Predictors of severity and in-hospital mortality in patients with influenza

Mariana Serino[1], Nuno Melo[2], João Paulo Caldas[3], Ana Ferreira[2], David Garcia[4], Patrícia Lourenço[2]

[1]Department of Pneumology; [2]Department of Internal Medicine; [3]Department of Infectious Diseases; [4]Department of Clinical Pathology, Centro Hospitalar Universitário de São João, E.P.E., Porto, Portugal

Abstract

Influenza virus is a common agent of acute respiratoty infections during epidemic periods. It is a major cause of morbidity and mortality and represent a significant burden on the healthcare system. We aimed to evaluate predictors of severity and of in-hospital mortality in patients hospitalized with influenza infection. We performed a retrospective cohort study of hospitalized, laboratory confirmed cases of influenza disease in Centro Hospitalar de São João between October 2016-May 2017 and October 2017-May 2018. The endpoints being analysed were severity and in-hospital mortality. A multivariate logistic regression analysis was used to determine independent predictors of severity and of in-hospital mortality. We studied 221 hospitalized influenza infection cases. Mean age 66±16 years, 57.9% were male, thirty-seven patients (16.7%) died in-hospital and 101 patients (45.7%) met severity criteria. C-reactive protein (CRP) was the only independent predictor of severity as well as the only independent predictor of higher in-hospital mortality in patients admitted due to influenza infection. Multivariate-adjusted CRP OR for severity was 1.10, 95% CI 1.06-1.15 per each 10 mg/L increase in CPR and for in-hospital mortality risk the OR was of 1.05, 95% CI 1.01-1.09, p=0.01, per each 10 mg/L increase. Concluding, in patients' hospital-admitted due to influenza infection CRP was the only predictor of severity with a 10% increased risk of inotropic support/ventilatory support/prolonged hospitalization needs and a 5% increased risk of in-hospital death per each 10 mg/l increase.

Correspondence: Mariana Serino, Department of Pneumology, Centro Hospitalar Universitário de São João, E.P.E., Porto, Portugal.
Tel. +351.914482831.
E-mail: mariana.serino@gmail.com

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Introduction

Seasonal influenza is an acute respiratory illness caused by influenza A or B viruses [1,2]. Outbreaks of influenza occur mainly during the winter months and represent a significant burden to the healthcare system [2,3]. The European Center for Disease Prevention and Control (ECDC) reported 146 184 and 240 000 influenza virus detections during the 2016–2017 and 2017–2018 influenza seasons, respectively [4]. The Portuguese Laboratory Network for Influenza Diagnosis reported 1702 seasonal influenza confirmed cases during the epidemic season of 2016-2017 [5] and 3715 during the 2017-2018 season [6]. During these two epidemic seasons an excess of all-cause mortality was reported, mainly among people aged 65 years or older [5,6].

Influenza infection usually presents with constitutional symptoms and manifestations of respiratory tract illness and it is commonly a self-limited infection. Some patients, however, develop complications and substantial morbidity and mortality [1,7]. Old age (65 years and older) and people of any age with certain chronic comorbidities are particularly vulnerable to severe disease with influenza virus infection [1,7,8]. Some of the chronic conditions that can increase susceptibility to severe disease are chronic lung disease, heart disease, diabetes mellitus, obesity, immunosuppressive conditions and being resident in a nursing home or other chronic care facility [1,7,8].

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Influenza vaccination is the most effective way to prevent influenza disease and its complications [7,9,10]. It is recommended that all individuals older than 6 months be vaccinated annually, especially the high-risk groups [10]. Influenza vaccines are updated annually, including viral strains that are predicted to circulate in that year [10,11]. Early antiviral treatment is recommended for patients at high-risk of complications and those requiring hospitalization with suspected or confirmed influenza [9-12]. Antiviral therapy appears to reduce symptoms' duration, length of hospital stay, complications from influenza infection and influenza-associated mortality [9,10,13-15].

Groups requiring vaccination and high-risk groups in need of early antiviral therapy are reasonably established. Predictors of in-hospital mortality and severity are not so consensual. We aimed to evaluate predictors of severity in adult patients with influenza infection, as well as to identify potential predictors of in-hospital mortality in these patients.

