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Outcome of Patients Admitted to Intensive Care Units due to Influenza-Related Severe Acute Respiratory Illness in 2017–2018 Flu Season: A Multicenter Study from Turkey

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Keywords
Acute respiratory distress syndrome · Critically ill · Influenza viruses · Mortality · Respiratory failure

Abstract
Background: Influenza can cause severe acute respiratory illness (SARI), which occurs as local outbreaks or seasonal epidemics with high intensive care unit (ICU) admission and mortality rates. Mortality is mainly due to SARI. ***Objective:*** The aim of this study was to evaluate the outcome of patients admitted to ICU due to influenza-related SARI in 2017–2018 flu season in Turkey. ***Methods:*** A retrospective multicenter study was conducted in 13 ICUs with a total of 216 beds from 6 cities in Turkey. All adult patients (over 18 years) admitted to the ICUs in 2017–2018 flu season (between September 1, 2017, and April 30, 2018) because of SARI and with a positive nasopharyngeal swab for influenza were included in the study. ***Results:*** A total of 123 cases were included in the study. The mean age of patients was 64.5 ± 17.5 years, and 66 (53.7%) patients were older than 65 years. The ICU mortality was 33.9%, and hospital mortality was 35.6%. Invasive mechanical ventilation (IMV), acute kidney injury (AKI), hematologic malignancy, and >65 years of age were the factors affecting mortality in influenza. ***Conclusion:*** SARI due to influenza carries a high mortality rate, and IMV, AKI, presence of hematologic malignancy, and older age are independent risk factors for mortality.

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Introduction

Influenza is an acute respiratory illness, which occurs as local outbreaks or seasonal epidemics. Seasonal influenza accounts for thousands of deaths and hospital admissions annually. During seasonal influenza epidemics, severe illness is observed in 3–5 million cases, leading to 300,000–500,000 deaths globally each year [1]. While most influenza patients have a self-limited respiratory illness, some of hospitalized patients may develop severe dyspnea or severe acute respiratory illness (SARI) requiring intensive care unit (ICU) admissions ranging from 5 to 48% [2–4].

The viruses can cause severe illness or even death in high-risk patient groups, such as pregnant women, children under 5 years, the elderly (>65 years), and individuals with chronic medical and immunosuppressive conditions [1–6]. Mortality is caused by the primary viral infection, which can have a fulminant disease course, and/or by secondary bacterial pneumonia [6].

SARI can progress to pneumonia and acute respiratory distress syndrome (ARDS) and can increase mortality ranging from 14 to 40% depending on early or delayed diagnosis [7–9]. Turkey is a country in the Northern Hemisphere and the influenza activity shows a seasonality with 1 predominant peak. In the 2015–2016 season, ICU admission and general mortality rate were reported to be 32.6 and 14.8%, respectively, among patients 5 years and older [4]. The aim of this study was to evaluate the outcome of patients admitted to ICU due to influenza-related SARI in 2017–2018 flu season in Turkey, to obtain a better insight into this patient group, and to evaluate mortality rate of critically ill influenza patients.

Materials and Methods

A retrospective multicenter study was conducted in 13 ICUs with a total of 216 beds from 6 cities in Turkey. All adult patients (over 18 years) admitted to the ICUs in 2017–2018 flu season (between September 1, 2017, and April 30, 2018) because of SARI and with a positive nasopharyngeal swab for influenza were included in the study. Influenza was confirmed by PCR on nasopharyngeal swab.

