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KLİNİK ÇALIŞMA
RESEARCH ARTICLE

Influenza or other respiratory viruses: does it matter as the cause of acute respiratory failure in the critically-ill patients?

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ABSTRACT

Influenza or other respiratory viruses: does it matter as the cause of acute respiratory failure in the critically-ill patients?

Introduction: Respiratory virus infections may cause serious respiratory failure requiring intensive care unit (ICU) admission. The objective of this study was to evaluate the clinical features and the outcome in patients with acute respiratory failure (ARF) due to viral infections comparing etiological agents.

Materials and Methods: ARF patients with positive viral serology were retrospectively recruited. Cohort was evaluated with regard to subgroups as influenza and other respiratory viruses (ORV), as well as survivors and non-survivors.

Results: Out of 938 admitted patients, 319 were followed as ARF and only 149 patients had viral respiratory panel results. In 49 patients with ARF, 52 positive viral results were detected and 47 patients with single positive viral isolates of either influenza or ORV were included. Among them, 62% had ORV with quite similar characteristics with influenza group apart from diabetes mellitus which was encountered more in influenza group ($p=0.02$). Overall ICU mortality was 32% and there was no difference between the two groups ($p=0.42$). Acute Physiology and Chronic Health Evaluation (APACHE) II score was independently associated with ICU mortality (OR: 1.25; 95% CI: 1.04-1.51; $p=0.02$).

Conclusion: *This study emphasizes to consider the possibility of other respiratory viruses for the cause of ARF with similar characteristics and mortality as influenza species.*

Key words: *Pneumonia; lower respiratory tract infection; influenza-like illness; critically-ill patients*

ÖZ

İnfluenza veya diğer solunum yolu virüsleri: kritik hastalarda akut solunum yetmezliğinin sebebi olarak önemli midir?

Giriş: *Solunum yolu virüsleri yoğun bakım ünitesi yatışı gerektiren ciddi solunum yetmezliğine neden olabilir. Bu çalışmanın amacı, viral enfeksiyonlara bağlı akut solunum yetmezliği (ASY) olan hastalarda etiyolojik ajanları karşılaştırmak, klinik özellikleri ve sonuçları değerlendirmektir.*

Materyal ve Metod: *Viral serolojisi pozitif olan ASY hastaları geriye dönük olarak değerlendirildi. Kohort, influenza ve diğer solunum virüsleri (DSV), sağ kalanlar ve kaybedilenler olarak alt gruplara ayrılarak incelendi.*

Bulgular: *Kabul edilen 938 hastanın 319'u ASY olarak takip edildi ve sadece 149 hastanın viral solunum paneli sonuçları mevcuttu. ASY'li 49 hastanın 52 pozitif viral sonucu tespit edildi ve influenza veya DSV'den tek pozitif viral izolatu olan 47 hasta çalışmaya dahil edildi. Bu hastaların %62'sini influenza grubu ile benzer özelliklere sahip DSV oluşturmaktaydı. Sadece diyabet mellitus influenza grubunda DSV grubuna göre daha fazla görüldü ($p=0.02$). Toplam YBÜ mortalitesi %32 idi ve iki grup arasında mortalite açısından fark yoktu ($p=0.42$). Akut Fizyoloji ve Kronik Sağlık Değerlendirmesi (APACHE) II skoru bağımsız olarak YBÜ mortalitesi ile ilişkili bulundu (OR: 1.25; %95 GA: 1.04-1.51; $p=0.02$).*

Sonuç: *Bu çalışma, ASY nedeni için influenza ile benzer özelliklere ve mortaliteye sahip diğer solunum virüsleri olasılığının düşünülmesi gerektiğini vurgulamaktadır.*

Anahtar kelimeler: *Pnömoni; alt solunum yolu enfeksiyonu; grip benzeri hastalık; kritik hastalar*

INTRODUCTION

Respiratory virus infections are characterized by sudden onset of fever, cough, fatigue, myalgia, and headache but are usually self-limiting. However, they are one of the leading causes of community-acquired pneumonia and sometimes exacerbations of asthma or chronic obstructive pulmonary disease (COPD) (1,2). Furthermore, they can also lead to acute respiratory failure (ARF), sepsis, multiple organ failure and death as we have experienced from unfortunate pandemics. Due to limited presence of exact and rapid diagnostic techniques, our knowledge on the real burden of viral infections as the cause of ARF has been limited. Besides, the prevalence of ARF due to viruses varies according to the case definitions, cohorts, seasons, geographical locations and even the diagnostic techniques used. In various studies, the detection rate of respiratory viral agents alters from 16% to 49% in patients requiring intensive care unit (ICU) admission due to ARF (3-5).

