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Sepsis/Infection

Influenza virus and factors that are associated with ICU admission, pulmonary co-infections and ICU mortality

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ABSTRACT

Purpose: While most influenza patients have a self-limited respiratory illness, 5–10% of hospitalized patients develop severe disease requiring ICU admission. The aim of this study was to identify influenza-specific factors associated with ICU admission and mortality. Furthermore, influenza-specific pulmonary bacterial, fungal and viral co-infections were investigated.

Methods: 199 influenza patients, admitted to two academic hospitals in the Netherlands between 01-10-2015 and 01-04-2016 were investigated of which 45/199 were admitted to the ICU.

Results: A history of Obstructive/Central Sleep Apnea Syndrome, myocardial infarction, dyspnea, influenza type A, BMI > 30, the development of renal failure and bacterial and fungal co-infections, were observed more frequently in patients who were admitted to the ICU, compared with patients at the normal ward. Co-infections were evident in 55.6% of ICU-admitted patients, compared with 20.1% of patients at the normal ward, mainly caused by *Staphylococcus aureus*, *Streptococcus pneumoniae*, and *Aspergillus fumigatus*. Non-survivors suffered from diabetes mellitus and (pre-existent) renal failure more often.

Conclusions: The current study indicates that a history of OSAS/CSAS, myocardial infarction and BMI > 30 might be related to ICU admission in influenza patients. Second, ICU patients develop more pulmonary co-infections. Last, (pre-existent) renal failure and diabetes mellitus are more often observed in non-survivors.

1. Introduction

Influenza virus infection is an important cause of mortality worldwide, leading to 250.000–500.000 deaths each year in the developed world [1]. While most influenza patients have a self-limited respiratory illness, 5–10% of hospitalized patients may develop severe dyspnea or respiratory distress requiring ICU admission [2]. Mortality is caused by the primary viral infection which can have a fulminant disease course [3], but also by influenza-associated pulmonary co-infections [4,5]. It is increasingly recognized that similar to sepsis, influenza can initiate immunosuppressive mechanisms [5,6], creating an ideal environment for opportunistic pathogens to grow out and induce co-infections. Pulmonary bacterial co-infections are predominantly caused by *Streptococcus pneumoniae, Staphylococcus aureus* and *Haemophilus influenzae* [5]. Also, invasive pulmonary aspergillosis (IPA) caused by the fungal *Aspergillus fumigatus* is recently recognized as a co-infection occurring in 20–25% of influenza patients who are admitted to the intensive care unit (ICU) [7,8]. Both bacterial as well as fungal pulmonary co-infections are associated with increased mortality rates [7,9-11]. In addition, viral co-infections [12] and reactivation of viruses that reside latent in the host, such as Cytomegalovirus (CMV), *Epstein barr virus* (EBV) and *Herpes simplex virus* (HSV) are frequently encountered in

Abbreviations: APACHE, Acute physiology and chronic health evaluation; BAL, Bronchoalveolar lavage; BMI, Body mass Index; CI, Confidence interval; CMV, Cytomegalovirus; CNS, Central nervous system; COPD, Chronic obstructive pulmonary disease; CSAS, Central sleep apnea syndrome; EBV, Epstein barr virus; ECLS, Extracorporeal life support; GCS, Glasgow coma scale; GFR, Glomerular filtration rate; HSV, Herpes simplex virus; ICU, Intensive Care Unit; IMV, Invasive mechanical ventilation; IPA, Invasive Pulmonary Aspergillosis; IU, International units; MAP, Mean arterial pressure; MUMC, Maastricht University Medical Center; NIV, Non-invasive ventilation; OR, Odds ratio; OSAS, Obstructive sleep apnea syndrome; PCR, Polymerase chain reaction; Radboudumc, Radboud university medical center; RIVM, Rijksinstituut voor Volksgezondheid en Milieu (Dutch National Institute for Public Health and the Environment); SAPS, Simplified acute physiology score.

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influenza patients as well [4,13]. Whether these infections are associated with increased mortality or merely reflect a manifestation of immunosuppression is not elucidated yet.

Influenza patients represent a heterogeneous patient population, presenting various age categories, comorbidities and are often treated with a diverse range of medical therapies, such as antibiotics, antiviral and immunosuppressive drugs. Due to this heterogeneity, it is not fully clarified which factors are protective and which factors are on the other hand associated with increased mortality in these patients.

