Blood Eosinophils and Mortality in Patients With Acute Respiratory Distress Syndrome: A Propensity Score Matching Analysis

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Research

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Abstract

Background: The effect of blood eosinophils on mortality in acute respiratory distress syndrome (ARDS) patients and whether this effect is impacted by corticosteroids are unclear. This study explored the relationship between blood eosinophils and 28-day mortality in ARDS patients and investigated whether the relationship varied according to corticosteroid use.

Methods: The Medical Information Mart for Intensive Care III database was employed to extract data. Patients with ARDS who were 16 years or older, used mechanical ventilation during the ICU stay and stayed in the ICU for at least 48 consecutive hours were screened for inclusion. Cox regression models using the stepwise backward method and propensity score matching (PSM) were employed to assess the relationship between blood eosinophil counts and 28-day mortality.

Result: A total of 3372 patients were included, and the 28-day mortality rate was 24.23% (817/3372). The crude 28-day mortality was significantly lower in patients with eosinophil count ≥2% (105/574 vs. 712/2798, p< 0.001) than in those with eosinophil count <2%. In the Cox regression model, the eosinophil count ≥2% showed a significant association with decreased 28-day mortality (hazard ratio (HR) 0.761; 95% confidence interval (CI) =0.620-0.935, p=0.009). In a subgroup analysis, we detected an interactive effect of eosinophils and corticosteroids use (p value for interaction, p=0.006). In the corticosteroid non-use subgroup, eosinophil counts ≥2% were significantly related to decreased 28-day mortality (HR=0.730, 95% CI =0.577-0.923), but the result was non-significant in the corticosteroid non-use subgroup model (p=0.231). A total of 574 well-matched pairs were obtained by a 1:1 matching algorithm after PSM. The 28-day mortality remained significantly lower in the eosinophil count ≥2% group than in the eosinophil count <2% group (105/574 vs 136/574, p=0.025).

Conclusions: Higher eosinophil counts are related to lower 28-day mortality in ARDS patients, and this relationship can be counteracted by using corticosteroids.

Introduction

Acute respiratory distress syndrome (ARDS) appears to represent an important public health problem worldwide, and it leads to a very high mortality of approximately 40%[1]. ARDS is associated with excess inflammation contributing to increased endothelial and epithelial permeability and leading to the accumulation of protein-rich alveolar oedema fluid in the lung interstitium[2]. During the process of ARDS, immune effector cells have key activities in the defence of the normal lung.

Eosinophils are key innate immune cells in host defence[3], and they have been found to be associated with mortality in patients with chronic obstructive pulmonary disease (COPD)[4, 5] and asthma[6, 7]. The blood eosinophil count (EOS) is considered a potential biomarker for the identification of COPD patients at risk and as a reference for the usage of inhaled corticosteroids, as recommended by the GOLD 2019 guidelines[8]. For ARDS, eosinophils have been indicated as an important immune response contributor, and they may be a diagnostic biomarker[9, 10]. The accumulation of eosinophils in patients with acute lung injury was documented to be a prognostic indicator of patient survival[11]. Recently, a retrospective analysis of 112 patients with ARDS conducted by Zhu et al.[12] found that surviving ARDS patients have higher blood eosinophil counts than non-survivors and that eosinophils may play a protective role in ARDS independent of corticosteroid use. However, ARDS patient prognosis is closely related to factors such as tidal volume[13, 14]. The relationship between blood eosinophil

count and mortality in patients with ARDS needs to be further evaluated with a large sample size after full consideration of confounders, and it may provide a potential therapeutic target for ARDS.

The purpose of our study was to detect the relationship between blood eosinophils and 28-day mortality in patients with ARDS after adjusting for possible confounding factors by Cox regression and propensity score matching (PSM). We also tested the relationship in both patients who used corticosteroids and those who did not to investigate whether this relationship varied by corticosteroid use.

Materials And Methods

Database introduction

Our data source was the Medical Information Mart for Intensive Care III (MIMIC-III, version 1.4), an open international database. The MIMIC-III database includes comprehensive, time-stamped information of over 46,000 unique patients from over 60,000 ICU stays at Beth Israel Deaconess Medical Center (BIDMC) in Boston, Massachusetts, between 2001 and 2012. Data were extracted by the author Chen, and access to the database was approved by the institutional review boards of the Massachusetts Institute of Technology after completing the National Institutes of Health's web-based course and passing the Protecting Human Research Participants exam (certification number: 37147539).

