Published in final edited form as:

J Crit Care. 2013 December ; 28(6): 985–991. doi:10.1016/j.jcrc.2013.08.011.

Pre-hospital Use of Inhaled Steroids and Incidence of Acute Lung Injury among Patients at Risk

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No conflicts exist for any of the authors

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Abstract

Purpose—Inhaled corticosteroids (ICS) attenuated lung injury in animal studies. We investigated the association between pre-hospital ICS and incidence of acute lung injury (ALI) among patients at-risk.

Methods—In this ancillary analysis of the large multicenter Lung Injury Prediction Study (LIPS) cohort, we developed a propensity score for pre-hospital ICS use followed by matching, for all patients and for a subgroup of patients with at least one risk factor for direct pulmonary injury. The primary outcome was ALI, secondary outcomes included ARDS, need for invasive mechanical ventilation and hospital mortality.

Results—Of the 5126 patients, 401 (8%) were using ICS. ALI developed in 343 (7%). The unadjusted incidence of ALI was 4.7% vs. 6.9% ($p=0.12$) among those in ICS compared to non-ICS group. In the “direct” lung injury subgroup, the unadjusted incidence of ALI was 4.1% vs. 10.6% ($p=0.006$). After propensity matching, the estimated effect for ALI in the whole cohort was 0.69 (95% CI 0.39–1.2; $p=0.18$) and in the “direct” subgroup was 0.56 (95% CI 0.22–1.46; $p=0.24$).

Conclusions—Pre-admission use of ICS in a hospitalized population of patients at-risk for ALI was not significantly associated with a lower incidence of ALI once controlled by comprehensive propensity matched analysis.

Keywords

Acute lung injury; acute respiratory distress syndrome; inhaled steroids; corticosteroids

INTRODUCTION

Acute Lung Injury/Acute Respiratory Distress Syndrome (ALI/ARDS) is a heterogeneous syndrome often characterized by early inflammatory dysregulation.¹ Despite significant progress, the mortality and long-term morbidity associated with ALI remains considerable.^{2–3} Given the abundance of negative pharmacological therapeutic trials in established ALI^{4,5}, the focus has shifted towards the development of preventive strategies.^{6–8} The current evidence-based recommendations for ALI prevention are limited to supportive measures such as lung-protective ventilation, timely resuscitation, and conservative transfusion practices.^{9–12}

Due to their potent anti-inflammatory effects, systemic corticosteroids have been extensively studied for the prevention and treatment of ALI, however, the results have been somewhat discrepant.^{13–19} Results of a large multicenter trial suggest systemic corticosteroids are

biologically active in acute lung injury (ALI) but may have negative systemic effects.¹⁸ Clinical trials of the inhaled corticosteroids (ICS) in ALI are lacking. However, in animal models of ALI, ICS have demonstrated consistent attenuation in surrogate measures of ALI severity.^{20–24} Also, in a study of patients at risk for pulmonary toxicity from chemotherapy, inhaled fluticasone reduced the incidence of delayed pulmonary toxicity compared with historical controls. While this population didn't have ARDS, the study at least suggested ICS may protect against a pulmonary injury.²⁵ In a retrospective cohort study of adult patients from Olmsted County, Minnesota, USA at risk for ALI, the use of ICS was associated with decreased risk of ALI in patients with pneumonia.²⁶

Given the experimental animal data and limited clinical trial experience, along with the established anti-inflammatory effects of corticosteroids and the potential to avoid negative systemic effects with inhaled delivery, we performed a propensity matched analysis of a multicenter prospective cohort to assess if pre-hospital ICS use reduced inpatient incidence of the ALI among at-risk patients.

MATERIAL AND METHODS

Setting

The United States Critical Illness and Injury Trials Group (USCIITG) investigated 5584 patients admitted to 22 hospitals in order to evaluate the Lung Injury Prediction Score (LIPS).⁶ This secondary analysis of the effect ICS on incidence of ALI, was accepted by the LIPS ancillary studies committee at the time of the conception of original LIPS study. The development of the LIPS cohort was approved and overseen by the Institutional Review Board at each participating center.