Although the impact of seasonal influenza varies depending on the type of virus, timing of the season, vaccine coverage and effectiveness of the vaccine, the rate of influenza-associated hospitalization places a substantial burden on health care resources. More importantly, early recognition of certain factors that influence the disease course of influenza-infected patients may improve current therapy strategies. In the present study, we investigated a cohort of influenza patients (2015–2016 season) admitted to two university hospitals in the Netherlands, to identify factors that are related to ICU admission and mortality. In addition, we investigated the incidence of influenza-associated pulmonary co-infections, their causative pathogens and their relationship with ICU admission and mortality.

2. Methods

2.1. Patient population

Data was collected from influenza patients who were admitted to the Radboud university medical center (Radboudumc) or Maastricht university medical center (MUMC), both located in the Netherlands. The local institutional review boards approved the protocol (METC 16–4-195 and CMO 2016–2777). The influenza epidemic of 2015–2016 started on November 1st 2015 and ended on May 1st 2016 according to the National Institute for Health and the Environment (RIVM Rapport 2016–0071). Patients who were admitted to the participating hospitals between October 1st 015 and April 1st 2016 were checked for eligibility for the study. Cases were identified using a database of the microbiology departments at both medical centers. Patients who were admitted to the hospital with clinical symptoms due to an acute infection with Influenza A or B were included. Virus samples were obtained from nose/throat swabs, sputum or bronchoalveolar lavage (BAL). The laboratory of microbiology of both hospitals confirmed a novel influenza infection by positive polymerase chain reaction (PCR; Diagenode, Belgium) for either influenza A (H1N1 / H2N3) or influenza B [14]. No distinction was made between self-referral, scheduled admission or emergency hospital admission. Patients who were initially admitted to regional hospitals before admittance to one of the university medical centers were included if they met the case definition and had not received antibiotic or antiviral treatments before admission. Patients with a positive influenza PCR who were already admitted to the hospital were excluded from the study if the sample was collected as part of a routine screening and no prior symptoms of infection were observed. The initial day of hospital admission was defined as day 0.

2.2. Data collection and study design

Detailed information was collected on demographics, comorbid medical conditions, use of immunosuppressive medication before hospitalization or chemotherapy, self-reported date of onset of illness, clinical signs and symptoms at presentation, need for treatment at the ICU, occurrence of organ failure, development of bacterial, fungal or viral co-infections, use of neuraminidase inhibitors (oseltamivir), need for antimicrobial therapy and final outcome.

BMI was subdivided in underweight (<18 kg/m^2), normal weight (18 to 25 kg/m^2), overweight (25 to 30 kg/m^2) and obese (>30 kg/m^2). Pregnancy was defined as any gestational age confirmed by ultrasonography. Ex-smokers who stopped smoking within the last 6 months were considered to be active smokers. Occasional alcohol consumption was defined as <21 international units (IU)/week and regular alcohol consumption was defined as >21 IU/week. Use of medication or chemotherapy was defined as current use or the use in the former 3 months. Comorbid medical conditions included: OSAS, defined as an apnea-hypopnea index (AHI) ≥ 5 with associated symptoms (eg, excessive daytime sleepiness, fatigue, or impaired cognition) or an AHI of 15 or greater, regardless of associated symptoms, CSAS defined as: AHI > 5 with >50% of the respiratory events occurring without any respiratory effort and associated with symptoms of either excessive sleepiness or disrupted sleep(1), asthma, Chronic Obstructive Pulmonary Disease (COPD) and other pulmonary diseases, hypertension, myocardial infarction, heart failure and other cardiovascular diseases, hepatic diseases, renal diseases, stroke and other neurological or neurodegenerative diseases, diabetes mellitus and other endocrine diseases, autoimmune diseases and malignancies. Comorbidities were considered present if they were mentioned in the patient's medical file or by the use of typical medication for a particular condition (e.g. insulin therapy for diabetes mellitus). Comorbidities were considered absent if the medical file stated that the patient has previously been healthy.

Patient delay was defined as the number of days from the onset of illness to hospital admission. Length of stay (for either hospital or ICU) was defined as the number of days from admission to discharge or death. *Re*-admission <7 days after discharge was considered as a continuous stay. ICU admission criteria included a quick deteriorating disease course with potential need for vasopressive therapy and/or mechanical ventilation. Organ failure was defined when ≥3 points on the SOFA scale were scored for a particular organ system [15]. Circulatory failure was defined as a mean arterial pressure (MAP) <65 mmHg, a decrease in MAP >20 mmHg relative to baseline, the need for vasopressive therapies or intravenous fluids (>40 mL/kg) for ≥24 h. Respiratory failure was defined as the need for any form of respiratory support, hepatic failure as a total bilirubin level > 20 μmol/L, central nerve system (CNS) failure as a Glasgow Coma Scale (GCS) <14 in the absence of sedatives, opioids or delirium. Hematological failure was defined as leukopenia, thrombocytopenia and/or anemia. Renal failure was defined as a twofold rise in serum creatinine level relative to baseline, 50% reduction of glomerular filtration rate (GFR) or a urine production <0.5 mL/kg/h for >12 h. Disease severity scores SAPS 2 and APACHE III were calculated in all ICU patients.

