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Corticosteroid treatment in critically ill patients with severe influenza pneumonia: A Propensity score matching study.

Short Running Title: Corticosteroid and influenza pneumonia

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CONFLICTS OF INTEREST

All named authors declare that they have no conflicting interests.

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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 other causes 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. Primary outcome was ICU-mortality. Cox proportional hazard and competing risks analysis was performed to assess the impact of corticosteroids on ICU-mortality.

Results: A total of 1,846 patients with primary influenza pneumonia were enrolled. Corticosteroids were administered in 604 (32.7%) patients, being methylprednisolone the corticosteroid most frequently used (578/604 [95.7%]). The median daily dose was equivalent to 80 mg of methyl-prednisolone (IQR 60-120) for a median duration of 7 days (IQR 5-10). Asthma, COPD, haematological disease and requirement of mechanical ventilation were independently associated with corticosteroid use. Crude ICU mortality was higher in patients who received corticosteroids (27.5%) compared to patients who did not received corticosteroids (18.8%, $p<0.001$). After PS matching, corticosteroid use was associated with ICU mortality in the Cox (HR=1.32 [1.08-1.60], $p<0.006$) and competing risks analysis (SHR=1.37 [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 should not be used as co-adjuvant therapy.

Keywords: Influenza, pneumonia, corticosteroids, ICU, mortality

INTRODUCTION

Pneumonia caused by influenza A(H1N1)pdm virus infection may lead to life-threatening acute respiratory failure (ARF) and acute respiratory distress syndrome (ARDS). Antiviral treatment is the cornerstone for influenza pneumonia [1–3]; moreover, intravenous corticosteroids have been used as adjuvant therapy in patients with ARF/ARDS to modulate lung inflammation and improve clinical outcomes[4–8]. However, no randomized clinical trials have been performed to test 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 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 if patients who were treated with corticosteroids did not have other corticosteroid indications or were 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 effect on survival of corticosteroid therapy compared to patients who did not receive it, 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 determine the factors associated with early corticosteroid use and its impact on intensive care unit (ICU) mortality using a propensity score (PS) matching analysis in ICU 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 between June 2009 and April 2014 (which represents approximately 50% of the ICUs in Spain). Data were obtained from a voluntary registry created by SEMICYUC (Sociedad Española de Medicina Intensiva, Crítica y Unidades Coronarias). All the consecutive cases admitted to the ICU were collected.

The study was approved by the Joan XXIII University Hospital Ethics Committee (IRB#11809). Patient identification remained anonymous and the requirement for informed consent was waived due to the observational nature of the study, as reported elsewhere [3,15–20].

Inclusion criteria: Subjects admitted with fever (>38ºC); 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. Moreover, patients with non-pulmonary influenza infection and patients with healthcare-associated pneumonia were also excluded.

The following variables were recorded at ICU admission: demographic data; co-morbidities; time from illness onset and hospital admission; time to first dose of antiviral delivery; microbiological findings; laboratory and chest radiological findings at ICU admission (all the collected variables are reported in the e-Table 1 of supplementary material). To determine illness severity, the Acute Physiology and Chronic Health Evaluation (APACHE) II score [21] was determined in all patients within 24 hours 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 "exacerbations" was defined according to COPD exacerbations guidelines of European Respiratory Society/American Thoracic Society [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 the acute or sub-acute 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 [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 hours 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 hours). 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/m2.

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. Moreover, the primary outcome was also 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 (yes vs. no); 5) inflammatory response to C-reactive protein (CRP <25mg/dL vs. ≥25 mg/dL); 6) presence of bacterial co-infection (yes vs. no) and 7) chronic lung disease as COPD (yes vs. no) and 8) asthma (yes vs. no). Cut-off of continuous variables was taken 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 patients' demographic and clinical characteristics, differences between groups were assessed using the chi-squared test and

Fisher's exact test for categorical variables and the Student's 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 examined 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 (more information about the propensity score full-matching analysis in electronic 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. Propensity score 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 for both 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 performed to track ICU mortality over time for patients treated and untreated with corticosteroids. 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% confidence intervals (CI) and adjusted survival plots. Because Cox hazard survival analysis is not satisfactory for describing ICU-patients 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 has been 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 subdistribution 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 entered in the regression models were the ones 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 22.0 (SPSS, Chicago, IL, US). Mixed-effects models were performed with R (cran.r-project.org).

RESULTS

A total of 2,684 patients with confirmed influenza pneumonia were enrolled at 148 ICUs in Spain during the study period (2009-2014). Of these, 1,846 (68.7%) met the inclusion criteria and were included in the study (Figure 1).