Inclusion and exclusion criteria

Patients with ARDS who were 16 years or older, used mechanical ventilation during the ICU stay and stayed in the ICU for at least 48 consecutive hours were screened for inclusion. To screen the patients with ARDS accurately, the diagnostic information recorded in the MIMIC-III database and the Berlin criteria[15] were considered simultaneously, and the following conditions were proposed: the onset of ARDS is acute, and patients must have PaO_2/FiO_2 values equal to or less than 300 mmHg when positive and expiratory pressure (PEEP) was at least 5 cmH_2O in the first 24 h of entering the ICU. Patients were excluded if they had no data on the EOS within the first 72 h of entering the ICU.

Data extraction

Structured query language (SQL) was used to extract the following data: age, sex, weight (kg), body mass index (BMI), comorbidities (COPD, asthma, diabetes, and sepsis), disease severity score (simplified acute physiology score (SAPS II)), laboratory outcomes (white blood cell count (WBC), red blood cell count (RBC), platelet count (PLT), pH, EOS, and characteristics of mechanical ventilation (tidal volume (mL/kg PBW) and minute ventilation (L/min)). The extracted data were obtained within 72 h after ICU admission. Corticosteroid use was also extracted from the database.

Stratification and definition

According to the cut-off of 2%, the maximum values of EOS within 72 h after ICU admission were used to divide the patients into EOS≥2% and EOS<2% groups. Corticosteroids can cause blood eosinophils to fall at least 50% after the administration of the first 4 h and then back to baseline within 24 h[16]. Therefore, in the subgroup analysis, all patients were assigned to two subgroups based on the usage of any corticosteroid drugs except the external administration route within 24 h before ICU admission to 72 h after ICU admission, including dexamethasone,

hydrocortisone, and methylprednisolone. The primary endpoint was the 28-day mortality, defined as death within 28 days from ICU admission. The secondary endpoints included ICU mortality, hospital mortality, length of ICU stay, and length of hospital stay. For patients with more than one ICU stay, only the first ICU stay of the first hospitalization was considered.

Propensity score matching

Because confounders such as comorbidities and characteristics of mechanical ventilation may bias the outcomes, PSM was used to reduce this effect. A multivariable logistic regression model was used to evaluate the propensity score according to the probability of patients being divided into EOS≥2% and EOS<2% groups. The propensity score was calculated by age, weight, BMI, COPD, asthma, sepsis, SAPS II score, WBC, RBC, pH, tidal volume and minute ventilation. A 1:1 nearest-neighbour matching algorithm was used with a calliper of 0.1. We also used kernel density plots of the p score to test the matching level.

Statistical analysis

Continuous variables were summarized as the mean ± standard deviation or median (interquartile range) when appropriate, and categorical data were summarized as proportions. The characteristics of patients with ARDS were compared using a Student's t-test, Wilcoxon rank-sum test, and χ^2 test according to the distribution of the data. The Kaplan-Meier method and log rank tests were used to compare 28-day mortality among the EOS≥2% and EOS<2% groups in patients with ARDS. Cox regression models were used to assess the relationship between blood eosinophil counts and 28-day mortality. A stepwise backward method with $p < 0.05$ was used to build the model. Twelve potential confounders with a p value <0.10 in the univariate analyses were included in the Cox regression models: age, weight, BMI, COPD, asthma, sepsis, SAP II score, WBC, RBC, pH, tidal volume and minute ventilation. The variance inflation factor (VIF) was used to test multicollinearity, and VIF≥10 indicates multicollinearity between variables. The proportional hazards assumption was tested using Schoelfeld residuals, with $p<0.05$ constituting evidence for non-proportionality. Subgroup analyses were also performed separately in patients who used corticosteroids and those who did not. PSM was used to balance the cofounders between the EOS≥2% and EOS<2% groups. All p-values were two-tailed, and $p < 0.05$ was considered statistically significant. Statistical analyses were performed using STATA (Version 16; Stata Corp., College Station, TX, USA).

