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ORIGINAL

Corticosteroid treatment in critically ill patients with severe influenza pneumonia: a propensity score matching study

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Abstract

Purpose: To determine clinical predictors associated with corticosteroid administration and its association with ICU mortality in critically ill patients with severe influenza pneumonia.

Methods: Secondary analysis of a prospective cohort study of critically ill patients with confirmed influenza pneumonia admitted to 148 ICUs in Spain between June 2009 and April 2014. Patients who received corticosteroid treatment for causes other than viral pneumonia (e.g., refractory septic shock and asthma or chronic obstructive pulmonary disease [COPD] exacerbation) were excluded. Patients with corticosteroid therapy were compared with those without corticosteroid therapy. We use a propensity score (PS) matching analysis to reduce confounding factors. The primary outcome was ICU mortality. Cox proportional hazards and competing risks analysis was performed to assess the impact of corticosteroids on ICU mortality.

Results: A total of 1846 patients with primary influenza pneumonia were enrolled. Corticosteroids were administered in 604 (32.7%) patients, with methylprednisolone the most frequently used corticosteroid (578/604 [95.7%]). The median daily dose was equivalent to 80 mg of methylprednisolone (IQR 60–120) for a median duration of 7 days (IQR 5–10). Asthma, COPD, hematological disease, and the need for mechanical ventilation were independently associated with corticosteroid use. Crude ICU mortality was higher in patients who received corticosteroids (27.5%) than in patients who did not receive corticosteroids (18.8%, $p < 0.001$). After PS matching, corticosteroid use was associated with ICU mortality in the Cox (HR = 1.32 [95% CI 1.08–1.60], $p < 0.006$) and competing risks analysis (SHR = 1.37 [95% CI 1.12–1.68], $p = 0.001$).

Conclusion: Administration of corticosteroids in patients with severe influenza pneumonia is associated with increased ICU mortality, and these agents should not be used as co-adjuvant therapy.

Keywords: Influenza, Pneumonia, Corticosteroids, ICU, Mortality

Introduction

Pneumonia caused by the influenza A(H1N1)pdm09 virus infection may lead to life-threatening acute respiratory failure (ARF) and acute respiratory distress syndrome (ARDS). Antiviral therapy is the cornerstone of

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treatment for influenza pneumonia [1–3]; in addition, intravenous corticosteroids have been used as co-adjuvant therapy in patients with ARF/ARDS to modulate lung inflammation and improve clinical outcomes [4–8]. However, no randomized clinical trials have investigated the potential benefit or harm of corticosteroid therapy for ARF/ARDS due to acute influenza pneumonia.

During the 2009 H1N1 pandemic, corticosteroids were widely used despite contradictory [9, 10], unfavorable [7, 9–11], or inconclusive [12, 13] available data. A recent Cochrane review [14] concluded that co-adjuvant corticosteroid therapy was associated with increased mortality in patients with influenza pneumonia. However, the data were derived from observational studies of very low quality and with several methodological limitations, including other clinical indications of corticosteroids as a major potential concern. Thus, it is impossible to be sure that patients who were treated with corticosteroids did not have other corticosteroid indications or were not more severely ill in the first place. We have previously reported that corticosteroid therapy does not improve survival in patients with primary viral pneumonia [12]. However, in that observational study, we assessed the effects of corticosteroid therapy on survival between patients who were and were not treated, but we did not apply a statistical method that would have balanced all the variables between the two groups. Therefore, the aim of the present study was to identify the factors associated with corticosteroid use and its impact on intensive care unit (ICU) mortality using propensity score (PS) matching analysis in ICU patients with influenza pneumonia. Preliminary results of this analysis were presented in the 38th International Symposium on Intensive Care and Emergency Medicine [15].

Take-home message

Systemic corticosteroids have been widely used as co-adjuvant therapy in patients ARF/ARDS due to influenza pneumonia to modulate lung inflammation, despite controversy on clinical outcomes. Our findings provide solid evidence to support the association of corticosteroids administration with increased ICU mortality in critically ill patients with influenza pneumonia.

Materials and methods

Study participants

This was a secondary analysis of prospective and observational cohorts of critically ill subjects admitted to 148 ICUs in Spain (which represents approximately 50% of the country's ICUs) between June 2009 and April 2014. Data were obtained from a voluntary registry created by SEMICYUC (Sociedad Española de Medicina Intensiva, Crítica y Unidades Coronarias). All consecutive cases admitted to the ICU were collected.

The study was approved by the Joan XXIII University Hospital Ethics Committee (IRB#11809). Patient identity remained anonymous, and the requirement for informed consent was waived due to the observational nature of the study, as reported elsewhere [3, 16–20].

Inclusion criteria Participants included patients admitted with fever (> 38 °C); respiratory symptoms consistent with cough, sore throat, myalgia, or influenza-like illness; acute respiratory failure requiring ICU admission; and microbiological confirmation of viral A, B, or C infection identified by reverse transcription polymerase chain reaction (rt-PCR) at ICU admission. Data were reported by the attending physician reviewing medical charts and radiological and laboratory records. The attending physician ordered all tests and procedures related to patient care.

Exclusion criteria Patients receiving corticosteroids as rescue therapy (due to shock) or due to chronic obstructive pulmonary disease (COPD)/asthma exacerbation were excluded (see definition below). Children < 15 years old were not enrolled in the study. Patients with non-pulmonary influenza infection and those with healthcare-associated pneumonia were also excluded.