Materials and Methods

We conducted a retrospective cohort study in adult patients with laboratory confirmed cases of influenza in Centro Hospitalar Universitário de São João (CHUSJ), a Portuguese tertiary care academic hospital, between October 2016-May 2017 and October 2017-May 2018. All cases considered presented, besides clinical suspicion of influenza infection, at least one laboratory-confirmed sample. Laboratory confirmation of influenza virus infection was based in reverse transcription-polymerase chain reaction test performed in nasopharyngeal swabs and by immunofluorescence tests performed in sputum samples and bronchial/bronchoalveolar lavage fluids. In order to determine predictors of severity and in-hospital mortality, we analysed the group of confirmed cases needing hospitalization. Non-hospitalized patients were excluded from the analysis despite positivity for influenza virus. Patients under 18 years were also excluded from the analysis. Demographic data, comorbidities, clinical and laboratorial admission data, influenza vaccination status, oseltamivir treatment and in-hospital mortality were gathered from individual medical records. Prolonged hospital stay was considered when patients were in hospital for at least 30 days. Severity was defined as the composite endpoint of need of mechanical ventilation, invasive or non-invasive; need of vasopressor support; or prolonged hospitalization. The endpoints being analysed were severity and in-hospital mortality. Severe and non-severe groups were created; patients were also divided in fatality and non-fatality. Groups of patients were compared.

Due to the retrospective nature of the study, informed consent was waived by the Ethics and Health Committee of Centro Hospitalar Universitário de São João. The registry's protocol conforms to the ethical guidelines of the declaration of Helsinki and it was approved by the Ethics and Health Committee of Centro Hospitalar Universitário de São João.

Statistical analysis

A chi square test was used for categorical variables, an independent samples t-test for continuous variables with a normal distribution and the Mann-Whitney U test for highly skewed distributed continuous variables. Multivariate logistic regression models were built in order to determine independent predictors of severity and independent predictors of in-hospital mortality. Variables considered in each model were those differently distributed between severe/non-severe and dead/survivors.

The p-value considered for statistical significance was 0.05. Data was stored and analyzed using SPSS software (IBM Corp., Armonk, NY, USA, version 20.0).

Results

Patients' characteristics

There were 221 cases of influenza confirmed infection that needed hospitalization in CHUSJ during the epidemic periods of 2016-2017 and 2017-2018. Patients' characteristics are described in Table 1. Mean age was 66±16 years and 128 (57.9%) were male, comorbidity burden was high – 55 (25.1%) patients were obese, 73 (33.0%) had diabetes, 48 (21.7%) had chronic kidney disease (CKD), 59 (26.7%) had heart failure (HF) and 102 (46.2%) chronic pulmonary disease; globally 58 (26.2%) of the patients could be considered as having some degree of immunosuppression for having at least one of the conditions: diabetes, organ transplantation history, active neoplasia, HIV or an autoimmune disease or/and were chronically treated with corticosteroids. One hundred and fifty-five (70%) patients were treated with oseltamivir and 79 (39.1%) patients had been vaccinated for influenza. Median length of hospital stay was 9 days (5-18). Thirty-seven patients (16.7%) died in-hospital and 101 patients (45.7%) met severity criteria.

Comparison between severe and less severe patients

Table 1 compares severe and less severe patients. Severe patients had worse renal function and higher C-reactive protein (CRP) on admission. Patients meeting severity criteria were also more treated with antiviral therapy. Table 2 shows multivariate models of independent predictors of severity. CRP was the only independent predictor of severity in patients admitted due to influenza infection with an OR of inotropic support or mechanical ventilation or prolonged hospitalization need of 1.10, 95% CI 1.06-1.15 per each 10 mg/L increase in CPR.