Comparison between subjects with and without corticosteroid therapy

Among 604 patients with corticosteroid therapy, 578 (95.7%) received methyl-prednisolone, 23 (3.8%) prednisolone and three (0.5%) dexamethasone. All patients whom received therapy with corticosteroids due to pneumonia, this was initiated within the first 24 hours of ICU admission. Patients received a median (interquartile range [IQR]) daily dose equivalent to 80 mg (IQR 60-120) of methyl-prednisolone, and the median duration of corticosteroid treatment was 7 (IQR 5-10) days. The frequency of corticosteroid treatment according to the study periods 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 a significant reduction was observed (p=0.02) in the indication of corticosteroid treatment as co-adjuvant therapy for pneumonia. No differences in ventilator-associated pneumonia rate 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 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. Mechanical ventilation 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 and 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 mechanical ventilation were the independent variables included in the model. As shown in Table 2, mechanical ventilation (OR=1.78), asthma (OR=2.38), COPD (OR=2.10) and hematological disease (OR=2.51) were independently associated with corticosteroid use.

Mortality analysis

In all, 166 of 604 patients (27.5%) who receive corticosteroid therapy died in the ICU, compared with 234 of 1242 (18.8%) of 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 (Figure 2) except for patients with SOFA score <5; CRP <25 mg/dl; non-ventilated patients; patients with bacterial co-infection; and asthma patients. 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 appendix). 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 appendix).

PS matching was applied, and 1242 control and 604 treated patients were matched. The summaries of balance for un-matched and matched data are shown in Table 3 (and e-Figure 1 in the supplementary appendix). 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.

The discrimination of the model (e-Figure 2 supplementary appendix) was good, with an AUROC=0.82 (95% CI 0.77-0.87, p<0.01). The accuracy of predictive model (training set) with respect to the validation set was 0.82. The e-Figure 3 (supplementary appendix) 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 Rang test 560.6, p<0.001). When we excluded patients with CARC, the results were similar (Log Rang Test 5.175, p=0.02) (e-Figure 4 supplementary appendix). However, in patients with CARC, only a trend

towards higher mortality related to corticosteroid treatment was observed (Log Rang Test 0.249, p=0.61) (e-Figure 5 supplementary appendix).

Finally, to determine the impact of corticosteroid use on ICU mortality, a Cox Hazard Regression analysis adjusted for APACHE II and potential confounding factors (see e-Figure 6 in supplementary appendix) was performed. The survival plot (Figure 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 (Figure 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 corticosteroid administration as 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 effect 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 hours 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 mechanical ventilation, asthma, COPD and haematological disease were independently associated with corticosteroid use.

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 haemorrhage [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, maintenance of endothelial integrity, and vascular permeability. Therefore, they may offer an adjunctive therapy option and, 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. However, despite these weaknesses, observational data are representative of current clinical practices, and applying modern methods such as PS matching may help to evaluate 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 SH *et al* [11] analysed 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 propensity score) and propensity score matching (one-to-one). Sixty-five pairs were generated, and 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, end-point observational period (ICU mortality vs 90-days mortality) and early recognition vs. standard of care. Interestingly, Kim *et al*, reported 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, and so 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 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 the important confounders through a PS matching analysis and competing risks analysis, we provide robust evidence to support the association of corticosteroids administration with increased mortality.

Interestingly, in contrast to asthma patients, the subgroup analysis showed that 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 our study are the homogeneous and uniform population, high number of critically ill patients included in our multicenter study, data about kind/indication of corticosteroid treatment and carefully analysis execution 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 mechanical ventilation 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 mechanical 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 propensity score matching and competing risks, 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.

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.

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Author contributions

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.

Conflicts of interests

All named authors declare that they have no conflicting interests.

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Ethics Committee Approval

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

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FIGURE LEGENDS

Figure 1: Flowchart of all excluded and included patients.

Figure 2: Subgroup analysis of ICU mortality according to corticosteroid treatment. Abbreviations: APACHE II: Acute Physiologic and Chronic Health Evaluation II score; MV: mechanical ventilation; SOFA: Sequential Organ Failure Assessment; CRP: C-Reactive Protein; COPD: Chronic Obstructive Pulmonary Disease.

Figure 3: Cox Regression survival plot during ICU admission according to corticosteroid therapy.

Figure 4: Cumulative Incidence function of ICU death and being discharged alive according to corticosteroid therapy