The following variables were recorded at ICU admission: demographic data, comorbidities, time from illness onset to hospital admission, time to first dose of antiviral delivery, microbiological findings, and laboratory and chest radiological findings at ICU admission (all the collected variables are reported in e-Table 1 of the supplementary material). To determine illness severity, the Acute Physiology and Chronic Health Evaluation (APACHE) II score [21] was estimated for all patients within 24 h of ICU admission. Organ failure was assessed using the Sequential Organ Failure Assessment (SOFA) scoring system [22], also at ICU admission. The indication of corticosteroid treatment was clearly reported in the case report form and was confirmed by the medical records.

Study definitions

Community-acquired pneumonia (CAP) was defined in accordance with current American Thoracic Society and Infectious Diseases Society of America guidelines (ATS/IDSA) [23].

The rt-PCR test for influenza was carried out in accordance with the guidelines of the Centers for Disease Control and Prevention (CDC) [24].

Primary viral pneumonia was defined as acute respiratory failure and unequivocal alveolar opacities involving two or more lobes, with negative respiratory and blood bacterial cultures during the acute phase of influenza virus infection at ICU admission [5].

COPD "exacerbation" was defined according to COPD exacerbation guidelines of the European Respiratory Society/ATS [25] as increased respiratory symptoms, particularly dyspnea, cough, and increased sputum purulence without pulmonary infiltrates in chest X-ray. COPD patients with pulmonary infiltrates in chest X-ray were considered as CAP and were included in the present analysis.

Asthma exacerbation was defined as acute or subacute episodes characterized by a progressive increase in one or more typical asthmatic symptoms (dyspnea, coughing, wheezing, and tightness of the chest [26] without infiltrates in the chest X-ray. Asthmatic patients with pulmonary infiltrates in chest X-ray were considered as CAP and were included in the present analysis.

Community-acquired respiratory co-infection (CARC) was considered in patients with confirmation of influenza virus infection showing recurrence of fever, increase in cough and production of purulent sputum plus positive bacterial/fungal respiratory or blood cultures at ICU admission [27, 28].

Refractory septic shock was defined in accordance with the Surviving Sepsis Campaign guidelines [29]; that is, patients in whom adequate fluid resuscitation and vasopressor therapy are unable to restore hemodynamic stability.

Ventilator-associated pneumonia was defined according to the new ATS/IDSA guidelines [30] among ICU patients who developed a new pneumonic event while mechanically ventilated for at least 48 h after clinical presentation.

Corticosteroid treatment: we considered the primary indication recorded by the treating physician as co-adjuvant treatment for viral pneumonia. Corticosteroid therapy was defined as corticosteroid administration at ICU admission (within the first 24 h). Patients receiving corticosteroids as rescue therapy (due to shock) or due to COPD/asthma exacerbation were excluded (see exclusion criteria).

Obese patients were defined as those with a body mass index (BMI) of >30 kg/m^2.

The ICU admission criteria and treatment decisions for all patients, including the decision to intubate and type of antibiotic, antiviral, or corticosteroid therapy administered, were not standardized between centers and were left to the discretion of the attending physician, according to the Spanish Society of Intensive Care recommendations [31].

Endpoints

Primary To determine whether corticosteroid use was associated with ICU mortality. In addition, the primary outcome was examined in eight pre-specified subgroups defined according to the following baseline characteristics: (1) severity of illness (APACHE score <15 vs. ≥ 15), (2) intensity of organ dysfunction (SOFA <5 vs. ≥ 5), (3) presence of shock upon ICU (yes vs. no), (4) need for mechanical ventilation (MV) upon ICU admission (yes vs. no), (5) inflammatory response to C-reactive protein (CRP <25 vs. ≥ 25 mg/dL), (6) presence of bacterial co-infection (yes vs. no), (7) chronic lung disease such as COPD (yes vs. no), and (8) asthma (yes vs. no). The cut-off for continuous variables was determined according to our population median value.

Secondary To determine risk factors associated with corticosteroid use. ICU length of stay (LOS) and MV days were also examined in survivors between groups receiving and not receiving corticosteroid therapy.

Statistical analysis

Discrete variables were expressed as counts (percentage) and continuous variables as means with standard deviation (SD) or medians and interquartile range 25–75% (IQR). For patient demographics and clinical characteristics, differences between groups were assessed using the chi-squared test and Fisher's exact test for categorical variables, and the Student t test or the Mann–Whitney U test for continuous variables.

To investigate the association between baseline (ICU admission) variables and corticosteroid use, a multivariate analysis (binary logistic regression) was performed. The multivariate model comprised factors of clinical interest and all significant covariates in the univariate analysis. The results are presented as odds ratios (OR) and 95% confidence intervals (CI). Model integrity was examined using standard diagnostic statistics and plots and goodness of fit for each model for all outcomes, and was assessed with the Hosmer–Lemeshow test.

After this first approach, we generated a full-matching PS analysis in order to minimize the effect of a corticosteroid treatment selection bias and to control for potential confounding factors (additional information about the PS full-matching analysis can be found in the electronic supplementary material) [32]. This allowed us to study two comparable (almost identical) cohorts: (1) the corticosteroid-treated group and (2) the control group, comprising patients who did not receive corticosteroid treatment. PS matching analysis attempts to compare outcomes between patients who have a similar distribution of all the covariates measured. An attractive feature of this approach is that it uses the entire sample. Using the PS methodology, all patients were assigned a weight between 0 and 1; this propensity-matched cohort was generated by choosing the best weight balance. This method optimizes the post-weighting balance of covariates between groups and, in this way, approximates the

conditions of random site-of-treatment assignment. To assess our PS adjustment, we checked for adequate overlap in propensity scores between groups with a cross-validation model. To do so, we divided the patients in the database into two subsets: (a) a "training set" with 1466 patients (80%), and (b) a "validation set" with 366 patients (20%).