Study Subjects

Details of the study population have been described previously.⁶ Briefly, adult patients (>18 years) admitted to academic and community acute care hospitals were eligible if they had at least one major risk factor for ALI, including sepsis, shock, pancreatitis, pneumonia, aspiration, high-risk trauma, or high-risk surgery (including major cardiac and thoracic surgery). Patients were excluded if they had ALI at the time of admission, were transferred from an outside hospital, died in the emergency department, were admitted for comfort or hospice care, or re-admitted during the study period.⁶

Predictor Variables

The exposure of interest was ICS therapy determined at the time of hospital admission, obtained from the patient or family and documented in the medical record. Any ICS medication, including combinations with beta agonists, was taken into account. Baseline characteristics consisting of demographic information and clinical data (co-morbidities, medications, vital signs, laboratory studies) were collected at the time of admission or preoperatively for surgical patients. These clinical variables were used to generate the LIPS score as a measure of the baseline risk of developing ALI at the time of admission. The Acute Physiology and Chronic Health Evaluation (APACHE) II score, was also assessed on the day of admission as a measure of disease severity⁶.

Outcome Variables

The primary outcome was the development of ALI during the hospitalization as determined by the standard AECC criteria at the time of the study conception.²⁷ The term ALI, therefore, included all the patients with hypoxemia in the range of PaO₂/FiO₂ <300. This is in contrast with the recent Berlin definition,²⁸ which reclassified ALI into ARDS of varying severity. Secondary outcome measures included the ARDS (hypoxemia in the range of PaO₂/FiO₂ <200), need for invasive mechanical ventilation, and hospital mortality. These secondary outcomes should be regarded as exploratory only, since we have not performed adjustments for multiple comparisons beyond the assessment for the primary outcome. Patients were followed for the duration of their hospital stay up to 90 days.

Statistical analyses

Patients were categorized into two groups on the basis of whether they were receiving ICS therapy at admission. The entire cohort was used to summarize the unadjusted risk for ALI and other outcome variables by the pre-hospital use of ICS.

To test the hypothesis that ICS are protective for the development of ALI, propensity scores were developed to facilitate matching of patients with pre-admission ICS use to those not exposed to ICS. This approach was implemented to account for the inherent differences in baseline characteristics between the two observational cohorts defined by the use of ICS at the time of admission. In order to approximate randomization, we used 50 variables captured at baseline (Table 1) to generate a comprehensive logistic regression model for the probability of being on ICS (i.e. the propensity score). The patient's baseline risk for developing ALI based on the LIPS score and the severity of illness from the APACHE II score were also incorporated into this model. Subsequently, each patient on ICS was matched based on the logit of their propensity score by a greedy algorithm (the shortest Euclidean distance within the caliper width of one quarter of standard deviation)²⁹ with up to 4 subjects not on ICS. Finally, by using each matched set as a stratum, a conditional logistic regression model was used to estimate the independent risk (odds ratio [OR]) of ALI and other secondary outcomes from the pre-hospital use of ICS. Given our previous experience where the use of ICS was associated with decreased risk of ALI in patients with pneumonia,²⁶ pre-planned identical analyses were also performed on a subgroup of patients with at least one risk factor for ALI by direct pulmonary mechanisms (pneumonia, documented aspiration on admission, chest contusion, smoke inhalation, and near drowning). We also performed a post-hoc sensitivity analysis on the primary outcome of ALI in a whole cohort by logistic regression that included ICS use and all 31 variables found to be statistically significant in the primary univariate analysis.

Risk estimates were reported as OR with their 95% confidence intervals (CI). A p-value of less than 0.05 was considered statistically significant. We used Fisher's exact test to compare contingency tables, and when appropriate, T-test, to compare distributions of continuous variables. All statistical analyses were performed using JMP 9.0 statistical software and SAS 9.1.3 (SAS Institute Inc., Cary, NC).

RESULTS

Baseline information and unadjusted analyses

A total of 5584 patients admitted to the hospital with risk factors for ALI were enrolled in the prospective LIPS cohort.⁶ We excluded 458 patients who were receiving systemic corticosteroids (SCS) at the time of admission. The remaining 5126 patients, 401 (8%) of which were using ICS at the time of the hospitalization, served as the sampling frame for the propensity score analysis (Figure 1). The sample characteristics of the 5126 patients are shown in Table 1. While presented p-values demonstrate initial imbalances, these should not be considered as indicators of the magnitude of the difference in the unadjusted analyses. Despite significant degree of imbalance in unadjusted characteristics between those with pre-hospital ICS use and those without, after assignment of the propensity score for all 5126 patients and subsequent matching, no imbalances remained (Table 1).