Influenza pandemics in the last decade raised our awareness and concern about viral causative agents in the pathophysiology of ARF. However, there is still paucity of epidemiological and microbiological data. Despite the fact that some subspecies of influenza virus such as swine origin H1N1 and H3N2 are the most frequent types of influenza in the influenza sea-

son, there is still limited data about other respiratory viral agents such as adenovirus, coronavirus, rhinovirus, respiratory syncytial virus (RSV), human metapneumovirus (hMPV) and parainfluenza Virus. The aim of our study was to evaluate the clinical characteristics and outcomes of patients who were admitted to our ICU with ARF and who had positive respiratory viral panel results according to etiological agents as influenza and other respiratory viruses (ORV).

MATERIALS and METHODS

Patients who were older than 18 years of age, admitted to the medical ICU between 1st January 2013 and 30th June 2016 due to ARF with positive viral respiratory panel results were retrospectively evaluated.

Age, gender, body mass index (BMI) of patients (classified as underweight (<18.5), normal weight (18.5-24.9), overweight (25.0-29.9) and obese (≥ 30)), smoking history, comorbidities, Charlson Comorbidity Index (CCI) (6), Acute Physiology and Chronic Health Evaluation (APACHE) II score (7), Sequential Organ Failure Assessment (SOFA) scores (8) in the first and last day of the ICU stay, and presence of sepsis and/or septic shock on admission according to Sepsis-3 Definitions (9) and acute respiratory distress syndrome (ARDS) according to Berlin definitions (10) were noted. ARF was defined as a respiratory rate greater than 30 breaths per minute, respiratory distress symp-

toms, PaO₂ lower than 60 mmHg or SaO₂ lower than 0.90 on room air or a need for ventilatory support (11). The use of non-invasive (NIMV) or invasive mechanical ventilation (IMV) in the hospital admission, IMV during ICU; antiviral, antibiotic and systemic steroid agents and durations in the ICU hospitalization were recorded. Lung zone counts with infiltration in X-ray and if it was utilized, thorax computerized tomography (CT) evaluations were done as ground glass opacity and consolidation, as well.

Real time polymerase chain reaction (PCR) in Bio-Rad CFX96 Touch™ was used to detect respiratory viruses from nasopharyngeal swab, nasopharyngeal aspirate and bronchoalveolar lavage specimens using Dual Priming Oligonucleotide (DPO™) technology and melting curve analysis method of Tagging Oligonucleotide Cleavage and Extension (TOCE™) technology. The viruses tested by this method were adenovirus (AdV), influenza A virus (FluA), influenza B virus (FluB), parainfluenza virus1 (PIV1), parainfluenza virus2 (PIV2), parainfluenza virus3 (PIV3), parainfluenza virus4 (PIV4), rhinovirus A/B/C (HRV) and Panel B: respiratory syncytial virus A (RSV A), respiratory syncytial virus B (RSV B), bocavirus 1/2/3/4 (HBoV), metapneumovirus (MPV), coronavirus 229E (CoV 229E), coronavirus NL63 (CoV NL63), coronavirus OC43 (CoV OC43) and enterovirus (HEV).

Primary viral infection was considered when respiratory and blood bacterial cultures were negative within first 72 hours during the acute phase of viral ARF. Bacterial co-infection was considered as positive culture results within the first 72 hours in patients with confirmed viral infection. Secondary bacterial infection was considered as positive culture results after 72 hours in patients with confirmed viral infection (12,13). Culture results of blood, catheter, urine, bronchoalveolar lavage and the other sites were noted. Opportunistic infections such as *Pneumocystis jirovecii*, *Cytomegalovirus* and *Aspergillus* species were also assessed. C-reactive protein (CRP), procalcitonin (PCT), lymphocyte, leukocyte and lactate levels at the time of respiratory viral positivity were recorded. Primary outcome variable was ICU mortality. Secondary outcome variables were hospital mortality, ICU and hospital length of stay (LOS).

Statistical Analysis

Statistical Packages for the Social Sciences v18.0 (SPSS Inc, Chicago, IL) software was used for statistical analyses. Descriptive statistical values of the

patients were expressed as number (percentage (%)) and median (interquartile range). Mann-Whitney U test and Chi-square or Fisher Exact tests were used for group comparisons, where appropriate. Variables significantly related with ICU mortality in bi-variate analysis were examined by logistic regression analysis to determine independent factors related with mortality. Results of logistic regression analysis were indicated as odds ratio (OR) and 95% Confidence Interval (CI). Kaplan-Meier curve with log rank was used to determine the effect of virus groups on ICU survival. $p < 0.05$ was considered as statistically significant.