After the matching, a Kaplan–Meier survival plot was generated to track ICU mortality over time for corticosteroid-treated and untreated patients. In addition, Cox proportional hazards regression models were fitted to assess the impact of corticosteroids on ICU mortality. The results are presented as hazard ratios (HR) and 95% CI and adjusted survival plots. Because Cox hazard survival analysis is not satisfactory for describing ICU patient mortality over time [33], we performed a competing risks analysis to confirm our results. First, we computed the cumulative incidence function (CIF) of death over time. At time *t*, the CIF defines the probability of dying in the ICU by that time *t* when the population can be discharged alive. The CIF was estimated from the data using the *cmprsk* package developed by Gray [34]. We used the Fine and Gray model [35], which extends the Cox model to competing risks data by considering the sub-distribution hazard (for instance, the hazard function associated with the CIF). The strength of the association between each variable and the outcome was assessed using the sub-hazard ratio (SHR), which is the ratio of hazards associated with the CIF in the presence of and in the absence of a prognostic factor.

In order to avoid spurious associations, the variables that we entered in the regression models were those with a relationship in the univariate analysis ($p<0.05$) or a plausible relationship with the dependent variable. Data analysis was performed using SPSS for Windows version 22.0 (IBM Corp., Armonk, NY, USA). Mixed-effects models were performed with R (cran.r-project.org).

Results

A total of 2684 patients with confirmed influenza pneumonia were enrolled at 148 ICUs in Spain during the study period (2009–2014). Of these, 1846 (68.7%) met the inclusion criteria and were included in the study (Fig. 1).

Comparison between subjects with and without corticosteroid therapy

Among 604 patients with corticosteroid therapy, 578 (95.7%) received methylprednisolone, 23 (3.8%) prednisolone, and three (0.5%) dexamethasone. For all patients who received therapy with corticosteroids due to pneumonia, this was initiated within the first 24 h of ICU admission. Patients received a median (interquartile range [IQR]) daily dose equivalent to 80 (60–120) mg of methylprednisolone, and the median duration of corticosteroid treatment was 7 (5–10) days. The frequency of corticosteroid treatment by study period was 34.9% in 2009, 39.6% in 2010, 29% in 2013, and 31.4% in 2014. Considering the 2009 period as baseline, we observed that only in 2013 was there a significant reduction ($p=0.02$) in the indication of corticosteroid treatment as co-adjuvant therapy for pneumonia. No differences in the rate of ventilator-associated pneumonia were observed between patients with ($n=46$, 7.6%) and without ($n=80$, 6.4%) corticosteroid therapy.

Clinical characteristics of patients and their distribution in the two groups are shown in Table 1. Patients

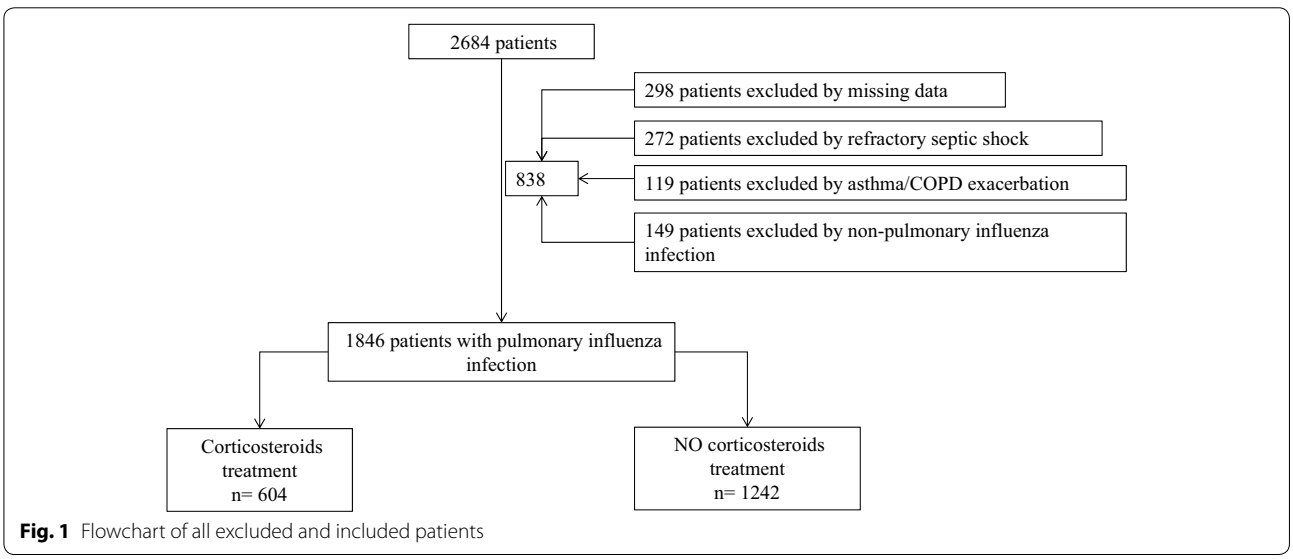

Fig. 1 Flowchart of all excluded and included patients

Table 1 Clinical characteristics of 1846 patients with influenza pneumonia included in the study according to receipt of corticosteroid treatment