Pulmonary bacterial co-infection was defined as a positive bacterial culture of either endotracheal or endobronchial secretions or a positive urine pneumococcal antigen test in combination with the start of antimicrobial therapy. Pulmonary fungal infections were detected by fungal culture of endotracheal or endobronchial secretions or a galactomannan optical index in BAL (>1) / in serum (>0.5) within three weeks of influenza diagnosis [16]. Viral infections and *Pneumocystis jirovecii* infections were detected by PCR. Based on recent work from *van de Veerdonk* et al., critically ill influenza patients with positive fungal cultures from deep pulmonary material (endotracheal or endobronchial secretions) were considered to be positive for pulmonary fungal infections [8].

Oseltamivir was started according to the local hospital protocol. Consequently at the Radboudumc, it was started in all influenza patients who suffered from clinical symptoms <5 days at admission. At the MUMC, oseltamivir was started in all influenza patients who had symptoms up to 48 h at admission. Exceptions included immunocompromised patients or patients with an interstitial or secondary bacterial pneumonia. In these patients, oseltamivir was started even after 48 h.

All data were abstracted from the patients' records and included: admission history, daily doctor's report, discharge letter, physical measurements, laboratory information system and information from ICU surveillance systems.

2.3. Statistical analysis

Categorical data were analyzed using Fisher exact tests. Continuous variables were analyzed using binary logistic regression. *P*-values were two-sided and values of <0.05 were considered statistically significant. Statistical analyses were performed using SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY, USA). An univariate descriptive analysis was performed to identify risk factors for ICU admission in patients admitted to the hospital for influenza virus infection. Chi-square tests and one-sided Fisher exact tests were used for dichotomous variables, unpaired *t*-tests for normally distributed continuous variables, and Mann-Whitney *U* tests for non-normally distributed continuous data. All results were verified with a logistic regression model. Next, a multivariate logistic regression was used to identify independent risk factors. Variables with a significance level of $p < .05$ were selected and those with the greatest odds ratio were included for the number of cases in the ICU-group. All individual variables in the multivariate model were tested on interaction. Odds ratios (OR) and 95% confidence intervals (CI) were calculated for each individual risk factor.

3. Results

3.1. Demographic characteristics

A total of 200 cases were identified. Data of one patient missed a lot of values and was excluded from further analysis. Demographic characteristics of the remaining 199 patients are listed in Table 1. The median age of the entire patient population was 56[30–67] yrs., including 31 children (<18 yrs.; 16%) and 52 elderly patients (>65 yrs.; 26%). 76/199 patients (38%) had a history of pulmonary disease, of which predominantly COPD. Pre-existing hypertension was reported in 101/199 patients (51%). Pre-existing neurological, renal and hepatic disease was documented in 65/199 (33%), 39/199 (20%) and 12/199 (6%) patients at admission. 119/199 (60%) patients were considered immunocompromised, when the systemic use of steroids and other immunosuppressive drugs was evident before hospitalization. The median duration of hospitalization was 5 [2-13] days. The overall mortality rate was 18/199 (9%).

Table 1
Characteristics of patients with influenza virus infection admitted to the hospital.

Demographic data (N = 199)	
Gender [Male/Female]	109/90 (55%)
Age group (in years)	
<18	31/199 (16%)
18–65	116/199 (58%)
>65	52/199 (26%)
BMI[1, 2] (kg/m^2)	
<18	11/167 (7%)
18–<25	85/167 (51%)
25–<30	40/167 (24%)
≥30	31/167 (19%)
Pregnancy	3/90 (3%)
Smoking habit[3]	53/134 (40%)
Ex-smoker	19/134 (14%)
Active smoking	34/134 (25%)
Alcohol consumption[4]	39/117 (33%)
Pulmonary disease (any)	76/199 (38%)
Asthma	17/199 (9%)
COPD	25/199 (13%)
OSAS	9/199 (5%)
Other	41/199 (21%)
Cardiovascular disease (any)	101/199 (51%)
Myocardial infarction	18/199 (9%)
Hypertension	66/199 (33%)
Heart failure	12/199 (6%)
Other	83/199 (42%)
Hepatic disease	12/199 (6%)
Renal insufficiency	39/199 (20%)
Neurological disease (any)	65/199 (33%)
Stroke	10/199 (5%)
CNS tumor	6/199 (3%)
Other	56/199 (28%)
Immunocompromised state (any)	119/199 (60%)
Diabetes	23/199 (12%)
Use of systemic steroids	67/199 (34%)
Use of immunosuppressants	47/199 (24%)

[1] Children (≤ 6 years) were excluded.
[2] Data of 12 patients were missing.
[3] Data of 65 patients were missing.
[4] Data of 65 patients were missing.