RESULTS

Among 938 hospitalized patients in the ICU during the study period, 319 (34%) patients were followed up with the diagnosis of ARF and 149 (47%) patients tested for respiratory viral panel were evaluated.

Fifty-two positive viral results were observed in 49 (33%) patients. Two patients in whom influenza A and RSV were detected simultaneously were excluded and 47 patients with single isolates of either influenza or any of the ORV were included in the study. ORV were detected in 29 (62%) of the patients, whereas influenza species were detected in 18 (38%). Median age was 63 (54-75) and 23 (49%) of them were above 65 years old. Twenty-two of them (47%) were male. The detection rate of a positive result increased over the years and 26 (55.3%) of them were detected in 2016. Majority of patients were seen in winter (61.7%) and spring (25.5%). Almost all influenza cases were seen during winter months (89%), while ORV had a seasonal distribution and 44.8% of the cases with ORV were seen in winter followed by spring (34.5%), autumn (13.8%) and summer (6.9%) ($p = 0.02$). Most of the comorbidities were hypertension, malignancy and COPD with a median CCI score of 5 (3-6). Median APACHE II score was 20 (14-25). Admission and last day SOFA scores were 5 (3-7) and 3 (2-12), respectively. On admission, 22 (46.9%) of patients had sepsis, 12 (26.5%) had septic shock and ARDS was diagnosed in 41 (87%) of cases. Moderate ARDS constituted the main group (55.3%). 40.4% of patients had four lung zone infiltration. Most of thorax CT (55.8%) revealed ground glass opacity. Systemic steroids were administered to 32 (68.0%) patients due to bronchoconstriction, sepsis and other comorbid conditions. All patients were mechanically ventilated on admission. Overall median NIMV and IMV days were 6 (4-10) and 7 (2.0-18.5) respectively.

In the comparison of influenza viruses and ORV, diabetes mellitus (DM) frequency was higher in the influenza group ($p=0.02$). In addition, mild ARDS was slightly high in influenza group ($p=0.08$), while moderate ARDS was slightly high in ORV group ($p=0.07$). There was no difference between patients with influenza and ORV regarding other variables. In microbiological evaluation, primary viral, bacterial co-infection, secondary bacterial and opportunistic infections were detected in 23, 45, 51 and 30% of patients, respectively (Table 1). Mostly encountered bacterial microorganisms were *Escherichia coli* ($n=7$) and *Staphylococcus aureus* ($n=5$); secondary bacterial agents were *Acinetobacter baumannii* ($n=10$), *Enterococcus faecium* ($n=10$), *Escherichia coli* ($n=7$), *Klebsiella pneumonia* ($n=7$) and *Pseudomonas aeruginosa* ($n=6$); opportunistic infections agents were Cytomegalovirus ($n=11$), *Aspergillus fumigatus* ($n=8$) and *Pneumocystis jiroveci* ($n=2$), respectively. All of the influenza positive patients received antiviral treatment, while 59.9% of the patients positive for ORV received antiviral treatment in which one patient with positive RSV result receiving ribavirin in addition to oseltamivir. Except one, all received antibacterial treatment.

Laboratory results are shown in Table 2. Almost 90% of cases had lymphopenia with no difference between groups. Lactate level was higher in the influenza group ($p=0.05$) and ratio of $\text{PaO}_2/\text{FiO}_2$ was lower in the ORV group ($p=0.02$). Other laboratory parameters were similar (Table 2). In the comparison of primary viral infection subgroup with others in subgroup analysis; median CRP (4.0 (2.0-30.0) vs. 13.0 (9.4-21.5), $p=0.29$) did not differ between groups. However, PCT (0.14 (0.12-0.26) vs. 0.28 (0.15-0.77), $p=0.08$) levels were slightly lower in primary viral infection group.

Rhinovirus was the most frequent agent in ORV group (21%). ICU mortality in cases with *parainfluenza* and *hMPV* were 50%, whereas there was no mortality in cases with *RSV* and *adenovirus* (Figure 1). Overall ICU and hospital mortality were %32 and %40; and median ICU length of stay were 11 (6-29) and 23 (14-47) days, respectively (Table 3).