Results

Patient characteristics

A total of 3372 patients were included, and the 28-day mortality rate was 24.23% (817/3372). The flow diagram for patient selection was shown in Figure S1. Compared with 28-day survivors, non-survivors were older and had significantly lower EOS, weight, BMI, RBC, pH and a lower proportion of patients who suffered asthma, and they had significantly higher proportions of patients who suffered from COPD or sepsis, SAPS II on admission, WBC, the proportions of corticosteroid use, tidal volume and minute ventilation. Sex, PLT and the proportions of patients who suffered from diabetes were not significantly different between survivors and non-survivors (Table 1). The comparison results between the EOS≥2% group and EOS<2% group are shown in Table S1.

Clinical outcome characteristics

The crude results of the comparisons of outcome characteristics between the EOS<2% and EOS≥2% groups are shown in Table 2. Without adjusting for covariates, the EOS≥2% group had a significantly lower 28-day mortality rate (105/574 (18.29%) vs 712/2798 (25.45%), p< 0.001), ICU mortality rate (86/574 (14.98%) vs 581/2798 (20.76%), p=0.002) and hospital mortality rate (99/574 (17.25%) vs 688/2798 (24.59%), p<0.001) than the EOS<2% group. In patients who did not use corticosteroids, the result was similar to the crude outcome, but this result was not observed in patients who used corticosteroids (Table 2). The differences in the median length of ICU stay and length of hospital stay were non-significant between the EOS≥2% group and the EOS<2% group. Kaplan-Meier survival curves depicting the 28-day survival distributions of patients with EOS≥2% or EOS<2% are presented in Figure 1, and the comparison between the two groups showed that patients with EOS≥2% have significantly better survival (log rank test; p<0.001).

Relationship between eosinophils and 28-day mortality

To assess the relationship between EOS and 28-day mortality and to test whether the relationship varied by corticosteroid used, three models were developed using Cox regression analyses (Table 3). Model 1 used all patients included in our study, and we observed that EOS≥2% showed a significant association with decreased 28-day mortality (hazard ratio (HR)= 0.761; 95% confidence interval (CI) =0.620-0.935, p=0.009) after adjustment for SAP II, weight, minute ventilation and asthma. Model 2 used patients who did not use corticosteroids, and the results were similar to those in Model 1, with a HR of 0.730 (95% CI =0.577-0.923, p=0.009) after adjusting for SAP II, weight, minute ventilation and age. However, in Model 3, which used patients who used corticosteroids, EOS was not included because p=0.231. We also detected an interactive effect of EOS and corticosteroids (p value for interaction, p=0.006).

Outcomes after propensity score matching

A total of 574 matched pairs were obtained by a 1:1 matching algorithm after PSM. No significant difference was observed in any confounders between the two matched groups, indicating excellent matching among all pairs (Table 4). We also graphically inspected the propensity scores between the groups (Figure 2). Among the 574 matched pairs, the 28-day mortality, ICU mortality, and hospital mortality rates were significantly lower in the EOS≥2% group than in the EOS<2% group. The length of ICU stay and the length of hospital stay were also shorter in the EOS≥2% group than in the EOS<2% group after matching.

Discussion

In our large-sample study, we demonstrated that increased blood eosinophil counts were related with a significantly decreased risk of 28-day mortality after ICU admission in patients with ARDS. After adjustment for covariates, this result remained consistent in the PSM analysis. However, an interaction was observed between blood eosinophil counts and corticosteroid use. The relationship between blood eosinophils and 28-day mortality was detected only in patients who did not use corticosteroid drugs, whereas this relationship was non-existent in patients who used corticosteroids. Our study suggests that eosinophils play a possible protective role in patients with ARDS, which has rarely been demonstrated previously. Recently, Zhu et al.[12] found that eosinophils can be grouped into CD101+ and CD101- subtypes by the CD101 marker. CD101+ eosinophils may play a pro-inflammatory role by overexpressing alarmins. CD101- eosinophils, the eosinophil subtype most elevated in patients with ARDS, might play a protective role in the inflammatory process by preventing neutrophil recruitment and stimulating clean-up of neutrophil debris through the production of protectin D1. This molecular mechanism supports our result.