3.2. Clinical characteristics

The majority of patients suffered from Influenza type A (141/199, 71%) (Table 1, supplementary material). Influenza subtyping was performed in 75/141 (53%) patients with type A influenza and showed that 74/75 (99%) suffered from subtype H1N1. Cough (161/197; 82%), fever (146/197; 74%), dyspnea, defined as the subjective feeling of shortness of breath (107/197; 54%) and general discomfort (100/197 51%) were the most common reported symptoms at admission. Oseltamivir was administered during admission in 92/199 (46%) patients. 53/199 patients (27%) already received antibiotic treatment before hospital admission, 89/199 patients (45%) were administered antibiotic treatment upon hospital admission and 17/199 (9%) patients received antibiotics at later time points during hospitalization. Empirical treatment at the ICU for community-acquired pneumonia consisted of ceftriaxone 2000 mg mg 2 times a day and of piperacillin-tazobactam 4500 mg 3 times a day for hospital-acquired pneumonia, according to the Dutch national guideline for community-acquired pneumonia in adults (SWAB) [17,18]. Antibiotic regimes were de-escalated when bacterial sputum cultures became positive for a specific bacterial pathogen. 45/199 (23%) of the influenza patients were admitted to the ICU, at a median of 4 [2-7] days after development of the first symptoms.

3.3. Factors related to ICU admission

45/199 (23%) patients were admitted to the ICU, with a mean age of 53[±22] years. Respiratory failure was the main cause of ICU admission: 39/45 (87%) patients received invasive mechanical ventilation (IMV), 4/45 (9%) patients received only non-invasive ventilation, and a non-rebreathing mask was applied in one (2%) patient. The median duration of IMV was 12 [3-33] days. Nitric oxide (NO) inhalation was used in 2/45 patients (4%), and epoprostenol inhalation in 4/45 patients (9%). One patient did not receive pulmonary supportive therapy (2%).

Factors related to ICU admission are shown in Table 2. OSAS/CSAS (11% vs. 3%; $p = .03$), a history of myocardial infarction (20% vs. 6%; $p = .007$) and BMI >30 (30% vs. 15%; $p = .04$) were more often observed in patients admitted to the ICU. No relation was found between age and ICU admission ($p = .13$). Influenza A infection occurred more often in the ICU population compared with influenza B (34 vs. 13%, $p = .007$). In addition, patients who were admitted to the ICU developed renal failure (47% vs. 5%; $p < .001$), secondary bacterial (36% vs. 7%; $p < .001$) and fungal pulmonary infections (29% vs. 1%; $p < .001$) more often during their hospital stay, compared with influenza patients who were not admitted to the ICU. Oseltamivir was administered more frequently in these patients (84% vs. 35%; $p < .001$). After multivariate analysis, age between 50 and 65 yrs., OSAS/CSAS, a history of myocardial infarction, dyspnea and influenza type A were identified as independent factors related to ICU admission in influenza patients (Table 3).

3.4. Influenza-associated ICU mortality

A total of 45 patients were admitted to the ICU. The ICU mortality of influenza patients was 17/45 (38%). Median SAPS2 and APACHE III scores were 46[39–55] and 99[86–116] respectively. Respiratory failure was the main indication for ICU admission: 40 patients received

Table 2
Factors related to ICU admission, univariate analysis.