Kaplan Meier survival analysis did not reveal any difference in ICU mortality, as well ($p=0.48$) (Figure 2). Bi-variate analysis of all parameters indicated that ICU survival was better in patients who were older than 65 years old ($p=0.04$); who had COPD ($p=0.02$)

and high $\text{PaO}_2/\text{FiO}_2$ ratio ($p=0.002$), whereas patients with high APACHE II score ($p=0.004$), SOFA score ($p=0.02$) and PCT level ($p=0.02$) had poorer prognosis (Table 4). Additionally, in subgroup analysis, primary viral infection was encountered more in COPD subgroup ($n=18$) ($p=0.01$), whereas secondary bacterial infections were more in non-COPD subgroup ($n=29$) ($p=0.05$). Sub-group analysis did not reveal any statistical difference for ICU mortality for primary viral infection, co-infection or bacterial secondary infection sub-groups ($p=0.46$, $p=0.13$, $p=0.20$, respectively). Logistic regression analysis showed that only APACHE II score was independently associated with ICU mortality (for each point increase in APACHE II score, OR: 1.25; 95% CI: 1.04-1.51; $p=0.02$) (Table 5; only parameters with significant results were given).

DISCUSSION

To the best of our knowledge; this is the first study that primarily aimed to compare general characteristics of patients with influenza and ORV separately, up to date. Our study verified that ORV were more frequently identified than influenza with comparable characteristics and mortality which shows that non-influenza agents are as important as influenza species in terms of etiology in adult patients hospitalized in a tertiary hospital medical ICU due to respiratory failure. Similar to our study, subgroup analysis of previously published studies revealed that ORV constituted major group of viral etiology with 64-80% prevalence, with no comparisons between influenza and ORV in those studies (11,14,15).

Current study showed that patients with influenza and ORV had similar characteristics (Table 1) except that in patients with influenza DM was more frequent than non-influenza agents ($p=0.02$). DM is a well-known risk factor for influenza virus infection. Patients with DM have six times higher probability to be hospitalized during influenza epidemics in comparison with non-diabetic patients (16). The prevalence of hospitalization due to influenza in diabetic patients varies from 6% to 34.2% (17-20).

There is a debate in the use of PCT for differentiation of bacterial from nonbacterial infections. It is suggested that PCT may be used in the differentiation of bacterial and viral etiology in respiratory infections where CRP is supposed to be high in either (21). However, at present, the evidence for the use of PCT level does not support the use of PCT alone to differ-

Table 1. General characteristics of patients

	All (n= 47)	Influenza (n= 18)	ORV (n= 29)	p
Age *, years	63.0 (54.0-75.0)	67.0 (56.5-84.5)	63.0 (51.5-71.5)	0.17
Patients > 65 years of age	23 (49.0)	9 (50.0)	14 (48.0)	0.90
Male sex	22 (47.0)	8 (44.0)	14 (48.0)	0.80
Years				0.21
2013	3 (6.4)	1 (5.6)	2 (6.9)	
2014	6 (12.8)	-	6 (20.7)	
2015	12 (25.5)	5 (27.8)	7 (24.1)	
2016	26 (55.3)	12 (66.7)	14 (48.3)	
Seasons				0.02
Winter	29 (61.7)	16 (89.0)	13 (44.8)	
Spring	12 (25.5)	2 (11.0)	10 (34.5)	
Autumn	4 (8.5)	-	4 (13.8)	
Summer	2 (4.3)	-	2 (6.9)	
BMI*, kg/m ²	27.0 (23.2-31.2)	27.3 (23.0-31.2)	27.0 (23.2-31.0)	0.98
Underweight	4 (8.5)	1 (5.5)	3 (10.4)	
Normal	14 (30.0)	7 (39.0)	7 (24.2)	
Overweight	15 (32.0)	3 (17.0)	12 (41.4)	
Obese	13 (29.5)	6 (33.0)	7 (24.0)	
Comorbidities				
Hypertension	20 (43.0)	10 (55.5)	10 (34.5)	0.15
Malignancy	19 (40.0)	6 (33.0)	13 (45.0)	0.43
COPD	18 (38.0)	7 (39.0)	11 (38.0)	0.95
CAD	17 (35.0)	8 (44.0)	9 (31.0)	0.35
DM	13 (28.0)	9 (50.0)	4 (14.0)	0.02
CKD	6 (13.0)	1 (5.5)	5 (17.0)	0.34
Rheumatological disease	5 (11.0)	1 (5.5)	4 (14.0)	0.64
Neuromuscular disease	3 (6.0)	2 (11.0)	1 (3.4)	0.55
Chronic liver disease	1 (2.0)	0 (0.0)	1 (3.4)	1.00
CCI*	5.0 (3.0-6.0)	6.0 (4.0-7.0)	4.0 (3.0-6.0)	0.20
APACHE II score*	19.0 (14.0-25.0)	20.0 (16.0-28.0)	18.0 (13.0-25.0)	0.51
SOFA score*				
Admission	5.0 (3.0-7.0)	5.0 (3.0-9.0)	6.0 (3.0-7.0)	0.88
Last day	3.0 (2.0-12.0)	3.0 (3.0-13.0)	3.0 (1.0-11.0)	0.45
Sepsis on admission	22 (47.0)	9 (50.0)	13 (45.0)	0.73
Septic shock on admission	12 (25.5)	4 (22.0)	8 (28.0)	0.75
Mechanical Ventilation				
Hospital admission				
NIMV	33 (70.0)	14 (78.0)	19 (65.5)	0.37
IMV	14 (30.0)	4 (22.0)	10 (35.5)	0.37
During ICU stay				
IMV	18 (38.3)	8 (44.4)	10 (35.5)	0.50
Overall duration*, days				
NIMV	6.0 (4.0-10.0)	6.0 (4.0-10.0)	6.0 (4.5-10.0)	0.72
IMV	7.0 (2.0-18.5)	11.0 (2.5-29.0)	6.5 (2.0-19.5)	0.49
ARDS on admission	41 (87.0)	15 (83.0)	26 (90.0)	0.28
Mild	11 (23.4)	7 (39.0)	4 (13.7)	0.08
Moderate	26 (55.3)	7 (39.0)	19 (65.5)	0.07
Severe	4 (8.5)	1 (5.5)	3 (10.3)	1.00