However, the relationship between blood eosinophils and outcome has not been consistently clarified in patients with asthma and those with COPD. In asthma, Price et al.[7] reported that higher blood eosinophil counts are associated with more severe exacerbations and poorer asthma control, while Håkansson et al.[6] found that a lower blood eosinophil count was related to both one-year readmission and mortality. In COPD, Casanova's longitudinal study[17] showed that patients with higher blood eosinophil counts for 2 years were more inclined to have a longer survival time. However, in a study conducted by Zysman et al.[18], no difference was found in the symptom characteristics, lung function, exacerbation rate, and three-year survival rate between COPD patients with higher blood eosinophil counts and those with lower blood eosinophil counts, suggesting that the relationship between blood eosinophil counts and mortality reported in previous studies may be caused by population-specific factors. We speculated that the contradictory results could be explained by the heterogeneity caused by the balance of two eosinophil subtypes in patients with COPD and asthma. Additionally, we speculated that the sensitivity of medicinal treatment was influenced by this balance relationship, which may affect patients' outcomes. However, whether this heterogeneity also exists in patients with ARDS has not been reported in a previous study, and further study should be conducted to fill in this research gap.

The progression of ARDS is rapid; however, no specific pharmacotherapies have yet been demonstrated to significantly improve patient outcomes. Corticosteroids have been the most widely studied drugs, and they may improve oxygenation and shorten mechanical ventilation times in ARDS[19]. However, no consistent result has been reported regarding whether corticosteroids should be routinely used in ARDS patients. A randomized controlled trial (RCT) conducted by Meduri et al.[20] found that methylprednisolone can significantly improve pulmonary and extrapulmonary organ dysfunction in patients with ARDS and reduce ICU mortality by downregulating systemic inflammation. Guidelines for corticosteroid insufficiency (CIRCI) also suggest that corticosteroids should be used in early moderate-to-severe ARDS[21]. However, in a clinical trial including 180 patients with ARDS, no benefit of corticosteroids was found in terms of hospital survival; moreover, using methylprednisolone two weeks after the onset of ARDS can significantly increase the 60-day and 180-day mortality rates[22]. A similar result was also detected in patients with sepsis-associated ARDS[23]. In our study, 28-day non-survivors, compared with survivors, had a higher ratio of corticosteroid use, and the relationship between eosinophils and 28-day mortality was non-existent in patients who used corticosteroids; this suggests that the potential protective role of eosinophils in decreasing the mortality rate can be counteracted by corticosteroid use. Although corticosteroids improve clinical symptoms to some extent, the clinical use of corticosteroids in ARDS should be considered with caution, taking into account both the negative effects and the use time.

The large sample size from the MIMIC III database was our study strength, and it allowed deeper analysis under full consideration of confounding variables and ensured robust results; however, the study also has limitations. First, in our study patients were divided based on the maximum value of blood eosinophil counts within 72 h after ICU admission. However, the eosinophils fluctuated with time and patient condition. The level of fluctuation and variation tendency may affect patients' prognoses, and this needs further study. Second, the best cut-off value of eosinophils has yet to be determined. A cut off of 2% has been most commonly used in previous studies of COPD[24]; therefore, we used 2% for our group standard, but this cannot avoid related bias. Third, missing data, such as on blood eosinophil value and weight, are pervasive in the MIMIC-III database. Blood eosinophils are the most important target variable in the present study; to avoid bias from estimating missing values, we excluded the patients who had no data on the blood eosinophil count within the first 72 h of entering the ICU, which led to a loss of many samples. The proportion of other missing data was less than 5% in this study, and we used the corresponding mean/median value to replace the missing data; this methodology cannot avoid bias. Fourth, the

subgroup analysis was conducted only according to whether corticosteroids were used within 24 h before ICU admission to 72 h after. Whether the dose of corticosteroids and the time courses of the corticosteroid treatment affect the relationship between eosinophils and the outcome of patients with ARDS needs to be explored in future studies. Finally, the present study is a retrospective study which only allowed us to deduce the relationships among the blood eosinophil count, corticosteroids, and mortality, and a definite causal relationship cannot be established. Further studies, such as RCTs, are needed to verify this relationship.

Conclusion

Higher eosinophil counts are related to lower mortality in patients with ARDS. This relationship was not influenced by confounders such as the characteristics of mechanical ventilation or the severity of disease. However, this result was significant only in patients who did not use corticosteroids. To definitively assess the protective role of blood eosinophil counts in ARDS, larger RCTs are needed.

Abbreviations

ARDS, acute respiratory distress syndrome; ICU, intensive care unit; COPD, chronic obstructive pulmonary disease; BMI, body mass index; SAPS II, simplified acute physiology score II; WBC, white blood cell; RBC, red blood cell; PLT, platelet count; EOS, eosinophil count; pH, hydrogen ion concentration; PBW, predicted body weight; PEEP, positive and expiratory pressure; MIMIC-III, Medical Information Mart for Intensive Care; BIDMC, Beth Israel Deaconess Medical Center; SQL, Structured query language; PSM, propensity score matching; HR, hazard ratio ; CI, confidence interval; VIF, variance inflation factor; RCT, randomized controlled trial; IQR interquartile range.