Comparison between surviving and non-surviving patients

Table 3 compares survivors and patients with in-hospital death. Patients dying in-hospital were significantly older and presented with higher blood urea, higher C-reactive protein and lower lymphocyte counts on admission. Both groups had similar comorbidity burden except for malignant neoplastic disease that was more prevalent among the fatality group. In a multivariate logistic regression model (Table 4) older patients tended to have higher in-hospital mortality (OR=1.03, 95% CI 1.00-1.06, p=0.06, per each 1-year increase). The only variable independently associated with in-hospital mortality was higher C-reactive protein (OR: 1.05, 95% CI 1.01-1.09, p=0.01, per each 10mg/L increase).

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Discussion

In our report on 221 cases of confirmed influenza infection that required hospitalization, the patients were mostly elderly and with a high burden of comorbidities. In-hospital mortality was 16.7% and almost half of the patients met severity criteria. CRP was the only independent predictor of severity and in-hospital mortality. Per each 10mg/L increase in CRP there was a 10% increased severity risk and a 5% increased risk of in-hospital mortality. Severe and less severe patients had similar age and comorbidity burden and the prevalence of influenza A and B was also non-different. There was a trend for severe patients to have lower prior vaccination compared to the non-severe counterparts (32.2% *vs* 44.3%, p-value 0.08). This may, in part, help explain the greater disease severity in

Table 1. Comparison between severe and less severe patients.

Characteristics	All pts (n=221)	Non-severe (n=120)	Severe (n=101)	p-value
Male gender, n (%)	128 (57.9)	69 (57.5)	59 (58.4)	0.89
Age (years), mean ±SD	66±16	66±17	67±13	0.60
Influenza A virus, n (%)	158 (71.5)	87 (72.5)	71 (70.3)	
Influenza B virus, n (%)	63 (28.5)	33 (27.5)	30 (29.7)	0.72
Obesity, n (%)	55 (25.1)	30 (25.0)	25 (25.3)	0.97
Diabetes mellitus, n (%)	73 (33.0)	38 (32.2)	35 (34.7)	0.70
Chronic kidney disease, n (%)	48 (21.7)	29 (24.6)	19 (18.8)	0.30
Atherosclerotic disease, n (%)	72 (32.6)	44 (37.0)	28 (27.7)	0.14
Heart failure, n (%)	59 (26.7)	28 (23.5)	31 (30.7)	0.23
Chronic pulmonary disease, n (%)	102 (46.2)	55 (45.8)	47 (46.5)	0.92
Organ transplantation, n (%)	15 (6.8)	11 (9.2)	4 (4.0)	0.18
Malignant neoplasia, n (%)	45 (20.4)	21 (17.5)	24 (23.8)	0.25
Chronic corticotherapy, n (%)	37 (16.7)	25 (20.8)	12 (11.9)	0.08
Autoimmune disease, n (%)	25 (11.3)	15 (12.5)	10 (9.9)	0.54
HIV infection, n (%)	8 (3.6)	6 (5.0)	2 (2.0)	0.30
Systolic BP (mmHg), mean ±SD	126±26	127±26	123±26	0.29
Heart rate (bpm), mean ±SD	94±21	92±20	96±22	0.28
Creatinine (mg/dL), median (IQR)	0.99 (0.74-1.53)	0.92 (0.64-1.46)	1.09 (0.82-1.59)	0.09
Urea (mg/dL), median (IQR)	49 (33-82)	46 (32-72)	55 (40-96)	0.04
Haemoglobin (g/dL), mean± SD	12.4±2.4	12.5±2.4	12.3±2.5	0.45
Leukocytes (cells/µL), median (IQR)	8480 (5325-11255)	8115 (5212-10700)	8800 (4900-12590)	0.24
Lymphocytes (cells/µL), median (IQR)	770 (520-1210)	840 (538-1270)	720 (495-1150)	0.21
Platelets (cells x10^3/µL), median (IQR)	174 (130-226)	171 (133-221)	177 (117-284)	0.82
C-reactive protein (mg/L), median (IQR)	75.0 (29.9-138.4)	45.6 (20.8-93.4)	106.4 (58.4-201.0)	<0.001
Vaccination status, n (%)	79/202 (39.1)	51/115 (44,3)	28/87 (32.2)	0.08
Oseltamivir treatment, n (%)	155 (70.1)	72 (60.0)	83 (82.2)	<0.001
Inotropic support, n (%)	44 (19.9)			
NIMV, n (%)	76 (34.4)			
IMV, n (%)	28 (17.2)			
LOS (days), median (IQR)	9 (5-19)	6 (4-10)	15 (8-30)	<0.001

BP, blood pressure; bpm, beats per minute; HIV, human immunodeficiency virus; IMV, invasive mechanical ventilation; IQR, interquartile range; NIMV, non-invasive mechanical ventilation; SD, standard deviation.