Variable	Corticosteroids yes ($n=604$)	Corticosteroids no ($n=1242$)	p value
Demographic factors and severity of illness			
Age, median (IQR), years	53 (41–62)	51 (39–61)	0.08
Male gender, *n* (%)	357 (59.1)	739 (59.5)	0.77
APACHE II score, median (IQR)	15 (10–20)	14 (10–19)	0.004
SOFA score, median (IQR)	5 (4–8)	5 (3–8)	0.33
Delay in hospital admission, mean (SD)	4 (2–6)	4 (2–6)	0.64
Quadrants with infiltrates in chest X-ray, median (IQR)	2 (2–4)	2 (2–4)	0.19
Oseltamivir treatment, *n* (%)	591 (97.8)	1198 (96.8)	0.13
Laboratory test results at ICU admission			
LDH, median (IQR), UI	584 (386–924)	608 (373–969)	0.45
WBC, median (IQR) ($\times 10^9$/L)	8.1 (4.6–12.9)	7.6 (4.3–12.1)	0.17
PCT, median (IQR) (ng/mL)	0.5 (0.2–2.0)	0.7 (0.2–3.8)	0.02
CRP, median (IQR) (mg/dL)	27 (12–80)	29 (14–105)	0.23
Comorbidities and risk factors, *n* (%)			
Asthma	79 (13.1)	75 (6.0)	0.001
COPD	154 (25.5)	178 (14.5)	0.001
Chronic heart disease	56 (9.3)	126 (10.1)	0.54
Chronic renal failure	53 (8.8)	98 (7.9)	0.52
Hematological disease	65 (10.8)	68 (5.5)	0.001
Pregnancy	21 (3.5)	52 (4.2)	0.45
Obesity	221 (36.8)	387 (31.2)	0.02
Complications, *n* (%)			
Acute kidney injury	128 (21.2)	284 (22.9)	0.44
Mechanical ventilation	506 (83.8)	921 (74.2)	0.001
Primary viral pneumonia	465 (77.0)	994 (80.0)	0.13
Bacterial co-infection	139 (23.0)	248 (20.0)	0.13
Ventilator-associated pneumonia	46 (7.6)	80 (6.4)	0.34
Shock at ICU admission	313 (52.2)	624 (50.2)	0.56
Outcomes			
Mechanical ventilation days[a], median (IQR)	8 (3–17)	8 (3–16)	0.96
ICU length of stay[a], median (IQR) days	10 (5–19)	8 (5–18)	0.50
ICU mortality rate, *n* (%)	166 (27.5)	234 (18.8)	0.001

IQR interquartile range, *APACHE II* Acute Physiology and Chronic Health Evaluation II score, *SOFA* Sequential Organ Failure Assessment, *SD* standard deviation, *ICU* intensive care unit, *LDH* lactate dehydrogenase, *WBC* white blood cells, *PCT* procalcitonin, *CRP* C-reactive protein, *COPD* chronic obstructive pulmonary disease

[a] Only in survival population

who received corticosteroid therapy were sicker according to the APACHE II score, more obese, and more likely to have asthma, COPD, and hematological diseases than those who did not receive treatment. MV use, serum procalcitonin concentrations, and ICU mortality rate were higher in patients who received corticosteroids. There were no significant differences between groups regarding ICU LOS or MV days. No other differences were found between the groups. Overall mortality was 21.6% (400/1846).

Factors for corticosteroid use in subjects with influenza pneumonia infection

To determine factors associated with corticosteroid use, a stepwise logistic regression model was performed. APACHE II score, asthma, COPD, obesity, hematological disease, and MV were the independent variables included in the model. As shown in Table 2, MV (OR = 1.78), asthma (OR = 2.38), COPD (OR = 2.10), and hematological disease (OR = 2.51) were independently associated with corticosteroid use.

Table 2 Multivariate analysis for factors associated with corticosteroid therapy

Variable	OR	95% CI	*p* value
APACHE II score	1.002	0.98–1.01	0.79
Asthma	2.38	1.68–3.38	0.001
COPD	2.10	1.63–2.71	0.001
Hematological disease	2.51	1.72–3.68	0.001
Mechanical ventilation	1.78	1.35–2.35	0.001
Obesity	1.16	0.93–1.40	0.16

APACHE II Acute Physiology and Chronic Health Evaluation II score, *COPD* chronic obstructive pulmonary disease

Mortality analysis

In all, 166 of 604 patients (27.5%) who received corticosteroid therapy died in the ICU, compared with 234 of 1242 (18.8%) patients who did not receive corticosteroids (OR = 1.6 [95% CI 1.3–2.0], $p < 0.001$). There were significant between-group differences in the rate of ICU death (Fig. 2), with the exception of patients with SOFA scores < 5 and CRP < 25 mg/dL, non-ventilated patients, patients with bacterial co-infection, and patients with asthma. Three hundred eighty-seven patients (26%) had CARC at ICU admission, and 111 (28.6%) of them died.

The most frequently isolated microorganism was *Streptococcus pneumoniae* ($n = 190$; 49.1%), followed by *Pseudomonas aeruginosa* ($n = 39$; 10.1%), methicillin-sensitive *Staphylococcus aureus* ($n = 29$; 7.5%), *Aspergillus* spp. ($n = 21$; 5.5%), and *Streptococcus pyogenes* ($n = 15$; 3.9%).

