	4 (26.6)	21 (21.9)	0.679	3 (15.7)	0.425
Shortness of breath	93 (83.7)	9 (60.0)	84 (87.5)	**0.007**	13 (68.4)	0.712
Symptom duration before admission (Mean ± SD)	4.3 ± 2.02	3.73(± 2.12)	4.43(± 1.9)	0.212	3.58 ± 2.03	0.770
Accompanying pneumonia	51 (45.9)	3 (20.0)	48 (50.0)	**0.03**	9 (47.3)	0.147
Antibacterial therapy	104 (93.6)	13 (86.6)	91 (94.8)	0.229	18 (94.7)	0.568
Antiviral therapy	29 (26.1)	7 (46.6)	22 (22.9)	0.052	4 (21.0)	0.142
ICU admission	28 (25.2)	1 (6.6)	27 (28.1)	0.075	5 (26.3)	0.196
Mechanical ventilation	15 (13.5)	2 (13.3)	13 (13.5)	0.982	3 (15.7)	1.000
Death during hospitalization	13 (11.7)	1 (6.6)	12 (12.5)	0.514	2 (10.5)	1.000
Length of hospital stay (mean ±SD)	11.3 ± 12.39	13.60 (± 14.22)	12.1 (± 12.3)	0.299	11.32 ± 15.38	0.235

*SD: standard deviation; **Trivalent influenza vaccine including influenza B Yamagata lineage.

10 code for the remaining 9 patients was not J11, although their primary physicians were informed about the influenza test results.

Discussion

The aim of the present study was the evaluation and surveillance of patients with community-acquired ILI requiring hospitalisation for at least 24 hours. The ICD-10 codes for ER admissions and the ILI case definition were used to screen patients, and viral infections were confirmed with laboratory methods.

In the present study, coronavirus was the most common non-influenza virus. Four human coronavirus subtypes—229E, HKU1, NL63 and OC43—are known to circulate globally, and the subtypes may vary from one season to the next [7]. In the present study, coronavirus 229E was detected in 8 patients in the 2013–2014 influenza season, and the OC43 subtype was detected in 3 patients in the 2014–2015 influenza season, which is in agreement with the general pattern for coronaviruses. Coronaviruses are known to cause co-infections with other respiratory viruses, especially with RSV [7]. In a previous study, the 229E subtype was found to be more likely involved in co-infections than the OC43 subtype [8]. In the present study, coinfection was detected in one-third of the coronavirus infections, and it is noteworthy that all the strains isolated from patients with co-infections were coronavirus 229E. In contrast to the findings of the present study, rhinovirus has been the most frequently identified virus in the majority of similar studies, which might be due to the older age of the patients, the higher incidence of comorbidities and the higher rate of severely ill patients requiring hospitalisation in the current study.

In the present study, we used the ECDC ILI definition that does not include fever as a necessary symptom and detected fever in 13 of the 15 patients with influenza virus positivity. Statistical analysis provided further support that fever was more frequent in the influenza virus-positive group than in the influenza virus-negative group, suggesting that fever might be an obligatory symptom in ILI case definition as suggested by CDC and WHO to detect influenza cases more accurately. Cough, malaise and dyspnoea were the other frequent symptoms, which have already been reported in several studies [9-11]. The incidence of pneumonia was also significantly higher in the influenza virus-negative group than the influenza-positive group. Bacteria might be the predominant etiological agent of pneumonia in the influenza virus-negative patients, although bacteriological examination was not performed in the respiratory specimens of the patients, precluding a clear conclusion. High rates of dyspnoea (87%) in the influenza virus-negative patients might also be the result of bacterial pneumonia in the influenza virus-negative patients.

All respiratory viruses cause similar symptoms and signs, which reduce the efficacy of influenza case definitions. In several studies, non-influenza respiratory viruses were detected in a significant proportion of patients with ILI [12,13]. In the literature, the overall rate of virus positivity ranges from 18% to 62% in ILI and acute respiratory infection cases. These findings support that fact that other respiratory viruses significantly contribute to ILI as well as hospitalisation. Therefore, respiratory viruses other than influenza virus are included in many surveillance programmes [14]. Based on these data, it is clear that the diagnosis of influenza with only clinical symptoms may lead to misdiagnosis and subsequent improper treatment. Achieving a correct diagnosis with the widespread use of rapid antigen tests and molecular methods may prevent the unnecessary use of antivirals and antibiotics and avoid unnecessary hospitalisation. In cases where laboratory tests are not available, clinicians should be reminded that fever is the most common presenting symptom of influenza, as demonstrated in the present study as well as several previous reports [12,15]. Therefore, patients with ILI presenting with fever in the influenza season should be assessed and diagnosed for influenza virus infection.