Declarations

Ethics approval and consent to participate

The right of this database was approved by the Massachusetts Institute of Technology (Cambridge, MA) and Beth Israel Deaconess Medical Center (Boston, MA) and consent was obtained for the original data collection. Patients' information in the MIMIC-III database was anonymized; therefore, informed consent was not required.

Availability of data and materials

The datasets presented in the current study are available in the MIMIC-III database.

Consent for publication

Not applicable.

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Authors' contributions

HC conceived and designed the study and extracted data. YM and JX performed all statistical analyses. XH and NZ were involved in drafting the manuscript and interpretation of the data. YW was also involved in interpretation of

the data and made critical revisions to the discussion section. All the authors gave final approval of the version to be published and agree to be accountable for all aspects of the work regarding questions related to the accuracy or integrity of any part of the work.

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Competing interests

The authors declare that they have no competing interests.

References

1. Bellani G, Laffey JG, Pham T, Fan E, Brochard L, Esteban A, Gattinoni L, van Haren F, Larsson A, McAuley DF et al. Epidemiology, Patterns of Care, and Mortality for Patients With Acute Respiratory Distress Syndrome in Intensive Care Units in 50 Countries. JAMA. 2016; 315(8):788-800.
2. Matthay MA, Zemans RL, Zimmerman GA, Arabi YM, Beitler JR, Mercat A, Herridge M, Randolph AG, Calfee CS. Acute respiratory distress syndrome. Nat Rev Dis Primers. 2019; 5(1):18.
3. Mesnil C, Raulier S, Paulissen G, Xiao X, Birrell MA, Pirottin D, Janss T, Starkl P, Ramery E, Henket M et al. Lung-resident eosinophils represent a distinct regulatory eosinophil subset. J Clin Invest 2016, 126(9):3279-3295.
4. Wu H-X, Zhuo K-Q, Cheng D-Y. Peripheral Blood Eosinophil as a Biomarker in Outcomes of Acute Exacerbation of Chronic Obstructive Pulmonary Disease. Int J Chron Obstruct Pulmon Dis. 2019; 14:3003-3015.
5. Oh Y-M, Lee KS, Hong Y, Hwang SC, Kim JY, Kim DK, Yoo KH, Lee J-H, Kim T-H, Lim SY et al. Blood eosinophil count as a prognostic biomarker in COPD. Int J Chron Obstruct Pulmon Dis. 2018; 13:3589-3596.
6. Håkansson KEJ, Rasmussen LJH, Godtfredsen NS, Tupper OD, Eugen-Olsen J, Kallemose T, Andersen O, Ulrik CS. The biomarkers suPAR and blood eosinophils are associated with hospital readmissions and mortality in asthma - a retrospective cohort study. Respir Res. 2019; 20(1):258.
7. Price DB, Rigazio A, Campbell JD, Bleecker ER, Corrigan CJ, Thomas M, Wenzel SE, Wilson AM, Small MB, Gopalan G et al. Blood eosinophil count and prospective annual asthma disease burden: a UK cohort study. Lancet Respir Med. 2015; 3(11):849-858.
8. Global strategy for the diagnosis, management, and prevention of COPD update 2019.2019. https://goldcopd.org/.
9. Modig J, Samuelsson T, Hällgren R. The predictive and discriminative value of biologically active products of eosinophils, neutrophils and complement in bronchoalveolar lavage and blood in patients with adult respiratory distress syndrome. Resuscitation. 1986; 14(3):121-134.
10. Hällgren R, Borg T, Venge P, Modig J. Signs of neutrophil and eosinophil activation in adult respiratory distress syndrome. Crit Care Med. 1984; 12(1):14-18.
11. Willetts L, Parker K, Wesselius LJ, Protheroe CA, Jaben E, Graziano P, Moqbel R, Leslie KO, Lee NA, Lee JJ. Immunodetection of occult eosinophils in lung tissue biopsies may help predict survival in acute lung injury. Respir Res. 2011; 12:116.
12. Zhu C, Weng Q-Y, Zhou L-R, Cao C, Li F, Wu Y-F, Wu Y-P, Li M, Hu Y, Shen J-X et al. Homeostatic and Early Recruited CD101 Eosinophils Suppress Endotoxin-induced Acute Lung Injury. Eur Respir J. 2020; doi:

0.1183/13993003.02354-2019.