Characteristic	No ICU admission *(N = 154)*	ICU admission *(N = 45)*	OR	95% CI	*P* value
Male sex	88/154 (57.1%)	21/45 (46.7%)	1.524	[0.782–2.969]	*0.236*
Age group (yrs) [mean]	46.82	53.02			*0.126*
<18	24/154 (15.6%)	7/45 (15.6%)	0.998	[0.073–0.636]	*0.002*
18–50	48/154 (24.0%)	4/45 (8.9%)	0.215	[0.073–0.636]	*0.002*
50–65	37/154 (62.7%)	22/45 (48.9%)	3.025	[1.515–6.040]	*0.003*
>65	45/154 (29.2%)	12/45 (26.7%)	0.881	[0.418–1.858]	*0.852*
BMI kg/m^2 [mean][1,2]	24.80	27.01			*0.058*
>30	19/127 (15.0%)	12/40 (30.0%)	2.436	[1.058–5.607]	*0.039*
Active smoking[3]	22/104 (21.2%)	12/30 (40.0%)	2.485	[1.042–5.925]	*0.055*
Alcohol consumption[4]	29/97 (29.9%)	10/20 (50.0%)	2.345	[0.881–6.238]	*0.117*
New renal failure	7/154 (4.5%)	21/45 (46.7%)	18.375	[7.049–47.897]	*<0.001*
Pulmonary disease (any)	52/154 (77.4%)	24/45 (53.3%)	2.242	[1.142–4.399]	*0.023*
OSAS/CSAS	4/154 (2.6%)	5/45 (11.1%)	4.688	[1.203–18.268]	*0.029*
Cardiovascular disease (any)	73/154 (47.4%)	28/45 (62.2%)	1.828	[0.925–3.610]	*0.092*
Myocardial infarction	9/154 (5.8%)	9/45 (20.0%)	4.028	[1.492–10.877]	*0.007*
Immunocompromised state (any)	91/154 (59.1%)	28/45 (62.2%)	1.140	[0.576–2.257]	*0.733*
Symptoms[5,6]					
Fever	121/154 (78.6%)	25/43 (58.1%)	0.379	[0.185–0.776]	*0.010*
Dyspnea	74/154 (48.1%)	33/43 (76.7%)	3.568	[1.644–7.743]	*0.001*
Duration[6] (days) [mean]	3.56	2.39			*0.474*
Influenza type A (vs. B)	102/154 (66.2%)	39/45 (86.7%)	0.302	[0.120–0.759]	*0.009*
Pulmonary bacterial co-infection	10/154 (6.5%)	16/45 (35.6%)	7.945	[3.279–19.252]	*<0.001*
Pulmonary fungal co-infection	2/154 (1.3%)	13/45 (28.9%)	30.875	[6.641–143.459]	*<0.001*
First antibiotic treatment					
Before admission	39/154 (25.3%)	14/45 (31.1%)	1.332	[0.643–2.758]	*0.448*
At admission	68/154 (44.2%)	21/45 (46.7%)	1.107	[0.568–2.155]	*0.865*
Use of oseltamivir	54/154 (35.1%)	38/45 (84.4%)	10.053	[4.206–24.030]	*<0.001*

[1] Children (≤ 6 years) were excluded.
[2] Data of 12 patients were missing.
[3] Data of 65 patients were missing.
[4] Data of 65 patients were missing.
[5] Data of 2 patients were missing.
[6] Duration first symptoms until hospital admission.

invasive mechanical ventilation (IMV), 4 patients non-invasive ventilation and a non-rebreathing mask was applied in one patient. The median duration of IMV was 12 [4-30] days. 9/45 (20%) patients were treated with continuous muscle relaxation for a median of 5 [4-7] days. 3/9 (33%) patients who were treated with continuous muscle relaxation therapy deceased ($p = 1.00$). Nitric oxide inhalation was used in 2/45 patients (4.4%), and epoprostenol inhalation in 4/45 (8.9%). 17/45 (38%) patients were ventilated in prone position, of which 8/17 (47%) did not survive ($p = .36$). Lung rescue therapies were used in 5 patients: 2/45 (4%) received extra-corporal CO_2 removal; 3/45 (7%) were treated with extracorporal membrane oxygenation (ECMO).

ICU survivors were compared with non-survivors (Table 4). Patients who died suffered more often from diabetes mellitus (OR 7.09, CI 95% 1.23–40.75; $p = .04$). Renal failure was a risk factor for mortality both present before or during ICU admission (OR 6.815, CI 95% 1.47–31.61; $p = .01$ and OR 8.13, CI 95% 2.03–32.57; $p = .002$ respectively). The use of immunosuppressive drugs (systemic steroids and non-steroids) before hospitalization showed a trend towards increased ICU mortality (OR 3.57, CI 95% 1.01–12.68; $p = .06$ and OR 4.54, CI 95% 0.96–21.56; p = .06).

Table 3
Independent factors related to ICU admission, multivariate logistic regression analysis.

Characteristic	OR	95% CI	P value
Age 50–65 years	3.85	[1.62–9.19]	0.002
Obesity[1]	0.95	[0.32–2.80]	0.924
OSAS	9.73	[1.30–73.06]	0.027
Myocardial infarction	4.58	[1.36–15.44]	0.014
Dyspnea	3.26	[1.26–8.47]	0.015
Influenza type A	3.66	[1.06–12.69]	0.041

OR; odds ratio, CI; confidence interval, OSA; obstructive sleep apnea, MI; myocardial infarction.
[1] Defined as a Body Mass Index > 30 kg/m^2.