Table 1. General characteristics of patients (continue)

	All (n= 47)	Influenza (n= 18)	ORV (n= 29)	p
Lung infiltration zone numbers				0.62
1	5 (10.6)	2 (11.0)	3 (10.3)	
2	12 (25.5)	5 (28.0)	7 (24.0)	
3	5 (10.6)	1 (5.5)	4 (13.8)	
4	19 (40.4)	9 (50.0)	10 (34.5)	
Thorax CT	34 (72.3)	11 (61.0)	23 (79.3)	0.38
Ground glass opacity	19 (55.8)	8 (73.0)	11 (48.0)	
Consolidation	9 (26.5)	2 (18.0)	7 (30.4)	
Systemic steroid	32 (68.0)	11 (61.0)	21 (72.4)	0.51
Antiviral administration	35 (74.4)	18 (100.0)	17 (59.0)	<0.01
Duration	5 (5-5)	5 (5-8)	5 (5-5)	0.32
Antibiotic administration	46 (98.0)	17 (94.4)	29 (100.0)	0.38
Primary viral infection	11 (23.0)	4 (22.0)	7 (24.0)	1.00
Bacterial co-infection	21 (45.0)	9 (50)	12 (41.0)	0.56
Secondary bacterial infection	24 (51.0)	11 (61)	13 (45)	0.28
Opportunistic infections	14 (30.0)	5 (28.0)	9 (31.0)	0.81

* Continuous variables are represented as median (IQR), all other categorical variables as n (%).

ORV: Other respiratory viruses, BMI: Body mass index, COPD: Chronic obstructive pulmonary disease, CAD: Coronary artery disease, DM: Diabetes mellitus, CKD: chronic kidney disease, CCI: Charlson Comorbidity Index, APACHE: Acute Physiology and Chronic Health Evaluation, SOFA: Sequential organ failure assessment, NIMV: Non-invasive mechanical ventilation, IMV: Invasive mechanical ventilation, ARDS: Acute respiratory distress syndrome, CT: Computerized tomography, IQR: Interquartile range.

Table 2. Laboratory results of patients

Parameters	All (n= 47)	Influenza (n= 18)	ORV (n= 29)	p
CRP* (0.0-0.8), mg/dL	13.0 (4.0-24.5)	18.30 (1.35-55.20)	12.0 (3.0-21.4)	0.15
PCT* (0.0-0.1), ng/mL	0.23 (0.13-0.75)	0.31 (0.02-85.73)	0.19 (0.12-0.49)	0.08
Lymphocyte count* (1300-3500), /mL	500 (300-800)	550 (200-1400)	500 (300-750)	0.49
Lymphopenia	42 (89.4)	15 (83.3)	27 (93.1)	0.36
Leukocyte count* (4300-10300), /mL	9900 (6000-12100)	9500 (2300-17400)	9000 (3600-12000)	0.48
Leukopeni	9 (19.1)	1 (5.6)	8 (27.6)	0.12
Leukocytosis	19 (40.4)	8 (44.4)	11 (37.9)	0.66
Lactate* (0.9-1.7), mMol/L	1.8 (1.3-3.0)	2.0 (1.1-5.1)	1.7 (1.2-2.7)	0.05
PaO ₂ /FiO ₂ *	184 (152-218)	220 (167-258)	171 (147-199)	0.02
Mild ARDS	218 (209-250)	242 (220-256)	211 (204-214)	0.06
Moderate ARDS	166 (149-184)	167 (149-193)	166 (148-183)	0.82
Severe ARDS	79 (66-98)	65 (65-65)	90 (68-90)	0.18

* Continuous variables are represented as median (IQR), all other categorical variables as n (%).