Table 2. Predictors of severity: multivariate models.

Variable	Model 1*		Model 2#	
	OR (95% CI)	p	OR (95% CI)	p
CRP (per 10 mg/L)	1.11 (1.06-1.15)	<0.001	1.10 (1.06-1.15)	<0.001
Urea (per 10 mg/dL)	1.01 (0.95-1.08)	0.70	1.08 (0.97-1.18)	0.16
Creatinine (per 1 mg/dL)			0.72 (0.48-1.10)	0.13
Chronic corticotherapy			0.46 (0.19-1.16)	0.10
Vaccination status			0.65 (0.34-1.22)	0.18

*Model 1 includes variables differently distributed between groups with a p-value<0.05; #model 2 all variables whose differences translated into a p-value <0.10; CI, Confidence interval; CRP, C-reactive protein; OR, odds ratio.

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the former group, since influenza vaccination can reduce disease severity [1,11].

Although most patients were treated with antiviral drugs, we had higher severity and mortality rates than reported in other studies [16,17]. There is evidence that early antiviral therapy reduces the duration of symptoms as well as influenza-associated complications [11,12,14,15], but the benefit has been questioned in high-risk patients [13]. In our opinion, this may partially justify our results. Nevertheless, we did not analyze the time between symptom onset and antiviral initiation, which could have also impacted on outcomes.

Comparing survivors and non-survivors, patients were older in the latter group, but both groups had similar comorbidity burden except for malignant neoplastic disease. Cancer was more prevalent among the fatality group. Malignant neoplastic disease and its treatments are associated with immunosuppression and disability; this, and the high mortality of neoplastic diseases may justify these results [18]. Upon admission, the non-survivor group presented with higher blood urea, lower lymphocyte counts and higher C-reactive protein. Similar laboratory results have been previously reported and associated with mortality [8]. However, the only variable independently associated with in-hospital mortality was the highest C-reactive protein, reinforcing its potential role as a predictor of severity and in-hospital mortality in influenza infection. Other studies have also suggested this association [16-20], but as far as the extensive literature can recover, we evaluated a larger number of adult patients hospitalized with confirmed influenza infection. Canak *et al*. [17], in particular, performed a retrospective study on 293 influenza patients

Table 3. Comparison between survivors and patients dying in-hospital.

Characteristics	Survivors (n=184)	In-hospital death (n=37)	p-value
Male gender, n (%)	104 (56.5)	24 (64.9)	0.35
Age (years), mean ±SD	66±16.0	71±13	0.04
Influenza A virus, n (%)	135 (73.4)	23 (62.2)	
Influenza B virus, n (%)	49 (26.6)	14 (37.9)	0.17
Obesity, n (%)	47 (25.5)	8 (21.6)	0.66
Diabetes mellitus, n (%)	58 (31.5)	15 (40.5)	0.31
Chronic kidney disease, n (%)	39 (21.2)	9 (24.3)	0.70
Atherosclerotic disease, n (%)	58 (31.5)	14 (37.8)	0.47
Heart failure, n (%)	45 (24.4)	14 (37.8)	0.10
Chronic pulmonary disease, n (%)	85 (46.2)	17 (45.9)	0.98
Organ transplantation, n (%)	11 (6.0)	4 (10.8)	0.29
Malignant neoplasia, n (%)	33 (7.9)	12 (32.4)	0.05
Chronic corticotherapy, n (%)	28 (15.2)	9 (24.3)	0.18
Autoimmune disease, n (%)	22 (12.0)	3 (8.1)	0.78
HIV infection, n (%)	7 (3.8)	1 (2.7)	1.00
Systolic BP (mmHg), mean ±SD	127±27	120±25	0.17
Heart rate (bpm), mean ±SD	94±21	94±22	0.93
Creatinine (mg/dL), median (IQR)	0.96 (0.70-1.48)	1.10 (0.84-1.68)	0.15
Urea (mg/dL), median (IQR)	46 (31-76)	58 (44-102)	0.02
Haemoglobin (g/dL), mean ±SD	12.5±2.3	11.9±2.8	0.14
Leukocytes (cells/µL), median (IQR)	8420 (5412-11208)	8680 (4530-12025)	0.87
Lymphocytes (cells/µL), median (IQR)	840 (560-1260)	565 (482-805)	0.05
Platelets (cells x10^3/µL), median (IQR)	174 (134-222)	171 (102-248)	0.72
C-reactive protein (mg/L), median (IQR)	64.8 (25.8-136.8)	112.8 (81.0-183.1)	0.001
Vaccination status, n (%)	70/177 (39.5)	9/25 (36.0)	0.73
Oseltamivir treatment, n (%)	125 (67.9)	30 (81.1)	0.11