Age, gender, body mass index (BMI), Acute Physiology and Chronic Health Evaluation (APACHE II) and Sequential Organ Failure Assessment (SOFA) scores, comorbidities (cardiac diseases, chronic respiratory diseases, malignancy, chronic kidney diseases [CKD], transplantation status, chronic liver diseases, and pregnancy), ARDS, sepsis, ventilatory support (such as noninvasive mechanical ventilation, invasive mechanical ventilation [IMV], high-flow nasal oxygen [HFNO], prone positioning, extracorporeal membrane oxygenation [ECMO]), vasopressor use, acute kidney injury (AKI), length of ICU stay, length of hospital stay, vaccination status, treatment (oseltamivir) for influenza, and patient outcome were recorded. Oseltamivir was started according to local hospital protocols. AKI was diagnosed according to Acute Kidney Injury Network classification [10]. ARDS was defined according to 2012 Berlin criteria [11]. The Third International Consensus Definition was used for sepsis and septic shock diagnosis [12]. Bacterial and viral pathogens detected within the first 72 h of ICU stay other than influenza from endotracheal or endobronchial secretions or a positive urine antigen test for legionella infection were recorded, as well.

For statistical analysis, Statistical Package for Social Sciences version 23.0.0.2 (SPSS, Chicago, IL, USA) was used. We used median (minimum-maximum) for continuous variables and *n* (%) for categorical variables. Comparisons were made for continuous variables using the nonparametric Mann-Whitney *U* test. χ^2 or Fisher's exact test was utilized for categorical comparisons. Logistic regression model was used to assess the impact of variables that were found to be associated with hospital mortality in bivariate analysis, and results are expressed as odds ratio and 95% confidence interval. Definition of significance was a p value <0.05.

Results

A total of 123 cases were identified. Demographic and clinical characteristics of survivor and nonsurvivor patients are listed in Table 1. The median age of patients was 66 (20–97), and 66 (53.7%) patients were older than 65 years. The ICU mortality was 33.9%, and hospital mortality was 35.6%. Chronic cardiac (51.2%) and chronic respiratory (43.1%) diseases were the most frequent comorbidities.

Fifty (40.7%) patients had ARDS, in whom 27 (54%) patients had severe ARDS with a PaO_2/FiO_2 ratio <100. Ten (20%) ARDS patients received corticosteroid treatment for ARDS. Prone position was used in only 2 patients. ECMO treatment was not applied at all. ICU and hospital mortality rates were high in ARDS patients (both 52%).

Sepsis was seen in 70 (56.9%) cases, whereas septic shock and AKI were seen in 43.1% of cases during their ICU stay. Eighty-seven (70.7%) patients received noninvasive mechanical ventilation and 71 (57.7%) received IMV. Only 7 (5.7%) patients received HFNO. In comparison of survivor and nonsurvivor patients in bivariate analysis, we found that age ≥65 years, high APACHE II and SOFA scores, having CKD and hematologic malignancy, presence of sepsis and ARDS, receiving IMV, AKI, and not receiving oseltamivir were associated with mortality (Table 1).

The majority of patients had influenza type A (60.2%), with an influenza type B frequency of 32.5%. Nine pa-