A total of 343 patients (7%) developed ALI and 206 (4%) met criteria for ARDS. Pre-hospital ICS use was associated with a lower incidence of ALI (4.7% vs. 6.9%, OR 0.68, 95% CI 0.42–1.09, $p=0.12$) and ARDS (2.2% vs. 4.2%, OR 0.53, 95% CI 0.27–1.04, $p=0.063$), but this did not reach prespecified statistical significance. Ninety percent (307) of patients with ALI required invasive ventilation. The rate of invasive mechanical ventilation was significantly lower in patients with pre-hospital ICS use compared with the non-ICS group (27% vs. 35%, $p=0.002$). Unadjusted hospital mortality was not different among groups (5.7% vs. 4.6%, $p=0.33$).

Baseline characteristics for the subset of 1386 patients with at least one risk factor for direct lung injury are shown in Table 2. Similar to cohort of all patients, despite significant imbalance in unadjusted characteristics between those with pre-hospital ICS use and those without, after assignment of the propensity score for this subcohort patients and subsequent matching, no imbalances remained. In this subset, 136 patients developed ALI. Pre-hospital ICS use was associated with a significantly lower incidence of ALI (4.1% vs. 10.6%, OR 0.36, 95% CI 0.16–0.78; $p=0.006$) and ARDS (2.3% vs. 6.9%, OR 0.32, 95% CI 0.12–0.88; $p=0.018$). Similar to the whole cohort, invasive mechanical ventilation was less frequent in patients on ICS (12% vs. 22%, $p<0.001$). Unadjusted hospital mortality was not different among groups, 5.8% ($p=1.0$).

Propensity score based analyses

A total of 348 ICS-exposed patients (87% of 401 in the whole cohort) were matched to 826 non-ICS patients for a total number of 1174 matched patients. The estimated effect, as quantified with the conditional OR for development of ALI was 0.69 (95% CI 0.39 – 1.2; $p=0.186$) and for ARDS 0.50 (95% CI 0.22 – 1.16; $p=0.107$). (Table 3)

In the subset of 1386 patients with at least one primary pulmonary risk factor for direct lung injury, a total of 166 (97% of 172 in the “direct” cohort) patients with pre-hospital ICS use were matched to 375 non-ICS patients for a total number of 541 matched patients. The final conditional logistic regression model was additionally adjusted for inhaled beta agonist use and COPD, which were the only imbalanced variables after the derivation of propensity score in the direct ALI subset (Table 2). The estimated effect, as quantified by the

conditional OR for development of ALI was 0.56 (95% CI 0.22 – 1.46; $p=0.237$) and for ARDS was 0.29 (95% CI 0.07 – 1.23; $p=0.093$). There were no significant associations between ICS use and need for mechanical ventilation or hospital mortality after propensity matching in either group (Table 3).

Sensitivity analysis

We performed a sensitivity analysis on the primary outcome of ALI in a whole cohort by logistic regression that included ICS use and all 31 variables found to be statistically significant in the primary univariate analysis (Table 1). Pre-hospital use of ICS was independently associated with the ALI as a primary outcome (OR 0.56, CI 0.31 – 0.99, $p=0.045$) as well as with ARDS (OR 0.44, CI 0.19–0.93, $p=0.032$) in this analysis (Table 4).

DISCUSSION

In this secondary analysis of the LIPS multicenter study, we attempted to demonstrate the association between prehospital ICS use and incidence of ALI. In unadjusted analysis, pre-hospital ICS use was associated with a lower incidence of ALI but this association reached significance only among patients with at least one risk factor for direct pulmonary injury. After the comprehensive propensity score matched analysis, the statistical significance was lost, however, the direction and magnitude of the proposed effect judged by crude vs. adjusted OR, remained very similar suggesting a possible type II error (a number of subjects was lost in the process of matching). Moreover, significant association that was confirmed by standard logistic regression in the sensitivity analysis suggests that overmatching might have occurred in the process. This is the largest study to date assessing the preventative role of ICS therapy among patients at risk for ALI, and although the number of patients with pre-hospital ICS use was relatively small, our findings create equipoise for preventative role of ICS for certain patient populations at-risk for developing ALI.