3.5. Influenza-associated pulmonary co-infections

Influenza-associated pulmonary co-infections and their causative pathogens are listed in Table 5. During the course of their admission, 40/199 (20.1%) of the hospitalized patients developed a pulmonary co-infection of either bacterial, fungal or viral origin or a combination of pathogens. The proportion of co-infections in ICU-admitted patients was significantly higher compared with patients at the normal ward (25/45, 55.6%, $P < .0001$). This was evident for bacterial, fungal and viral pathogens ($p = .0008$, $p = .0003$ and $p = .02$ respectively). The most common bacterial pathogens included *Staphylococcus aureus* (11%) and *Streptococcus pneumoniae* (7%). *Aspergillus fumigatus* was most common among the fungal pathogens (18%), followed by *Pneumocystis jirovecii* (7%). Patients with a pulmonary co-infection received oseltamivir more often (OR 0.65, CI 95% 0.47–0.90, $p = .002$). No association was observed between the use of immunosuppressive drugs before hospitalization and the development of pulmonary co-infections. Also, no relationship was found between the development of a pulmonary co-infection and ICU mortality (OR 1.24, CI 95% 0.37–4.19; $p = .76$).

4. Discussion

The present study supports the high morbidity and mortality rates of influenza patients admitted to the ICU described in previous work [1,19]. Independent factors related to ICU admission in the 2015–2016 seasonal influenza outbreak were influenza type A, dyspnea, a history of myocardial infarction and OSAS/CSAS. Co-infections with bacterial,

Table 4
Mortality rates of influenza patients at the ICU, univariate analysis.

Characteristic	Death ($n = 17$)	No death OR ($n = 28$)		95% CI	*P* value
Male sex	7 (41.2%)	14 (50.0%)	1.429	[0.423–4.826]	*0.759*
Comorbidity					
Pulmonary disease (any)	8/17 (47.1%)	16/28 (57.1%)	0.667	[0.199–2.239]	*0.552*
Cardiovascular disease (any)	12/17 (70.6%)	16/28 (57.1%)	1.800	[0.498–6.500]	*0.528*
Neurological disease (any)	9/17 (52.9%)	9/28 (32.1%)	2.375	[0.688–8.202]	*0.216*
Diabetes mellitus	6 (35.3%)	2 (7.1%)	7.091	[1.234–40.752]	*0.039*
Renal insufficiency	3 (17.6%)	3 (10.7%)	1.786	[0.317–10.061]	*0.658*
Immunocompromised state (any)	13/17 (76.5%)	15/28 (53.6%)	2.817	[0.734–10.805]	*0.205*
Systemic steroids	10 (58.8%)	8 (28.6%)	3.571	[1.006–12.679]	*0.063*
Non-steroids	6 (35.3%)	3 (10.7%)	4.545	[0.958–21.562]	*0.063*
Renal failure					
Before ICU admission[1]	8/17 (47.1%)	3/26 (11.5%)	6.815	[1.469–31.612]	*0.014*
During ICU admission	13 (76.5%)	8 (28.6%)	8.125	[2.027–32.574]	*0.002*
Dialysis	7 (41.2%)	7 (25.0%)	2.100	[0.578–7.630]	*0.326*
Oseltamivir during ICU stay	15 (88.2%)	23 (82.1%)	1.630	[0.279–9.516]	*0.693*
Pulmonary co-infections	10 (58.8%)	15 (53.6%)	1.238	[0.366–4.187]	*0.767*
Bacterial	4 (23.5%)	12 (42.9%)	0.410	[0.107–1.579]	*0.219*
Fungal	6 (35.3%)	7 (25.0%)	1.636	[0.441–6.076]	*0.511*
Viral	3 (17.6%)	1 (3.6%)	5.786	[0.550–60.875]	*0.144*

OR; odds ratio, CI; confidence interval, OSA; obstructive sleep apnea, MI; myocardial infarction.
[1] Regarding to renal failure before ICU admission, data of 2 patients were missing.

fungal and viral pathogens developed more often in patients who were admitted to the ICU.

Similar to previous seasons, our data indicate that pre-existing respiratory disease is associated with ICU admission in the 2015–2016 influenza season [20]. From our database, dyspnea appeared to be the most determinative clinical sign for influenza-associated ICU admission. Also, OSAS/CSAS could be a new independent factor related to ICU admission, although the total numbers of patients in this group was only 9. Possibly, a decreased breathing quality weakens pulmonary function in OSAS/CSAS patients and thereby increases the risk for ICU admission. Other mechanisms may influence pulmonary function as well, such as activation of the sympathetic nervous system, vascular endothelial dysfunction, inflammation and oxidative stress as described as OSAS/CSAS-related (cardiovascular) complications [21].