Table 1. Comparison of clinical characteristics in survivors and nonsurvivors

	All (n = 123)	Survivors (n = 79)	Nonsurvivors (n = 44)	p value
Age, years	66 (20–97)	62 (20–93)	72 (22–97)	0.002
Age >65 years*	66 (53.6)	35 (44.3)	31 (70.5)	0.010
Male gender*	66 (53.7)	41 (51.9)	25 (56.8)	0.570
BMI, kg/m^2	26.1 (14.4–51.9)	26.1 (14.4–51.9)	25.5 (15.7–36.3)	0.270
APACHE II	20 (5–42)	18 (5–31)	25.5 (11–42)	<0.001
SOFA	5 (0–17)	4 (0–17)	8 (2–17)	<0.001
Comorbidities*				
Cardiac disease	63 (51.2)	38 (48.1)	25 (56.8)	0.350
Chronic respiratory disease	53 (43.1)	36 (45.6)	17 (38.6)	0.440
Malignancy	24 (19.5)	8 (10.1)	16 (36.4)	0.001
Hematologic	14 (11.4)	4 (5.1)	10 (22.7)	0.003
Solid	12 (9.8)	5 (6.3)	7 (15.9)	0.340
Chronic kidney diseases	20 (16.3)	9 (11.4)	11 (25.0)	0.030
Transplantation	8 (6.5)	7 (8.9)	1 (2.4)	0.180
Chronic liver disease	5 (4.1)	3 (3.8)	2 (4.5)	0.770
Pregnancy	1 (0.8)	1 (1.3)	–	0.470
PaO_2/FiO_2	141.2±79.6	145.6±82.3	132.4±71.7	0.680
ARDS*	50 (40.7)	24 (29.6)	26 (59.1)	0.001
Mild	5 (10)	4 (16.7)	1 (3.8)	
Moderate	18 (36)	6 (25)	12 (46.2)	
Severe	27 (54)	14 (58.3)	13 (50.0)	
Sepsis*	70 (56.9)	38 (48.1)	32 (72.7)	0.005
Septic shock*	53 (43.1)	26 (32.9)	27 (61.4)	<0.001
Noninvasive ventilation*	87 (70.7)	58 (73.4)	29 (65.9)	0.170
Invasive mechanical ventilation*	71 (57.7)	30 (38.0)	41 (93.2)	<0.001
High-flow nasal oxygen*	7 (5.7)	6 (7.6)	1 (2.3)	0.600
Prone position*	2 (1.6)	1 (50.0)	1 (50.0)	0.720
Vasopressor use*	60 (48.8)	22 (27.2)	38 (90.5)	<0.001
Acute kidney injury*	53 (43.1)	19 (24.1)	34 (77.3)	<0.001
ICU LOS, days	9 (1–70)	9 (1–70)	12 (1–38)	0.420
Hospital LOS, days	19 (1–166)	17 (3–166)	20 (1–65)	0.680

Values denote median (min–max) unless specified otherwise. APACHE II, Acute Physiology and Chronic Health Evaluation Score; SOFA, Sequential Organ Failure Assessment; ARDS, acute respiratory distress syndrome; ICU, intensive care unit; LOS, length of stay. * N (%).

tients had both type A and B. Of type A influenza cases, 10 had subtype H1N1. Mortality rate of H1N1 patients was 30%. Rhinovirus (11.4%) and respiratory syncytial virus (8.1%) were the most common co-viruses detected in influenza patients. In 29.3% of the patients, bacteria were isolated, *Acinetobacter baumannii* being the most common (Table 2). There was no isolation of *Aspergillus* spp.

Oseltamivir was administered in 119 (96.7%) patients during their admissions. The dosages of oseltamivir were 2 × 75 mg in 87 (70.7%) patients, 1 × 75 mg in 21 (17.1%) patients, and 2 × 150 mg in 11 (8.9%) patients. Four patients who did not receive oseltamivir died and 2 of them had cancer. There were no data about vaccination status of 59 (48%) patients. Of these, 15 were cancer patients. In multivariate analysis, IMV, AKI, hematologic malignancy, and >65 years of age were the factors affecting hospital mortality (Table 3).

Discussion

In this study, we evaluated patients with seasonal influenza requiring ICU admission during influenza season in 2017–2018 from 13 ICUs in Turkey, with a finding of 35.6% of hospital mortality rate. Independent factors related to hospital mortality were IMV, AKI, hematologic malignancy, and >65 years of age.

In this study, 53 (43.1%) patients developed AKI and 33 (62.3%) of them died. In a prospective observational

Table 2. Comparison of survivors and nonsurvivors regarding infection causes and treatment