Corticosteroid use was independently associated with ICU mortality (OR = 1.37 [95% CI 1.01–1.87], $p = 0.001$; e-Table 2, supplementary material). Corticosteroid therapy was associated with higher mortality in both A(H1N1)pdm09 virus (27.1% vs. 18.8%, $p = 0.001$) and non A(H1N1)pdm09 (29.8% vs. 19.5%; e-Table 3, supplementary material).

PS matching was applied, and 1242 control and 604 treated patients were matched. The summaries of balance for unmatched and matched data are shown in Table 3 (and e-Fig. 1 in the supplementary material). The APACHE II score, SOFA score, delay at ICU admission, number of quadrants infiltrated in chest X-ray, serum lactate dehydrogenase (LDH), white blood cell (WBC) count, continuous renal replacement therapy (CRRT), serum CRP, MV, shock, chronic heart disease, human immunodeficiency virus (HIV/AIDS), primary viral pneumonia, bacterial co-infection, and corticosteroid use were the variables included in the logistic regression analysis of the PS model.

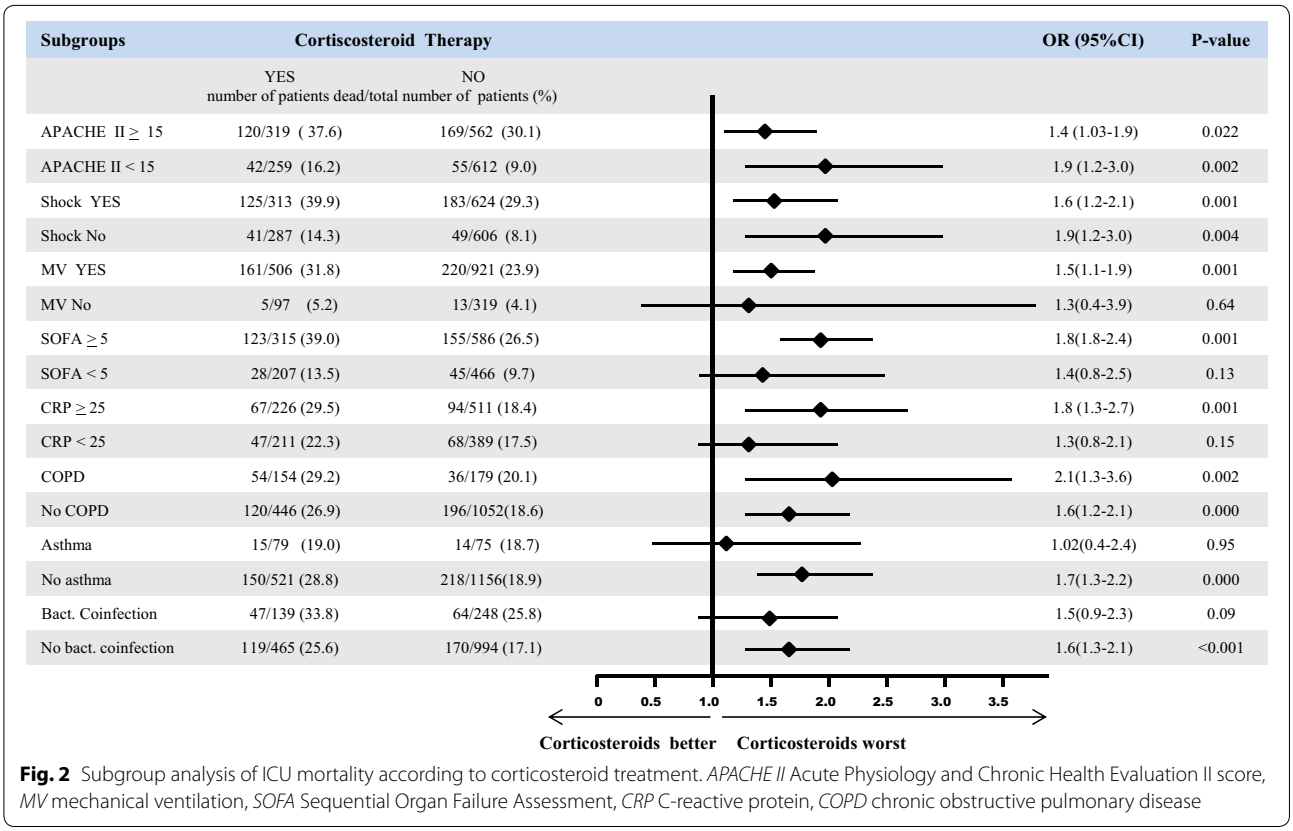

Fig. 2 Subgroup analysis of ICU mortality according to corticosteroid treatment. *APACHE II* Acute Physiology and Chronic Health Evaluation II score, *MV* mechanical ventilation, *SOFA* Sequential Organ Failure Assessment, *CRP* C-reactive protein, *COPD* chronic obstructive pulmonary disease

Table 3 Comparison of baseline characteristics between treated and untreated subjects in the original sample and in the propensity score-matched sample