The number of patients in our cohort with influenza A virus infections was substantially higher than the number of patients with influenza B virus infections, which is usually the case in influenza epidemics [22]. H1N1 was most prevalent in our study cohort, which is representative for the global prevalence of this subtype in the community during the 2015–2016 influenza season [22]. In our study, patients with influenza type A were admitted more often to the ICU than patients with subtype B, probably due to H1N1 being the most prevalent circulating subtype during this season. In addition, H1N1 is associated with a more severe disease course and higher mortality rates, compared

Table 5
Influenza-associated pulmonary co-infections.1

Pulmonary co-infections – No. (%)	All patients	ICU patients	P value
Total number of patients with a pulmonary co-infection	40/199 (20.1%)	25/45 (55.6%)	<0.0001
Bacterial infections – no. (%)	26/199 (13.1%)	16/45 (35.6%)	0.0008
Staphylococcus aureus	5/199 (2.5%)	5/45 (11.1%)	
Streptococcus pneumoniae	7/199 (3.5%)	3/45 (6.7%)	
Haemophilus influenzae	3/199 (1.5%)	1/45 (2.2%)	
Streptococcus pyogenus[1]	2/199 (1.0%)	1/45 (2.2%)	
Bordetella bronchoseptica	1/199 (0.5%)	1/45 (2.2%)	
Enterobacter cloacae	1/199 (0.5%)	1/45 (2.2%)	
Escherichia coli	1/199 (0.5%)	0/45 (0%)	
Haemophilus + Enterobacter spp	1/199 (0.5%)	1/45 (2.2%)	
Moraxella catarrhalis	1/199 (0.5%)	0/45 (0%)	
Pseudomonas spp	1/199 (0.5%)	1/45 (2.2%)	
Stenotrophomonas spp	1/199 (0.5%)	1/45 (2.2%)	
Unknown pathogen	2/199 (1.0%)	1/45 (2.2%)	
Fungal infections – no. (%)	15/199 (7.5%)	13/45 (28.9%)	0.0003
Aspergillus fumigatus	8/199 (4.0%)	8/45 (17.8%)	
Pneumocystis jirovecii	4/199 (2.0%)	3/45 (6.7%)	
Candida albicans	2/199 (1.0%)	1/45 (2.2%)	
Unknown pathogen	1/199 (0.5%)	1/45 (2.2%)	
Viral infections – no. (%)	8/199 (4.0%)	4/45 (8.9%)	0.0233
Adenovirus + Coronavirus	1/199 (0.5%)	0/45 (0%)	
Cytomegalovirus (CMV)	1/199 (0.5%)	1/45 (2.2%)	
Human metapneumovirus	1/199 (0.5%)	0/45 (0%)	
Parainfluenza	2/199 (0.5%)	0/45 (0%)	
Parainfluenza + Herpes simplex virus (HSV)	1/199 (0.5%)	0/45 (0%)	
Respiratory syncytial virus (RSV)	1/199 (0.5%)	1/45 (2.2%)	
Unknown pathogen	1/199 (0.5%)	0/45 (0%)	

[1] *Haemolytic streptococcus group A.*

with influenza B and other influenza A subtypes like H3N2, being less virulent [22].

In the current study, 23% of hospitalized influenza patients were admitted to the ICU, which is more than the 5–10% described in literature [2]. This could be due to selection of the patients, composed from a database of two tertiary centers in the Netherlands which overall represent the most severely ill and therefore logically associated with an increased number of ICU admissions. The ICU population was treated more often with oseltamivir in comparison with patients at the normal ward. Oseltamivir is a neuraminidase inhibitor that blocks the viral neuraminidase, an enzyme that is essential for the release of newly formed virions from the host cells. A Cochrane analysis concluded that oseltamivir reduced the time to first alleviation of symptoms by 16.8 h, but had no effect on hospitalization risk [23]. Oseltamivir had no effects on mortality among patients with type A/H1N1 influenza during the 2009 pandemic [24]. In our study, oseltamivir was administered to every influenza patient upon admission, except when clinical symptoms were prevalent >5 days, most likely reflecting a less severe influenza disease course in these patients. The increased use of oseltamivir in patients admitted to the ICU is therefore more likely due to selection bias, and not a true risk factor for ICU admission. Also, an increasing trend for ICU mortality was observed for the systemic use of steroids and non-steroid immunosuppressive drugs before hospitalization. The latter suggests that an immunosuppressive state, caused by (pre-existent) immunomodulatory therapy or as a direct result of influenza infection leading to increased susceptibility towards secondary infections, might influence the disease course and prognosis of influenza infection. Further research is needed to identify risk factors for a complicated disease course.