BP, blood pressure; bpm, beats per minute; HIV, human immunodeficiency virus; IQR, interquartile range; LOS, length of hospital stay; SD, standard deviation.

Table 4. Predictors of in-hospital mortality in patients with influenza virus infection: multivariate model.

Variable	OR (95% CI)	p
CRP (per 10 mg/L)	1.05 (1.01-1.09)	0.001
Age (per year)	1.03 (1.00-1.06)	0.06
Urea (per 10 mg/dL)	1.02 (0.94-1.12)	0.58
Lymphocytes (per 100 cell/µL)	0.98 (0.91-1.05)	0.59
Malignant neoplasia	1.79 (0.74-4.29)	0.19

CI, confidence interval; CRP, C-reactive protein; OR, odds ratio.

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and reported higher CPR levels in patients admitted to ICU than in those not admitted to ICU. Despite the greater number of patients studied, the population included many pediatric patients and only 4.1% of them had confirmed influenza infection. Also, no multivariate adjustment was made to assess the independent prognostic role of CRP and death occurred in only 2 patients precluding any assumption concerning the impact of CRP in mortality. These results suggest that knowledge of CRP at admission of patients with influenza infection can be a useful tool to predict the course of the disease and to define the management of patients. CRP is produced in the liver in response to pro-inflammatory cytokines released after the onset of infection [19,21,22]. Cytokine levels may be related to viral load and an excessive activation of the inflammatory cascade could play a role in the pathogenesis of influenza [19,21]. CRP as a surrogate marker of inflammatory activation, has been widely suggested as a prognostic marker in cardiovascular diseases; if it is a causal agent or an innocent bystander is still an unanswered question [23]. A similar thought can be transposed to our group of patients with elevated chronic disease burden that were hospitalized due to an acute influenza infection. It is possible that an acute superimposed bacterial infection could have contributed to the CRP elevation, however, we cannot exclude that, in an already elder group of patients with pro-inflammatory conditions, the exacerbated inflammation might have contributed to the overall gloomy outcome.

The present study has some limitations. Being a single center study of a small sample size poses generalizability concerns. Data were collected retrospectively from individual medical records; this has inherent problems, namely related with the quality of the registries. Data on timing of antiviral treatment initiation were not taken into consideration and this may have also impacted on mortality and overall outcome. Severity and in-hospital mortality were considered attributable to influenza infection; however, it is possible that not all the endpoints were directly related to influenza. Decompensation of comorbidities and hospital superinfections may justify some of the events. Also, we did not consider superimposed pneumonia or other bacterial infections complicating influenza. Superimposed bacterial infections could have contributed to both, a CRP elevation and the outcome.

Despite the aforementioned limitations, CRP appears to be consistently associated with the outcome of influenza infection. Our results suggest that CRP can be explored as an early biomarker in the identification of hospitalized influenza patients at high risk of complications and death.

Conclusions

Higher CRP was the only independent predictor of severity and in-hospital mortality in patients with influenza. Further studies should assess CRP as an early predictor of disease severity.

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