Baseline variables	Original sample			Matched sample		
	Treated group ($n=604$)	Control group ($n=1242$)	Mean difference	Treated group ($n=604$)	Control group ($n=1242$)	Mean difference
Global distance	0.3726	0.2981	0.0745	0.3726	0.3723	0.0002
Demographics data						
Age	52.1780	51.0113	1.1667	52.1780	51.8061	0.3719
Female	0.4068	0.4042	0.0026	0.4068	0.4156	−0.0088
Male	0.5932	0.5958	−0.0026	0.5932	0.5844	0.0088
Severity of illness						
APACHE II score	16.0763	15.1216	0.9547	16.0763	15.6660	0.4102
SOFA score	5.8797	5.8277	0.0520	5.8797	5.6419	0.2378
Health care and disease						
Delay at hospital admission	4.8610	4.7206	0.14	4.8610	4.6045	0.2565
Delay at ICU admission	2.6864	2.1578	0.5286	2.6864	2.5346	0.1519
Primary viral pneumonia	0.7746	0.8003	−0.0257	0.7746	0.8010	−0.0264
Bacterial co-infection	0.2254	0.1997	0.0257	0.2254	0.1990	0.0264
Number of quadrants infiltrated in chest X-ray	2.4864	2.4308	0.0557	2.4864	2.4880	−0.0016
Laboratory						
Serum LDH levels	832.2373	832.3132	−0.0759	832.2373	837.3178	−5.0805
Serum CPK levels	1633.3464	1564.6452	68.7013	1633.3464	1608.0373	25.3092
WBC count	10,058.1576	9255.0539	803.1037	10,058.1576	10,008.3259	49.8318
Serum PCT levels	6.0390	6.8203	−0.7813	6.0390	5.3273	0.7117
Serum CRP levels	65.1844	75.8709	−10.6865	65.1844	65.3580	−0.1736
Serum urea levels	52.0131	51.5584	0.4547	52.0131	49.5200	2.4931
Comorbidities						
Asthma	0.1305	0.0604	0.0701	0.1305	0.1339	−0.0034
COPD	0.2593	0.1441	0.1152	0.2593	0.2568	0.0025
Chronic heart disease	0.0898	0.1023	−0.0124	0.0898	0.0895	0.0003
Chronic renal disease	0.0864	0.0805	0.0059	0.0864	0.0920	−0.0056
Hematological disease	0.1085	0.0556	0.0529	0.1085	0.0939	0.0146
Pregnancy	0.0356	0.0419	−0.0063	0.0356	0.0400	−0.0406
Diabetes mellitus	0.1712	0.1683	0.0029	0.1712	0.1733	−0.0021
Obesity	0.3695	0.3140	0.0555	0.3695	0.4101	−0.0406
HIV-AIDS	0.0390	0.0193	0.0197	0.0390	0.0224	0.0166
Neuromuscular disease	0.0203	0.0290	−0.0086	0.0203	0.0274	−0.0071
Autoimmune disease	0.0508	0.0298	0.0211	0.0508	0.0497	0.0011
Complications						
Acute kidney failure	0.2102	0.2303	−0.0201	0.2102	0.1977	0.0124
CRRT	0.0983	0.0910	0.0073	0.0983	0.0953	0.0030
Mechanical ventilation	0.8390	0.7432	0.0958	0.8390	0.8587	−0.0197
Shock	0.5153	0.5072	0.0080	0.5153	0.4875	0.0278

APACHE II Acute Physiology and Chronic Health Evaluation II score, *SOFA* Sequential Organ Failure Assessment, *ICU* intensive care unit, *LDH* lactate dehydrogenase, *CPK* creatine phosphokinase, *WBC* white blood cells, *PCT* procalcitonin, *RCP* C-reactive protein, *COPD* chronic obstructive pulmonary disease, *HIV/AIDS* human immunodeficiency virus/acquired immunodeficiency syndrome, *CRRT* continuous renal replacement therapy

The discriminatory power of the model (e-Fig. 2, supplementary material) was good, with an area under the receiver operating characteristic curve of 0.82 (95% CI 0.77–0.87, $p<0.01$). The accuracy of the predictive model (training set) with respect to the validation set was 0.82. e-Figure 3 (supplementary material) shows the Kaplan–Meier estimates of the mortality rate during ICU admission, differentiating between patients with and without corticosteroid use. The cumulative survival was lower in patients with corticosteroid therapy than in untreated patients (log-rank test 560.6, $p<0.001$). When we excluded patients with CARC, the results were similar (log-rank test 5.175, $p=0.02$; e-Fig. 4, supplementary material). However, in patients with CARC, only a trend towards higher mortality related to corticosteroid treatment was observed (log-rank test 0.249, $p=0.61$; e-Fig. 5, supplementary material).

Finally, to determine the impact of corticosteroid use on ICU mortality, a Cox regression analysis adjusted for APACHE II and potential confounding factors (see e-Fig. 6 in supplementary material) was performed. The survival plot (Fig. 3) showed that the use of corticosteroids was significantly associated with a higher ICU mortality rate (HR 1.32 [95% CI 1.08–1.60], $p<0.006$). When a multivariate Fine and Gray regression model was used (Fig. 4 and e-Table 4 in the supplementary material), corticosteroid use remained as a factor associated with mortality (SHR = 1.37 [95% CI 1.12–1.68], $p<0.001$).

Discussion

Our results strongly suggest that administration of corticosteroids as co-adjuvant therapy to standard antiviral treatment in critically ill patients with severe influenza pneumonia is associated with increased ICU mortality. This negative effect was evident in all subgroups considered and after careful adjustments, including a PS matching analysis.