ORV: Other respiratory viruses, CRP: C-reactive protein, PCT: Procalcitonin, PaO₂/FiO₂: Ratio of arterial oxygen partial pressure to fractional inspired oxygen, ARDS: Acute respiratory distress syndrome, IQR: Interquartile range.

entiate accurately between viral and bacterial causes (22). In this study, subgroup analysis of patients with primary viral infections revealed no difference in terms of CRP levels (median (4.0 (2.0-30.0) vs. 13.0 (9.4-21.5), $p = 0.29$), however a tendency towards

lower PCT levels (0.14 (0.12-0.26) vs. 0.28 (0.15-0.77), $p = 0.08$). PO₂/FiO₂ ratio in ORV group was lower than influenza group. Although it wasn't significant, most of moderate and severe ARDS patients were from ORV group. It can be postulated that

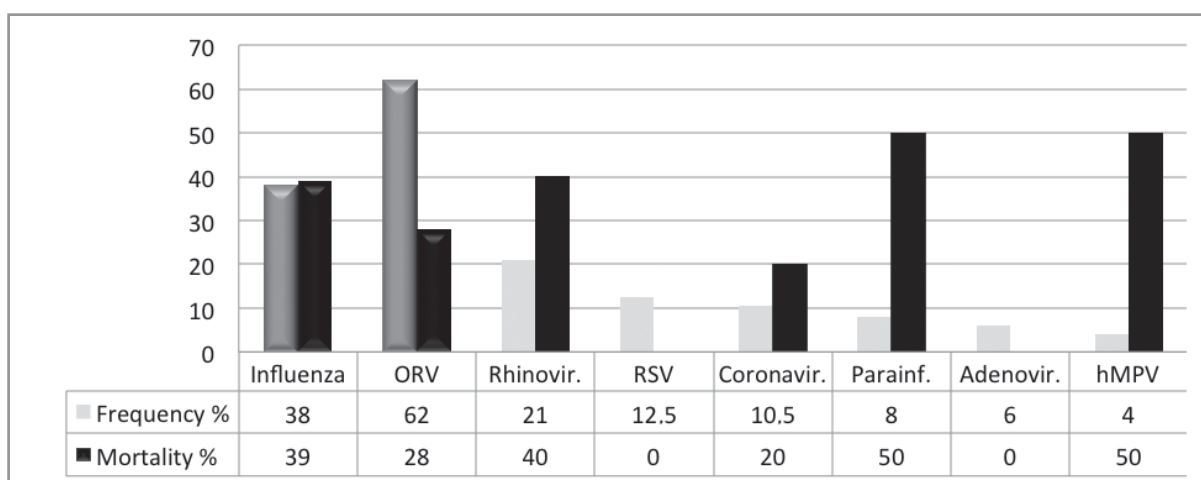


Figure 1. Distribution of viral agents and their mortality rates.

Table 3. Outcome variables

	All (n= 47)	Influenza (n= 18)	ORV (n= 29)	p
ICU mortality	15 (32.0)	7 (39.0)	8 (28.0)	0.42
Hospital mortality	19 (40.0)	11 (55.0)	10 (34.5)	0.29
ICU LOS	11.0 (6.0-29.0)	11.0 (5.0-26.0)	11.0 (8.0-30.0)	0.73
Hospital LOS	23.0 (14.0-47.0)	26.0 (13.0-67.0)	23.0 (13.5-44.5)	0.98

Results are represented as median (IQR), all other categorical variables as n (%).
 ORV: Other respiratory viruses, ICU: Intensive care unit, LOS: Length of stay, IQR: Interquartile range.