13. Chan M-C, Chao W-C, Liang S-J, Tseng C-H, Wang H-C, Chien Y-C, Yang K-Y, Chen W-C, Perng W-C, Kao K-C et al. First tidal volume greater than 8 mL/kg is associated with increased mortality in complicated influenza infection with acute respiratory distress syndrome. J Formos Med Assoc. 2019; 118(1 Pt 2):378-385.
14. Shen Y, Cai G, Gong S, Dong L, Yan J, Cai W. Interaction between low tidal volume ventilation strategy and severity of acute respiratory distress syndrome: a retrospective cohort study. Crit Care. 2019; 23(1):254.
15. Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, Camporota L, Slutsky AS. Acute respiratory distress syndrome: the Berlin Definition. JAMA. 2012; 307(23):2526-2533.
16. Thorn GW, Renold AE, Wilson DL, Frawley TF, Jenkins D, Garcia-Reyes J, Forsham PH. Clinical studies on the activity of orally administered cortisone. N Engl J Med. 1951; 245(15):549-555.
17. Casanova C, Celli BR, de-Torres JP, Martínez-Gonzalez C, Cosio BG, Pinto-Plata V, de Lucas-Ramos P, Divo M, Fuster A, Peces-Barba G et al. Prevalence of persistent blood eosinophilia: relation to outcomes in patients with COPD. Eur Respir J. 2017; 50(5).
18. Zysman M, Deslee G, Caillaud D, Chanez P, Escamilla R, Court-Fortune I, Nesme-Meyer P, Perez T, Paillasseur J-L, Pinet C et al. Relationship between blood eosinophils, clinical characteristics, and mortality in patients with COPD. Int J Chron Obstruct Pulmon Dis. 2017; 12:1819-1824.
19. Mammen MJ, Aryal K, Alhazzani W, Alexander PE. Corticosteroids for patients with acute respiratory distress syndrome: a systematic review and meta-analysis of randomized trials. Polish archives of internal medicine. 2020; 130(4):276-286.
20. Meduri GU, Golden E, Freire AX, Taylor E, Zaman M, Carson SJ, Gibson M, Umberger R. Methylprednisolone infusion in early severe ARDS: results of a randomized controlled trial. Chest. 2007; 131(4):954-963.
21. Annane D, Pastores SM, Rochwerg B, Arlt W, Balk RA, Beishuizen A, Briegel J, Carcillo J, Christ-Crain M, Cooper MS et al. Guidelines for the diagnosis and management of critical illness-related corticosteroid insufficiency (CIRCI) in critically ill patients (Part I): Society of Critical Care Medicine (SCCM) and European Society of Intensive Care Medicine (ESICM) 2017. Intensive Care Med. 2017; 43(12):1751-1763.
22. Steinberg KP, Hudson LD, Goodman RB, Hough CL, Lanken PN, Hyzy R, Thompson BT, Ancukiewicz M. Efficacy and safety of corticosteroids for persistent acute respiratory distress syndrome. N Engl J Med. 2006; 354(16):1671-1684.
23. Tongyoo S, Permpikul C, Mongkolpun W, Vattanavanit V, Udompanturak S, Kocak M, Meduri GU. Hydrocortisone treatment in early sepsis-associated acute respiratory distress syndrome: results of a randomized controlled trial. Crit Care. 2016; 20(1):329.
24. Bafadhel M, Pavord ID, Russell REK: Eosinophils in COPD: just another biomarker? Lancet Respir Med. 2017; 5(9):747-759.

Tables

Table 1 Comparisons of baseline characteristics between survivors and non-survivors.