To assess the potential effects of corticosteroids on these severely ill patients, we limited our analysis to a well-defined cohort of ICU patients with severe influenza pneumonia, and excluded those with other indications for corticosteroid use. The effect analysis of corticosteroids was restricted to early administration (within the first 24 h of ICU admission) in order to avoid the inclusion of patients receiving rescue therapy and to reduce the effects of time-dependent confounders. We found that MV, asthma, COPD, and hematological disease were independently associated with corticosteroid use.

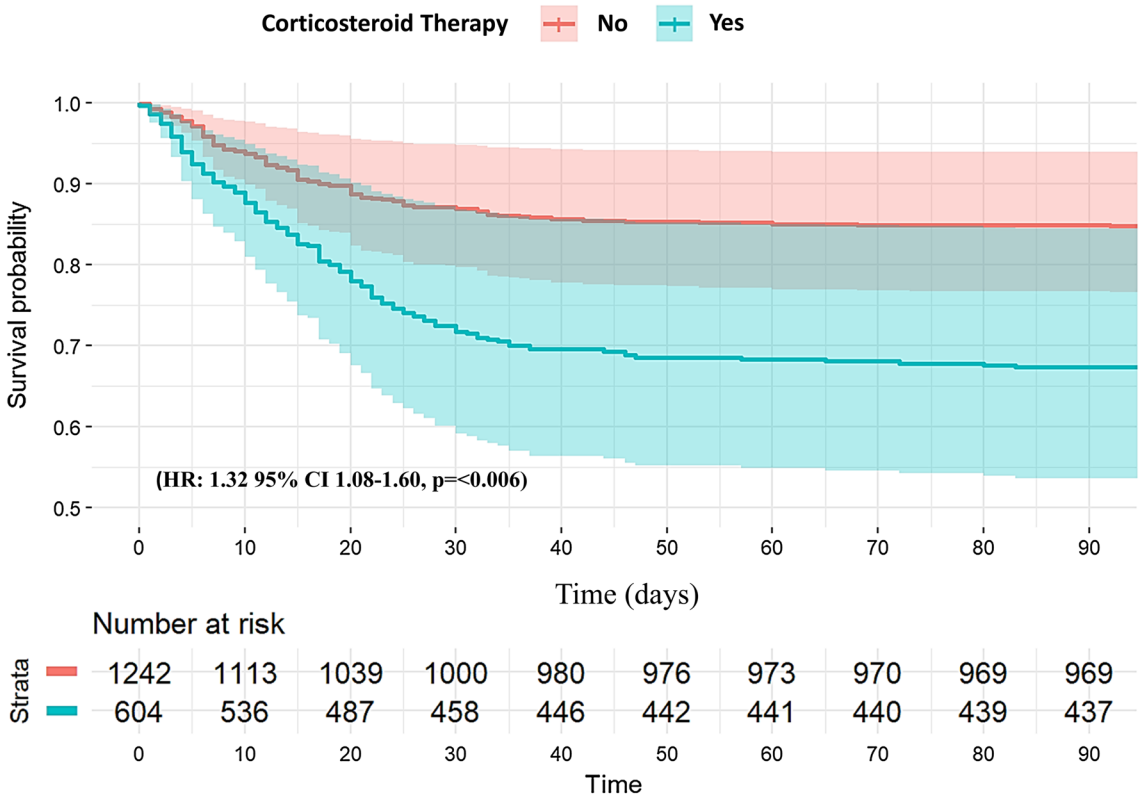

Fig. 3 Cox regression survival plot during ICU admission according to corticosteroid therapy

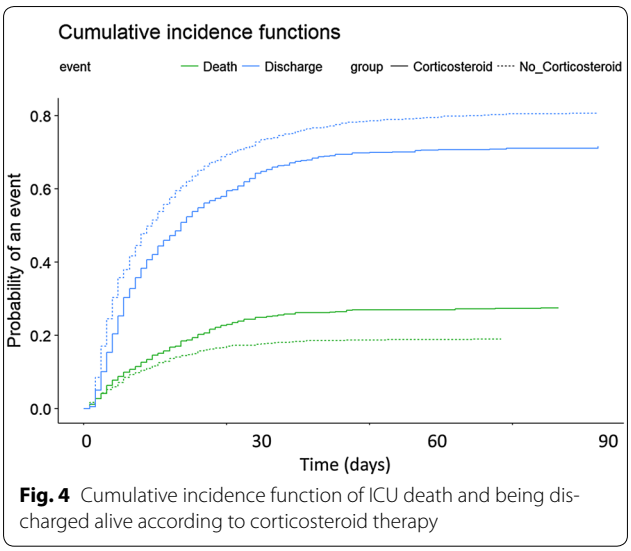

Fig. 4 Cumulative incidence function of ICU death and being discharged alive according to corticosteroid therapy

Severe acute lung injury following influenza infection is characterized by uncontrolled local and systemic inflammation [36–38]. This damage is caused by an excessive host innate response with exaggerated migration of macrophages, neutrophils, and pro-inflammatory cytokines, leading to classic exudative diffuse alveolar damage, severe necrotizing bronchiolitis with predominantly neutrophilic inflammation, and intense alveolar hemorrhage [4]. Corticosteroids have several anti-inflammatory, immunomodulatory, and vascular properties, including inhibition of pro-inflammatory cytokines, reduction of leukocyte trafficking, stimulation of apoptosis in T-lymphocytes, and maintenance of endothelial integrity and vascular permeability. Therefore, they may represent an option for adjunctive therapy; however, although they are frequently prescribed in critically ill patients with influenza pneumonia, their potential benefits and harms are controversial [4, 7, 9, 39, 40].