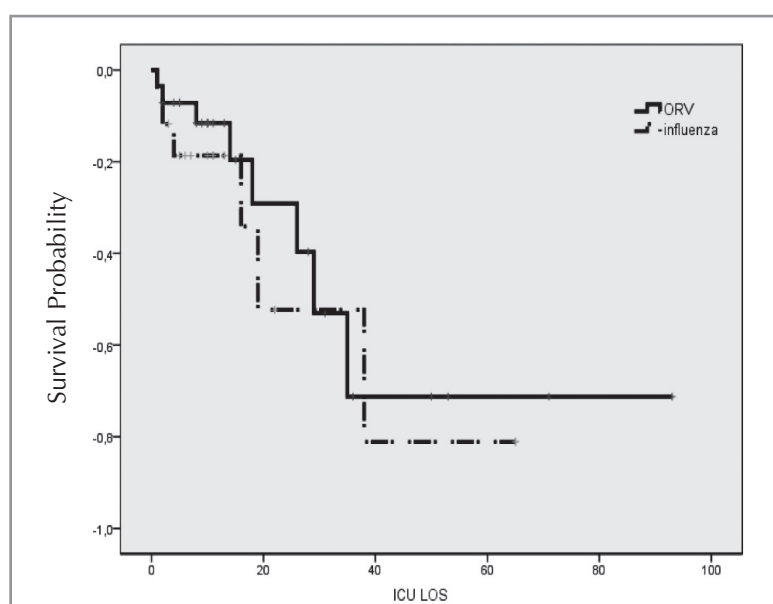


Figure 2. Kaplan Meier survival curve.

Kaplan Meier survival analysis according to viral groups as influenza and ORV did not reveal difference in ICU mortality ($p= 0.48$).

ORV: Other respiratory viruses, LOS: Length of stay.

Table 4. Statistically significant admission variables in bi-variate analysis comparing ICU survivors and non-survivors

Significant Variables	Survivors (n= 32)	Non-survivors (n= 15)	p
Patients > 65 years old	19 (59.0)	4 (27.0)	0.04
COPD	16 (50)	2 (13)	0.02
APACHE II score*	17.0 (12.0-24.0)	25.0 (20.0-28.0)	0.004
SOFA score*	4.0 (2.0-7.0)	7.0 (6.0-8.0)	0.02
PCT* (0.0-0.1), ng/mL	0.19 (0.12-0.34)	0.60 (0.22-1.93)	0.02
PaO ₂ /FiO ₂ *	197 (166-252)	147 (121-187)	0.002

* Continuous variables are represented as median (IQR), all other categorical variables as n (%).

COPD: Chronic obstructive pulmonary disease, APACHE: Acute Physiology and Chronic Health Evaluation, SOFA: Sequential Organ Failure Assessment, PCT: Procalcitonin, PaO₂/FiO₂: Ratio of arterial oxygen partial pressure to fractional inspired oxygen, IQR: Interquartile range.

Table 5. Multivariate analysis of factors influenced mortality

Independent Variables	Odds Ratio	95% Confidence Interval	p
APACHE II score (for each value)	1.25	1.04-1.51	0.02
ORV vs. Influenza (reference ORV)	3.05	0.33-27.77	0.32
PaO ₂ /FiO ₂ <200 (reference PaO ₂ /FiO ₂ >200)	3.01	0.23-39.30	0.40
SOFA score (for each value)	1.03	0.83-1.28	0.78
PCT (for each 1 ng/mL)	0.98	0.93-1.03	0.32
Patients > 65 years old	0.32	0.03-3.32	0.34
COPD	0.15	0.01-1.83	0.14

APACHE: Acute Physiology and Chronic Health Evaluation, ORV: other respiratory viruses, PaO₂/FiO₂: ratio of arterial oxygen partial pressure to fractional inspired oxygen, SOFA: Sequential Organ Failure Assessment, PCT: procalcitonin, COPD: chronic obstructive pulmonary disease.

non-influenza agents must be considered as much as influenza and management should be directed properly even if therapeutic options are limited for ORV. All of our patients with influenza received antiviral treatment as expected. In the other group, 59% of the patients received antiviral treatment, since WHO and Centers for Disease Control and Prevention (CDC) recommend empiric oseltamivir therapy for while the diagnostic tests are pending, in critically-ill high-risk patients (23).

Although seasonal influenza is a self-limited infection with relative annual mortality rate of only 1.4 to 16.7 deaths per 100.000 persons in the general population, patients older than 65 years of age, living at nursing homes, with pregnancy, with chronic medical conditions, with immune compromised status and with obesity have increased mortality and higher rate of ICU admissions. In contrast to this characteristic of seasonal influenza, in 2009 H1N1 pandemic, mortality rate was 100-5000/100.000 in all over the world. In a study by Jain et al. (18) about hospitalized patients during 2009 H1N1 pandemic in United