ICS use represents an unexplored option for prevention and early treatment of ALI/ARDS. In established ALI/ARDS, the epithelial surface loses its function and integrity, which may reduce its responsiveness to subsequent therapies. A viable concern is that in established ALI/ARDS the drug's distribution upon inhalation into the target organ might not reach its action site. ALI/ARDS is a terminal/distal airway disease in which injury is regionally heterogeneous and inhaled drug delivery might be preferentially distributed to well-ventilated areas while sparing areas affected by incipient edema and atelectasis. Therefore, the potential benefit of ICS may be more applicable to prevention and early therapy of ALI among spontaneously breathing patients where the drug distribution is likely to be more distal and homogenous. In addition, targeted delivery to the site of potential injury, void of systemic side effects associated with SCS use are advantages of ICS and might be underlying reasons for the observed difference in frequencies of ALI/ARDS in LIPS cohort between ICS and SCS users (4.7% versus 7.7%, respectively).³⁰

There is a biologically plausible role for ICS in the prevention of epithelial activation and inflammatory dysregulation and animal models provide evidence for prevention of experimental lung injury induced by direct pulmonary insults. Wang et al. exposed pigs to inhaled budesonide or placebo at 0, 30, 60 minutes after direct pulmonary insult. Significant

improvements occurred in PaO₂, PVR and lung compliance.²³ Similarly, Jansson et al. demonstrated that pre-treatment with ICS decreased the recovery of tumor necrosis factor, interleukin 6 and I β on bronchoalveolar lavage in a rat model of lung injury.²⁴ These animal studies of direct lung injury suggest that concomitant or subsequent administration of ICS might improve pulmonary mechanics, decrease inflammatory surrogates and attenuate hypoxemia. We hypothesized that ICS delivery to the relatively preserved epithelium, early in the course of ALI, might ameliorate its injury by direct (and possibly indirect) mechanisms. Based on the Olmsted county study,²⁶ we decided at the time of the conception of this study, to perform subgroup analysis of patients with at least one risk factor for ALI by direct pulmonary mechanisms. In both univariate and propensity matched analyses, the estimated effects of ICS were more pronounced among patients within the “direct” lung injury subgroup compared to the whole cohort. Despite described biological plausibility for inhaled medications, the reasons for this observation can not be elucidated from our study.

The statistically nonsignificant trend for protective effect of ICS, which was evident in the entire cohort, as well as in the “direct” subcohort, was stronger for ARDS rather than ALI prevention. We do recognize the pitfalls of dividing patients into those with ALI and ARDS per the AECC definition²⁷, with ARDS being more severe form of the same clinical syndrome. However, from the secondary prevention standpoint, it is important to make this distinction as it seems plausible that preventative and/or early therapeutic interventions could result in relative amelioration of severity of the lung injury. The results of our study further support this notion.

Since there is no control over the treatment assignment in observational studies, there may be large differences between the treated and control groups leading to biased estimates of treatment effects. Therefore, we used the propensity score, defined as the conditional probability of being treated given the covariates. Subsequently, we performed matching to balance the two groups, in an attempt to reduce the hidden bias. Selection of variables for inclusion in the propensity score calculation is of critical importance and is controversial. Selecting only variables suspected to be clinically relevant or only statistically imbalanced baseline characteristics may not fully account for unrecognized sources of bias. Instead, we chose more rigorous and conservative methodology and included 50 available variables in our propensity analysis. By choosing this method, we reduced the chance for hidden bias but also increased the risk of overmatching. Overmatching, a form of statistical bias, results from matching on variables that do not pertain to the treatment or the outcome, introducing additional variance and widening of the confidence intervals, thus increasing the probability of a type II error. To formally assess for overmatching, we performed a sensitivity analysis on the primary outcome of ALI in the whole cohort by using traditional logistic regression that adjusted on all variables found to be significantly imbalanced in the primary univariate analysis. This methodology is very commonly utilized, where at least 10 subjects from both treatment and control groups are required per each modeled covariate, a stability criterion that was met in our sensitivity analysis. Importantly, besides LIPS and APACHE II, the only covariate significantly associated with the primary outcome of ALI in a whole cohort was ICS use (Table 4.).