All the patients in the present study were categorised in the severe influenza category on the basis of their need for hospitalisation. The most important risk factors for severe influenza are advanced age and comorbidity. In the present study, 53.3% of the influenza virus-positive patients were older than 65 years, and 80% of whom had at least one comorbid disease. In a multi-center study, comparison of outpatients and in-patients with influenza revealed that the incidence of chronic illnesses was significantly higher in the in-patients than in the outpatients [16]. In another study assessing patients hospitalised for influenza, 56% of the patients were older than 65 years, and 82% had at least one comorbid disease [11]. Pulmonary diseases such as COPD, chronic bronchitis and asthma were the most common comorbid diseases in these patients, which is in agreement with the findings of the present study [9].

Influenza may present with neurological complications such as encephalopathy, encephalitis, aseptic meningitis, transverse myelitis, and Guillain–Barré syndrome in some patients [17-19]. Neurological

manifestations are more common in children and young adults [17]. In the present study, 2 of the 15 patients with influenza presented with neurological complications; intriguingly, both the patients were younger than 35 years and were admitted with viral encephalitis.

We determined that the antibiotic use was very high in the cohort in the present study. Specifically, antibacterial agents were administered to 94% of the patients with ILI and 86.6% of the influenza virus-positive patients during hospital stay. In a study conducted in China, which included 1790 SARI cases, the rate of antibiotic use was 100%, whereas another study in Canada reported a high rate of antibiotic use of 90% [9,14]. We predict that the rates of antibiotic use are generally very high in patients with ILI because of the severe disease presentation and comorbidities and that the differentiation of bacterial and viral infections in these patients is especially challenging.

Clinical trials have indicated that early antiviral therapy shortens the symptom duration and reduces the complications associated with influenza. However, some studies have demonstrated that treatment for 4–5 days after the onset of symptoms also provides beneficial results [20-23]. In the present study, oseltamivir treatment was initiated in 26% and 47% of the patients with ILI and influenza, respectively, and 76% of the patients who were initiated on antiviral therapy had a symptom duration of > 48 hours. These results suggest that the physicians considered the severity of the disease as more important than the symptom duration while deciding on the antiviral treatment. In similar studies, the rate of antiviral therapy initiation changed between 12% and 41% in patients who were positive for influenza virus [11,14,24], and the low rates of antiviral therapy might be because of the low frequency of the diagnostic test use for influenza.

The most important approach for protection from influenza is vaccination. Several studies in Turkey have found that the vaccination rate was approximately 4.5% in the general population, 5.9%–26.8% in patients aged > 65 years and 14.9%–37% in patients with COPD [25-28]. In the present study, the vaccination rate was 19.8% in all the groups, 22.3% in patients aged > 65 years and 25.9% in patients with COPD or asthma. The assessment of the patients according to the risk groups for vaccination recommended by the WHO revealed that only 22 of the 100 patients expected to be vaccinated are actually vaccinated [29]. The vaccination rate in the present study cohort was below the target rate, which is similar to that reported by other studies in Turkey.

Hospital admission and discharge ICD-10 diagnostic codes are used in various surveillance studies. However, the validity of these diagnostic codes in detecting confirmed influenza cases was rarely studied. Moore *et al*. reported a sensitivity of 86.1%, a positive predictive value of 84.1% and a specificity of 98.6% for influenza-specific ICD-10 diagnostic codes (J10 and J11) in a study of hospitalised paediatric patients [30]. In the present study, the sensitivity of the ICD-10 diagnostic codes included in the present surveillance was very low, thereby indicating that physicians might not be adhering to the diagnostic code system. This finding implies that the use of influenza-specific diagnostic codes alone might not reflect true rates in surveillance studies in this region.

In the present study, R06 (respiratory abnormalities) was the most common hospital admission diagnosis, and J18 (pneumonia) was the hospital discharge code in patients with confirmed influenza. The diagnostic codes obtained in the above studies account for only 46.6% of the influenza virus-positive cases in the present study, suggesting that the selection of diagnostic codes by physicians in the emergency department might differ among countries, centres and even seasons. These differences are predicted to be reflected in the findings of ICD-10 code-based influenza surveillance studies.

The present study had some limitations. The most important limitation is that the number of study patients was less for such a common condition as respiratory viral infections. Nosocomial cases and patients who were not hospitalised for at least 24 hours in the ER were excluded from the study to select community-acquired severe ILI cases, and these factors limited our sample size.

Conclusion

The diagnostic codes used in influenza surveillance are less likely to detect actual influenza cases, and studies evaluating the influenza burden using diagnostic codes might lead to false results. Non-influenza respiratory viruses also contribute to ILI by causing serious illness; therefore, close monitoring of these viruses is also important. All the respiratory viruses lead to similar clinical presentations; therefore, it may not be possible to differentiate influenza based on the clinical findings alone. However, it is reasonable to evaluate and treat patients with ILI presenting with fever as patients with probable influenza virus infection during the influenza season. However, influenza cannot

be definitively diagnosed by clinical findings, and laboratory methods should be more frequently used to prevent unnecessary antibacterial treatment and to initiate appropriate antiviral treatments. The vaccination of elderly individuals with underlying diseases who are prone to influenza complications and hospitalisation due to influenza is important. Influenza might rarely be associated with neurological complications, which should be considered in the differential diagnosis of encephalitis during the influenza season.

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Authors' contributions

All authors contributed equally to the study.

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