	All (n = 123)	Survivors (n = 79)	Nonsurvivors (n = 44)	p value
Influenza				
A	74 (60.2)	4 (58)	28 (63.6)	
B	40 (32.5)	26 (32.1)	15 (34.1)	0.690
A + B	9 (7.3)	8 (9.9)	1 (2.3)	
Other viruses	35 (28.5)	20 (24.1)	15 (35.7)	
Rhinovirus	14 (11.4)	10 (12.7)	4 (9.1)	
RSV	10 (8.1)	5 (6.3)	5 (11.4)	
Coronavirus	7 (5.7)	1 (1.3)	6 (13.6)	0.160
CMV	3 (2.4)	1 (1.3)	2 (4.5)	
Parainfluenza virus	2 (1.6)	2 (2.5)	–	
Adenovirus	1 (0.8)	1 (1.3)	–	
Oseltamivir therapy	119.0 (96.7)	79.0 (100)	40.0 (90.8)	0.010
Vaccination				
Yes	6 (4.9)	4 (4.9)	3 (6.8)	
No	56 (45.5)	40 (50.6)	16 (36.4)	0.140
Unknown	59 (48)	36 (45.6)	25 (56.8)	
Isolated bacteria	36 (29.3)			
Acinetobacter baumannii	14 (11.4)	10 (12.7)	4 (9.1)	
Pseudomonas aeruginosa	7 (5.7)	5 (6.3)	2 (4.5)	
Staphylococcus aureus	6 (4.9)	5 (6.3)	1 (2.3)	
Klebsiella pneumoniae	3 (2.4)	2 (2.5)	1 (2.3)	0.540
Corynebacterium spp.	2 (1.6)	1 (1.3)	1 (2.3)	
Escherichia coli	1 (0.8)	1 (1.3)	0.0	
Nocardia	1 (0.8)	–	1 (2.3)	
Legionella pneumophila	1 (0.8)	–	1 (2.3)	
Burkholderia cepacia	1 (0.8)	–	1 (2.3)	

Values denote n (%). RSV, respiratory syncytial virus; CMV, cytomegalovirus.

Table 3. Logistic regression analysis of factors associated with hospital mortality

	OR (95% CI)	p value
Invasive mechanical ventilation	20.4 (3.3–124.9)	0.001
Acute kidney injury	14.2 (1.69–93.31)	0.016
Hematologic malignancy	12.5 (2.5–74.6)	0.006
Age >65 years	5.8 (1.7–20.6)	0.005

OR, odds ratio; CI, confidence interval.

multicenter study, the authors identified 211 (34%) adult H1N1 patients who developed AKI and found that AKI patients had an increased risk of hospital death (36 vs. 8%, adjusted odds ratio 6.69) compared with patients without AKI [13].

Chronic illnesses and hematologic malignancies are causes of morbidity and mortality in influenza infections [14, 15]. Patients with hematologic malignancy were more likely to progress to pneumonia [15]. In previous studies, mortality rate of critically ill cancer patients infected with influenza was up to 100% [15, 16]. In this study, 62.5% of malignant patients and 71.4% of the hematologic malignancy patients had died.

Mortality in elderly patients were higher than that in younger ones, similar to previous studies [17–20]. This might be due not only to the fact that elderly patients have more severe disease or have comorbidities but also to the age-dependent changes in immune system [21]. In this study, APACHE II and SOFA scores were higher in patients who died than in those who survived, also in the elderly (25.3 ± 8.3 vs. 17.4 ± 6.1; $p < 0.001$ and 8.7 ± 4.0 vs. 4.9 ± 3.5; $p = 0.003$, respectively). In contrast to the studies evaluating risk factors for severe influenza in 2009 pandemic, which revealed that H1N1 virus infections were primarily in the nonelderly [22–24], >50% of our patients were >65 years old.

Sepsis (56.9%) and ARDS (40.7%) were common in our patients. ARDS rate was similar to other studies [25, 26]. Similar to previous studies, mortality rate was higher in our patients with ARDS [25–27]. As most of the patients had moderate-to-severe ARDS, HFNO use was less in this study. The rescue therapies as prone position (1.6%) were used less, and ECMO was not used at all. In LUNG SAFE study, the use of prone positioning was 7.9% and use of ECMO was 3.2% [28].

Influenza type A was predominant, which is similar to previous studies [29–31]. Ten patients (13.5%) among influenza type A had H1N1 subtype. According to a recent study, H1N1 was associated with severe disease course and higher mortality rates, compared to influenza B and other influenza A subtypes like H3N2 [32]. In this study, 3 patients with H1N1 died. Influenza B was also high (32.5%). This result was consistent with the previous study [33], in which influenza B was high in COPD. In this study, 40% of patients with influenza B had chronic respiratory disease.