We recognize several important limitations of our study. We were limited by the study's observational design and limited number of patients exposed to ICS. Given the multicenter character of the study we cannot be certain of the reliability of the ICS exposure variable. This example of misclassification bias, however, is nondifferential and as such would bias the results toward the null hypothesis, which might, in part, explain the lack of significance in the current study relative to the findings from a single center analysis of patients with pneumonia.²⁶ Also, we did not have data on the dose and the duration of ICS prior to hospitalization. However, animal studies demonstrated preventative effects of ICS when administered concurrently or subsequently to the injurious agent, which possibly limits the relative importance of the duration of prior exposure to ICS on their effect. Moreover, we are not certain that ICS were continued during the hospital stay in all patients and it is likely that not continuing ICS could blunt their possible protective effects. Although our methodological approach was the most conservative for reducing bias and confounding, the potential for overmatching was increased. The possible effects of overmatching and a type II error are suggested by the stability, magnitude and direction of the estimated effect as judged by the OR, despite the widening of the confidence interval and the loss of statistical significance.

CONCLUSIONS

In this large multicenter cohort, pre-admission use of ICS in a hospitalized population of patients at-risk for ALI was not significantly associated with a lower incidence of ALI once controlled by comprehensive propensity score matched analysis. The overall direction, magnitude and stability of the association, however, suggest a clinical equipoise and warrant future research.

Acknowledgments

The work was supported in part by: HL78743-01A1, 1 KL2 RR024151 and the Mayo Clinic Critical Care Research Committee

EF: Guarantor of the content of the manuscript, including the data and analysis. Participated in the conception and design of the study; acquisition, analysis and interpretation of data; drafting and revising of the manuscript; approval of the submitted manuscript and had full access to the data (co-primary author).

EO: Participated in the conception and design of the study; acquisition, analysis and interpretation of data; drafting and revising of the manuscript; approval of the submitted manuscript and had full access to the data (co-primary author).

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Figure 1.
Study flow

Table 1

Baseline characteristics, unadjusted and propensity score matched analyses on all patients

Clinical characteristics	ICS (N=401)	No ICS (N=4725)	Unadjusted p value	Propensity score* adjusted p value
Age, median (IQR)	64 (52–76)	56 (42–70)	<0.001	0.99
Male gender	169 (42%)	2738 (58%)	<0.001	0.798
Caucasian race	274 (68%)	2842 (60%)	0.001	0.77
APACHE II, median (IQR)	11 (7–15)	8 (5–13)	<0.001	0.628
BMI > 30	136 (34%)	1181 (25%)	<0.001	0.875
Alcohol use	23 (6%)	446 (9%)	0.011	0.727
Active smoking	96 (24%)	1180 (25%)	0.674	0.8
LIPS, median (IQR)	3 (2–4.5)	2.5 (1.5–4)	0.002	0.919
Admission from home	319 (80%)	3747 (79%)	0.949	0.86
Aspiration	11 (3%)	189 (4%)	0.28	0.904
Pneumonia	169 (42%)	890 (19%)	<.0001	0.538
Lung contusion	2 (0.5%)	187 (4%)	<0.001	0.977
Smoke inhalation	0	25 (1%)	0.257	NA
Near drowning	0	3 (<0.1)	1	NA
Sepsis	149 (37%)	1414 (30%)	0.003	0.357
Shock	23 (6%)	328 (7%)	0.41	0.952
Pancreatitis	18 (4%)	295 (6%)	0.191	0.533
Long bone fracture	9 (2%)	314 (7%)	<0.001	0.876
Brain injury	9 (2%)	478 (10%)	<0.001	0.776
Cardiac surgery	47 (12%)	478 (10%)	0.304	0.439
Aortic surgery	8 (2%)	114 (2.5%)	0.733	0.817
Thoracic surgery	17 (4%)	152 (3%)	0.305	0.433
Spine surgery	24 (6%)	434 (9%)	0.029	0.684
Acute abdomen	11 (3%)	267 (6%)	0.011	0.794
Emergency surgery	10 (2.5%)	317 (7%)	<0.001	0.682
Diabetes Mellitus	111 (28%)	1056 (22%)	0.018	0.399
Cirrhosis	7 (2%)	106 (2%)	0.722	0.966
Chronic hemodialysis	13 (3%)	170 (4%)	0.888	0.946
CHF NYHA IV	27 (7%)	136 (3%)	<0.001	0.561
COPD	180 (45%)	324 (7%)	<0.001	0.502
Asthma	122 (30%)	261 (5%)	<0.001	0.892
Interstitial lung disease	7 (2%)	25 (0.5%)	0.01	0.739
Immunosuppression	14 (3.5%)	316 (6%)	0.011	0.796
Lymphoma	9 (2%)	63 (1%)	0.178	0.782
Leukemia	5 (1%)	38 (1%)	0.382	0.464
Metastatic solid cancer	16 (4%)	227 (5%)	0.54	0.948
Chest radiation	12 (3%)	47 (1%)	0.002	0.611
Sleep apnea	45 (11%)	177 (4%)	<0.001	0.858
GERD	103 (26%)	523 (11%)	<0.001	0.641