Three recent systematic reviews and meta-analyses [41–43] concluded that corticosteroid therapy is significantly associated with mortality, even in the subgroup of patients with influenza hospitalized in or outside the ICU. These systematic reviews recognize similar limitations such as the heterogeneity of the studies, lack of sufficient data on indication for corticosteroids, dosage, therapy timing, type of corticosteroid use, and severity of illness. A recent Cochrane review [14] reported an association between corticosteroid therapy and increased mortality. However, all studies included were observational (only seven studies included patients admitted to the ICU) and of very low quality due to confounding by indication. Therefore, it was impossible to determine whether additional corticosteroid therapy is indeed harmful in patients with influenza infection.

Several observational studies have evaluated the impact of corticosteroids on mortality in patients with influenza infection [6–9, 11, 14, 40, 44–46], and have offered conflicting perspectives. Observational studies are potentially susceptible to bias and do not provide robust results. Despite these weaknesses, however, observational data are representative of current clinical practice, and applying modern methods such as PS matching may help in evaluating the effects of certain interventions in clinical settings and may help to guide decision-making.

To the best of our knowledge, only one study has used an analysis similar to ours in patients with influenza infection. In 245 critically ill patients, Kim et al. [11] analyzed the effect of corticosteroid treatment on 90-day mortality with a similar methodology to ours, applying multivariate adjustment (controlling for variables that differed between the two groups and incorporating the PS) and PS matching (1:1). Sixty-five pairs were generated, and the 90-day mortality rate was higher in the corticosteroid group (54% vs. 31%, $p=0.004$). These data are in concordance with our results; however, the mortality rate in our patients was substantially lower. This discrepancy might be due to several factors, including differences in severity of illness, endpoint observational period (ICU mortality vs. 90-day mortality), and early recognition vs. standard of care. Interestingly, Kim et al. reported that half of the patients treated with corticosteroids received hydrocortisone, a non-standard co-adjuvant treatment of pneumonia. The authors did not report the treatment indication for corticosteroid therapy; thus many patients in this cohort may have received corticosteroids for a reason other than influenza-induced acute lung injury. In contrast, our population comprised only patients treated with corticosteroids as an co-adjuvant therapy for severe viral pneumonia, excluding patients with other indications for corticosteroids (such as shock). Therefore, with a homogeneous group of critically ill patients, and after carefully controlling for important confounders through a PS matching analysis and competing risks analysis, we provide robust evidence to support the association between corticosteroid administration and increased mortality.

Interestingly, the subgroup analysis showed that, in contrast to patients with asthma, COPD patients treated with corticosteroids had a higher risk of ICU mortality than those without corticosteroid therapy. We are not able to explain this finding using our database because we did not collect data on the degree of COPD severity. COPD patients may be at an advanced stage of disease. This condition, and other uncontrolled confounding factors, may explain the higher mortality among COPD patients even after excluding patients with COPD exacerbation.

The main strengths of this study are the homogeneous and uniform population, the high number of critically ill patients included in our multicenter study, data regarding the kind/indication of corticosteroid treatment, and the carefully executed analysis to resolve confounding factors including the presence of competing risks. However, we recognize some limitations. First, our results were obtained in a homogeneous population of patients with influenza pneumonia and cannot be extrapolated to other populations. Second, we did not review the duration of viral shedding or appearance of drug-resistant virus in either group. Third, PS matching analysis may also be a limitation, because this method may not reflect the possible biases in observational studies, and some residual confounding may persist. However, as PS matching analysis can balance the population and reduces observational bias, it is the best evidence available for physicians. Fourth, data on MV of patients were not recorded. Lung-protective ventilation is the standard of care for patients with acute lung injury/ARDS because of the evidence that it decreases mortality. Although we did not provide data regarding ventilation of patients, it is broadly accepted in this country that applying protective ventilation improves results and is one of the national quality indicators. Finally, we did not record data about muscle weakness or metabolic alterations related to corticosteroid treatment.

Conclusion

In a homogeneous group of critically ill patients with severe influenza pneumonia, after adequate adjustment by PS matching and competing risks, co-adjuvant corticosteroid therapy was significantly associated with increased ICU mortality. Our data strongly suggest that corticosteroids should not be used as co-adjuvant therapy in patients with influenza pneumonia.

Electronic supplementary material

The online version of this article (https://doi.org/10.1007/s00134-018-5332-4) contains supplementary material, which is available to authorized users.

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GM, AR, JSV, IML, ED and AT conceived and designed the study. All authors, apart from MR, LFR, JG, and AS, contributed to the acquisition and local preparation of the constituent database. GM, AR, EC, ST, IML, ED, JGM, LS, and JCY contributed to database creation and standardization, design of statistical analyses, and data analysis. GM, AR, LFR, JG, JSV, ED, MB, ST, JG, JCY, AS, JGM, LS, MVO, JMC, MVV, MIR, AT, and IML made important intellectual contributions and actively participated in the interpretation of the data and wrote the paper. All authors contributed to critical examination of the paper for important intellectual content and approval of the final manuscript.

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Compliance with ethical standards

Conflicts of interest

All named authors declare that they have no conflicting interests.

Ethical approval

The institutional review board of Joan XXIII Hospital approved the original study (IRBRef#11809).

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