States, 25% of the enrolled 272 patients were admitted to an intensive care unit. Patients who were under the age of 18 years consisted 45% of cases and only 5% were 65 years of age or older. Median age of non-survivors was 26 years. Estimated global mortality study by Dawood et al (24) indicated that higher mortality due to respiratory reasons due to H1N1 virus was seen more frequently in younger patients. Possible explanations of this contrast result in comparison with seasonal influenza could be higher susceptibility of younger patients to viruses and lack of vaccination. In our cohort, ICU mortality was 32%. Survivors were older than non-survivors as seen during 2009 pandemic. In addition, presence of COPD was encountered more in survivors. Well-known risk factor for COPD exacerbation is respiratory infections, up to 60% of COPD exacerbations being secondary to the respiratory viruses (25). Subgroup comparison of patients with and without COPD showed that primary viral etiology was higher in COPD group (n= 18) than in non-COPD (n= 29), in our cohort (p= 0.01). Moreover, secondary bacte-

rial infections were slightly more encountered in patients without COPD ($p=0.05$). The lower mortality observed in COPD patients could be due to the fact that viral etiology as the cause of exacerbation carries better prognosis than bacterial causes (3). Higher APACHE II, admission SOFA scores and PCT levels and lower $\text{PaO}_2/\text{FiO}_2$ ratio were associated with higher mortality in bi-variate analysis. However, multivariate analysis disclosed that only APACHE II score was independently associated with ICU outcome.

Distribution of viral agents in our study showed that ORV is the leading group for viral ARF (Figure 1). Among them, *rhinovirus* was the most frequent (35%) agent. *Rhinovirus* is the most encountered reason of viral upper respiratory tract infections (26). A retrospective study (27) revealed that mortality rate of *rhinovirus* cases could reach to 30% which was 40% in our cohort. Although RSV is the most known cause of lower respiratory tract infections in pediatric age, it is generally not identified in adults (28). In this study, almost 21% of ORV was RSV with no fatality similar to *adenovirus*.

Global Influenza Hospital Surveillance Network (GIHSN) has been founded for recording the influenza infections in acute care setting (29). Since influenza A (H1N1) pandemic observed in 2009, there have been several case series about influenza-associated critical illness. In a study from Ortiz et al. (30), it was estimated that influenza-associated events account for 1.3% of all critical illness hospitalizations and 3.4% of critical illness hospitalizations during the influenza season. They found that influenza diagnosis in the adult ICUs were underestimated. Potential explanations for this result are lack of common case definitions, unavailability of timely appropriate sensitive tests and belief of ineffectiveness of influenza treatment. In our cohort, only 47% of ARF patients were assessed for the viral serology which could prevent to reflect the exact burden of viral etiology. A multicenter surveillance study by Tanriover et al (31), in the context of GIHSN in Turkey pointed out that influenza was detected 18.7% of 1351 screened acutely-ill patients with influenza-like disease and among them 32.6% were admitted to ICU. In our study, almost 5% of 939 patients admitted to ICU were detected with viral etiology for ARF. Patient numbers tended to increase over the study duration, most patients being detected during the last 6-months

of the study period probably due to increased awareness and availability of more appropriate and timely sensitive tests.

The main limitations of this study are relatively low patient numbers and its single center retrospective design which prevents generalization of findings. Unfortunately, we don't have any information about subtypes of influenza species like H1N1 or H3N2. As molecular assays may detect influenza viral RNA in respiratory tract specimens for longer periods after illness onset, the cause and effect relation cannot be put with 100% accuracy (32). Hence, co-infection might be purely bacterial infection and the outcome might be affected only by bacterial etiology. Unknown information about where samples were sent from such as nasal, oropharynx and lower respiratory ways is another limitation. Tropism of some viruses to different parts of the respiratory tract might interfere with interpretation of the results. The probability of co-incidental upper respiratory viral infection should be kept in mind. Unfortunately, we do not have any data about how many patients received antimicrobial agents before ICU admission. Therefore, some patients might have had false-negative findings regarding bacterial growth, and the proportion of patients infected by the virus only, might have been overestimated. We also do not know the vaccination history of patients which could have changed the prevalence and outcomes in each group.

CONCLUSION

This study draws attention to consider possibility of other respiratory viruses more than influenza species with comparable characteristics and similar ICU mortality rates. These results need to be confirmed by multicenter surveillance studies with more patients using standardized highly sensitive tests. By this way, it could be possible to understand the real burden and causality of ORV for ARF in critically ill patients.

Ethical Committee Approval: The approval for this study was obtained from Hacettepe University Institutional Ethical Committee (Decision no: 16/598-09 Date: 27.09.2016).

CONFLICT of INTEREST

The authors of this original article declare that they have no conflict of interest.

AUTHORSHIP CONTRIBUTIONS

Concept/Design: BH, PH, EO, SO

Analysis/Interpretation: EO, SO, MDT, AT

Data Acquisition: BH, PH

Writing: BH, PH, AT

Critical Revision: All of authors

Final Approval: All of authors

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