Clinical characteristics	ICS (N=401)	No ICS (N=4725)	Unadjusted p value	Propensity score [*] adjusted p value
ARB	46 (11.5%)	226 (5%)	<0.001	0.532
ACE inhibitor	100 (25%)	914 (19%)	0.009	0.906
Statin	156 (39%)	1116 (24%)	<0.001	0.842
Aspirin	136 (34%)	1222 (26%)	<0.001	0.631
Amiodarone	6 (1.5%)	36 (1%)	0.138	0.649
Oral hypoglycemic	62 (15%)	519 (11%)	0.008	0.433
Insulin	47 (12%)	434 (9%)	0.108	0.734
Inhaled beta-agonist	278 (69%)	357 (8%)	<0.001	0.286
PPI	168 (42%)	921 (19%)	<0.001	0.686
H2 blocker	27 (7%)	241 (5%)	0.161	0.954
Chemotherapy	13 (3%)	115 (2%)	0.315	0.928

^{*} Propensity score based analysis with matching up to 1:4 (1174 patients)

Table 2

Baseline characteristics, unadjusted and propensity score matched analyses on patients with at least one risk factor for direct lung injury

Clinical characteristics	ICS (N=172)	No ICS (N=1214)	Unadjusted p value	Propensity score adjusted p value [*]
Age, median (IQR)	64 (53–77)	58 (43–75)	<0.001	0.785
Male gender	74 (43%)	722 (59%)	<0.001	0.941
Caucasian race	104 (60%)	743 (61%)	0.868	0.796
APACHE II, median (IQR)	12.5 (8.5–17)	10 (6–15)	<0.001	0.285
BMI > 30	45 (26%)	227 (19%)	0.024	0.706
Alcohol use	12 (7%)	130 (11%)	0.141	0.603
Active smoking	43 (25%)	355 (29%)	0.28	0.865
LIPS, median (IQR)	3.5(2.5–5.4)	3.5(2.5–5)	0.848	0.629
Admission from home	135 (78%)	891 (73%)	0.164	0.6
Aspiration	11 (6%)	189 (16%)	0.001	0.455
Pneumonia	169 (98%)	890 (73%)	<0.001	0.388
Lung contusion	2 (1%)	187 (15%)	<0.001	0.928
Smoke inhalation	0	25 (2%)	0.063	NA
Near drowning	0	3 (0.25%)	1	NA
Sepsis	67 (39%)	393 (32%)	0.1	0.38
Shock	4 (2%)	87 (7%)	0.013	0.756
Pancreatitis	0	6 (0.5%)	1	NA
Long bone fracture	0	33 (3%)	0.027	NA
Brain injury	0	41 (3%)	0.007	NA
Cardiac surgery	0	3 (0.25%)	1	NA
Aortic surgery	0	3 (0.25%)	1	NA
Thoracic surgery	0	7 (0.5%)	1	NA
Spine surgery	0	5 (0.5%)	1	NA
Acute abdomen	0	8 (0.5%)	0.606	NA
Emergency surgery	0	30 (2.5%)	0.043	NA
Diabetes Mellitus	53 (31%)	276 (23%)	0.022	0.359
Cirrhosis	4 (2%)	19 (2%)	0.517	0.81
Chronic hemodialysis	6 (3.5%)	51 (4%)	0.838	0.685
CHF NYHA IV	12 (7%)	44 (4%)	0.058	0.819
COPD	92 (53%)	135 (11%)	<0.001	0.014 [‡]
Asthma	47 (27%)	93 (8%)	<0.001	0.315
Interstitial lung disease	3 (2%)	18 (1.5%)	0.738	0.819
Immunosuppression	7 (4%)	100 (8%)	0.065	0.502
Lymphoma	7 (4%)	17 (1.5%)	0.022	0.748
Leukemia	3 (2%)	12 (1%)	0.418	0.962
Metastatic solid cancer	7 (4%)	67 (5.5%)	0.586	0.612
Chest radiation	9 (5%)	14 (1%)	0.001	0.61