Vaccination is important for preventing the influenza infection and is associated with reduction in the severity of disease and hospitalization [34–37]. We did not have information on vaccination status of the majority of the patients. So we could not evaluate the association between vaccination and mortality.

Oseltamivir was used in 96.7% of the patients. A Cochrane analysis revealed that oseltamivir reduced the time to first alleviation of symptoms but had no effect on hospitalization risk [34]. According to a previous study, oseltamivir reduced mortality in influenza patients [35]; however, it did not affect mortality among patients with type A/H1N1 influenza during the 2009 pandemic [36]. Most of our patients received oseltamivir; however, 4 patients who did not receive oseltamivir had died, still emphasizing the importance of timely treatment.

Coinfections with bacteria, virus, and fungi are frequently seen in severe influenza [37, 38]. *Staphylococcus aureus* and *Streptococcus pneumoniae* were the most common bacterial pathogens with prevalence of 11 and 7%, respectively, in influenza patients admitted to the ICU [39]. In a prospective, multicenter cohort of 220 patients hospitalized with severe H1N1 influenza A infection in the ICUs, hospital-acquired pneumonia was clinically suspected in 79 patients (35.9%) [40]. Incidence of hospital-acquired pneumonia due to *Pseudomonas aeruginosa* was 92.3% and due to *A. baumannii* was 71.4% in patients receiving corticosteroids [40]. Among our patients, 29.3% developed secondary bacterial infections during their ICU stay. Forty (32.5%) patients received corticosteroid treatment (10 for ARDS and 30 for other reasons) and 12 of them had coinfections. In this study, the most common bacterial pathogens were *A. baumannii* and *P. aeruginosa,* as causes of nosocomial pneumonia. Bacterial coinfection was not found to be related to mortality. Viral coinfections as rhinovirus, respiratory syncytial virus, and cytomegalovirus were seen, as well. However, whether these pathogens are clinical causes of SARI could not be evaluated. Although *Aspergillus* spp. were important causes of coinfections in influenza [41, 42], there were no *Aspergillus* spp. isolates in the patients.

There is another multicenter study evaluating hospitalized patients with influenza in 11 centers of a single city of Turkey, which revealed 9% of ICU admission with 5.3% of mortality [3]. To our knowledge, this is the first multicenter study including a significant number of ICUs from different geographical regions investigating outcome in influenza patients, all requiring ICU admission in Turkey. This is an important study focusing only on the SARI cases due to influenza and demonstrating independent risk factors of mortality. This study also emphasizes the importance of bacterial and viral coinfections and timely treatment in ICU patients. However, there are some limitations of this study. It was a retrospective study, with no control group, with limited variables. Although all patients were influenza positive, it is difficult to explain the cause and effect relationship between infectious etiology and outcome. We could not evaluate the hospital-wide burden of influenza, since many patients could have not been admitted to ICUs.

In conclusion, influenza patients requiring ICU admission had a hospital mortality of 35.6%. IMV, AKI, hematologic malignancy, and >65 years of age were independent predictors of mortality. Influenza should be timely managed in critically ill patients as it is associated with complications and carries a high mortality rate.

Statement of Ethics

The study protocol was approved by the Ethics Committee of the Hacettepe University (Date/No: 2018/387-40).

Conflict of Interest Statement

E.O.E., B.E, F.C., A.G., K.S., B.A., G.A., F.B., S.A., B.C., H.S., D.A., K.R., S.T., and A.T. have no conflicts of interest to disclose.

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Author Contributions

E.O.E., B.E., and A.T. undertook conception and design. F.C., A.G., K.S., B.A., G.A., F.B., S.A., B.C., H.S., D.A., K.R., and S.T. performed all measurements and treatments. Analysis was performed by E.O.E and A.T.; B.E. acquired data. All authors have read, improved, and approved the final manuscript.

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