Co-infections were more often observed in patients admitted to the ICU, which could probably be the result of an influenza-induced immunosuppressed state, which hampers the initiation of an adequate immune response to eradicate invading pathogens. As expected, *Staphylococcus aureus* and *Streptococcus pneumonia* were the most common bacterial pathogens determined, prevalent in respectively 11% and 7% of influenza patients at the ICU, causing a transition from normal colonization of the upper respiratory tract to infectious disease [5,25]. Influenza predisposes to secondary infections by direct effects, including the disruption of epithelial cell barriers and suppression of the production of antibacterial peptides and upregulation of bacterial adhesion molecules [1,26,27], but also by indirect immunomodulatory effects, such as impairing antigen presenting capacity in the draining lymph nodes [27,28] and altered expression of costimulatory molecules and cell surface receptors [5,27,28]. The high incidence of fungal co-infections in the subgroup of ICU patients, in particular caused by *Aspergillus fumigatus* (18%) is in line with previous reports, showing that the pathogen *Aspergillus fumigatus* is observed in 20–25% of influenza patients [7,29-34]. The high incidence of co-infections caused by *Streptococcus pneumonia*, *Staphylococcus aureus* and *Aspergillus fumigatus* indicates that a specific immune defect could be present in influenza patients, increasing the susceptibility towards these pathogens, which is currently under investigation [35]. Our data indicates that although pulmonary co-infections are more often observed in ICU patients, compared with patients at the normal ward, this is not necessarily associated with increased mortality. The majority of previous studies illustrate increased mortality resulting from infections with *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Aspergillus* spp. following influenza infection [4,36,37]. Possibly, the increased mortality could not be demonstrated due to the low number of patients in the current study. Of note, we cannot exclude that the high incidence of pulmonary fungal and bacterial co-infections in the current study is related to selection bias, because both selected hospitals for this study are tertiary hospitals, generally receiving the most severely ill influenza patients.

In our population, in-hospital mortality was 9% and ICU mortality reached 38%. The majority of patients died from therapy-resistant respiratory failure and multi-organ failure. These relatively high mortality rates may be attributed to the influenza virus itself. However, the 2015–2016 seasonal influenza epidemic in the Netherlands did not result in increased mortality compared with previous seasonal outbreaks (RIVM, Rapport 2016–0071). More likely, this high in-hospital and ICU-associated mortality is a reflection of the referral function of a university medical center.

Other limitations to our study include the large spreading of some data and relatively small sample size of the study cohort, arising from one seasonal outbreak and subsequently limited events in the regression models. Also, the method of analyses could have influenced the data. In the current study, we used the Frequentist interpretation that views probability as the limit of the relative frequency of an event after a large number of trials. This instead of for example the Bayesian approach in which the conditional probability of an event based on data as well as prior information about the event or conditions related to the event is taken into account. All factors above have influenced the scientific impact of the data. However, even with the limited number of study subjects, independent risk factors and several statistical significant relationships were identified using a multivariate logistic regression analysis. However, complications logically occur in the most severely ill and one could suggest that these factors would therefore merely reflect disease severity than being true risk factors. Nevertheless, despite the limited validity due to large spreading and small sample sizes, the identified factors may contribute to a complicated disease course and could represent a tool for early recognition of the influenza patients at risk for a complicated disease course.

5. Conclusions

The current study indicates that a history of OSAS/CSAS, myocardial infarction, dyspnea, influenza type A, BMI > 30, the development of renal failure and bacterial and fungal co-infections, were observed more frequently in influenza patients who were admitted to the ICU, compared with patients at the normal ward. Also, pulmonary co-infections were observed more often in ICU patients, mainly caused by *Staphylococcus aureus*, *Streptococcus pneumoniae*, and *Aspergillus fumigatus*. Last, non-survivors suffered from diabetes mellitus and (pre-existent) renal failure more often.

Ethics approval and consent to participate

This study was approved by the local medical ethics committee ((METC 16–4-195 and CMO 2016–2777)). Informed consent for each patient was waived because of the anonymous nature of the data.

Availability of data and material

The datasets used and analyzed in the current study are available at the corresponding author on reasonable request. All data generated or analyzed during this study are included in this published article.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

MCB: Drafting/revising the manuscript, statistical analysis and interpretation of data. RMK: Drafting/revising the manuscript, interpretation of data. DVB, AMOL, FLV, EK, JGH and DCB: Revising the manuscript. CWEH: Revising the manuscript, statistical analysis and interpretation of data, accepts responsibility for conduct of research and final approval.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2018.11.013.

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