Clinical characteristics	ICS (N=172)	No ICS (N=1214)	Unadjusted p value	Propensity score adjusted p value [*]
Sleep apnea	18 (10.5%)	46 (4%)	<0.001	0.698
GERD	44 (26%)	123 (10%)	<0.001	0.441
ARB	21 (12%)	64 (5%)	0.001	0.653
ACE inhibitor	42 (24%)	218 (18%)	0.047	0.461
Statin	64 (37%)	279 (23%)	<0.001	0.712
Aspirin	64 (37%)	302 (25%)	<0.001	0.693
Amiodarone	2 (1%)	15 (1%)	1	0.734
Oral hypoglycemic	30 (17%)	122 (10%)	0.006	0.658
Insulin	21 (12%)	122 (10%)	0.421	0.73
Inhaled beta-agonist	134 (78%)	172 (14%)	<0.001	<0.001 [†]
PPI	74 (43%)	271 (22%)	<0.001	0.618
H2 blocker	10 (6%)	56 (5%)	0.447	0.851
Chemotherapy	6 (3.5%)	39 (3%)	0.818	0.814

^{*} Propensity score based analysis with matching up to 1:4 among patients with at least one risk factor for direct lung injury (541 patients)

[†] The final conditional logistic regression model was additionally adjusted for inhaled beta agonist use and COPD

Primary and secondary outcomes of prehospital ICS exposure by propensity score matching among all patients and patients with at least one risk factor for direct lung injury

Table 3

	All patients (N= 5126)			Patients with “direct” lung injury (N=1386)		
	Adjusted OR	95% CI	p-value	Adjusted OR	95% CI	p-value
ALI	0.69	0.39 to 1.20	0.186	0.56	0.22 to 1.46	0.237
ARDS	0.50	0.22 to 1.16	0.107	0.29	0.07 to 1.23	0.093
Mechanical Ventilation	1.00	0.75 to 1.34	0.986	0.83	0.45 to 1.53	0.555
Hospital Mortality	0.74	0.41 to 1.32	0.308	1.07	0.41 to 2.78	0.885

Table 4

Logistic regression model on all patients for ALI as the primary outcome, including all statistically significant variables from the Table 1.

Term	Odds Ratio	Lower 95%	Upper 95%	p-value
Inhaled steroid	0.56	0.30	0.98	0.045 *
(For ARDS) *	(0.44)	(0.19)	(0.93)	(0.032) *
LIPS	1.46	1.37	1.56	<0.001 *
APACHE II	1.04	1.02	1.06	<0.001 *
Age	0.99	0.98	1.0	0.168
Male gender	1.18	0.91	1.52	0.202
Caucasian race	0.84	0.65	1.08	0.187
BMI> 30	1.28	0.97	1.69	0.076
Alcohol use	0.87	0.58	1.26	0.478
Pneumonia	0.93	0.68	1.28	0.688
Lung contusion	1.02	0.58	1.73	0.922
Sepsis	0.86	0.64	1.15	0.322
Long bone fractures	0.92	0.55	1.49	0.764
Brain injury	0.72	0.47	1.08	0.120
Spine surgery	1.10	0.60	1.89	0.726
Acute abdomen	0.96	0.55	1.59	0.884
Emergency surgery	1.14	0.74	1.73	0.543
Diabetes mellitus	0.80	0.54	1.18	0.286
CHF NYHA IV	0.96	0.49	1.75	0.913
COPD	0.93	0.60	1.43	0.769
Asthma	0.89	0.51	1.48	0.671
Interstitial lung disease	0.67	0.03	3.39	0.693
Immunosuppression	1.24	0.73	2.01	0.395
Chest radiation	0.48	0.07	1.66	0.284
Sleep apnea	1.15	0.65	1.95	0.601
GERD	0.83	0.52	1.27	0.412
ARB	1.07	0.61	1.79	0.793
ACE inhibitor	1.24	0.90	1.70	0.171
Statin	0.90	0.64	1.25	0.533
Aspirin	0.87	0.63	1.20	0.421
Oral hypoglycemic	1.20	0.73	1.97	0.459
Inhaled beta agonist	1.21	0.76	1.88	0.399
PPI	1.04	0.74	1.44	0.801

* Denotes statistical significance