Variable	Total (n=3372)	Survivors (n=2555)	Non-survivors (n=817)	P
Age (years)	65.17 (53.00-76.68)	63.38 (51.51-75.27)	69.92 (57.17-80.17)	<0.001
Male, n (%)	1861 (55.19%)	1414 (55.34%)	447 (54.71%)	0.753
Weight (kg)	81 (67.8-97.1)	82 (69-98.5)	77.5 (63.3-92.3)	<0.001
BMI (kg/m^2)	27.95 (23.92-33.16)	28.29 (24.28-33.33)	26.93 (22.64-32.01)	<0.001
Comorbidities, n (%)				
COPD	588 (17.43%)	422 (16.52%)	166 (20.32%)	0.013
Asthma	223 (6.61%)	193 (7.55%)	30 (3.67%)	<0.001
Diabetes	956 (28.35%)	736 (28.81%)	220 (26.92%)	0.30
Sepsis	2133 (63.26%)	1562 (61.14%)	571 (69.89%)	<0.001
Severity of illness				
SAPS II	44 (35-55)	42 (34-52)	52 (44-63)	<0.001
Laboratory data				
WBC (*10^9/L)	12.9 (8.9-18.2)	12.6 (8.8-17.7)	13.9 (9-19.3)	0.001
RBC (*10^9/L)	3.575 (3.11-4.11)	3.58 (3.13-4.12)	3.54 (3.07-4.07)	0.042
PLT (*10^9/L)	205 (144-285)	206 (150-279)	202 (127-302)	0.193
EOS initial (*10^9/L)	0.2 (0-1)	0.3 (0-1)	0.1 (0-0.6)	<0.001
EOS min (*10^9/L)	0.2 (0-0.9)	0.2 (0-1)	0.1 (0-0.4)	<0.001
EOS max (*10^9/L)	0.4 (0-1.1)	0.5 (0.1-1.3)	0.2 (0-1)	<0.001
pH	7.35 (7.27-7.42)	7.36 (7.28-7.42)	7.33 (7.25-7.41)	<0.001
Mechanical ventilation				
Tidal volume (mL/kg PBW)	6.61 (5.33-8.01)	6.51 (5.27-7.89)	6.85 (5.56-8.26)	<0.001
Minute ventilation (L/min)	9.7 (7.9-12.1)	9.5 (7.8-11.8)	10.2 (8.1-13.2)	<0.001
Corticosteroid use, n (%)	631 (18.71%)	404 (15.81%)	227 (27.78%)	<0.001

Values are shown as the median (IQR) unless otherwise indicated.

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; SAPS II, simplified acute physiology score II; WBC, white blood cell; RBC, red blood cell; PLT, platelet; EOS, blood eosinophil count; pH, hydrogen ion concentration; PBW, predicted body weight; IQR, interquartile range.

Table 2 Comparisons of outcome characteristics between the EOS<2% and EOS≥2% groups.

	Total (n=3372)			Patients who used corticosteroids (n=631)			Patients who did not use corticosteroids (n=2741)		
Variable	EOS<2% (n=2798)	EOS≥2% (n=574)	P	EOS<2% (n=570)	EOS≥2% (n=61)	P	EOS<2% (n=2228)	EOS≥2% (n=513)	P
28-day mortality, n (%)	712 (25.45%)	105 (18.29%)	0.000	203 (35.61)	24 (39.34)	0.564	509 (22.85)	81 (15.79)	0.000
ICU mortality, n (%)	581 (20.76%)	86 (14.98%)	0.002	178 (31.23)	24 (39.34)	0.197	403 (18.09)	62 (12.09)	0.001
Hospital mortality, n (%)	688 (24.59%)	99 (17.25%)	0.000	202 (35.44)	23 (37.70)	0.725	486 (21.81)	76 (14.81)	0.000
Length of ICU stay (days)	6.17 (3.71-11.96)	6.08 (3.46-12.38)	0.623	7.27 (4.33-13.96)	9.08 (4.24-12.29)	0.954	6 (3.5-11.5)	6.04 (3.42-12.58)	0.992
Length of hospital stay (days)	11.96 (7.29-19.83)	11.67 (7-21.042)	0.856	13.125 (7.88-23.08)	13.42 (7.5-16.92)	0.302	11.77 (7.21-18.85)	11.54 (7-21.29)	0.392

Abbreviations: EOS, blood eosinophil count; ICU, intensive care unit.

Table 3 Association between EOS and 28-day mortality

	Model 1			Model 2			Model 3		
Variable	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
EOS	0.761	0.620-0.935	0.009	0.730	0.577-0.923	0.009	/	/	/
SAP II	1.037	1.032-1.041	<0.001	1.037	1.031-1.042	<0.001	1.033	1.024-1.042	<0.001
Weight	0.993	0.990-0.996	<0.001	0.993	0.989-0.997	<0.001	/	/	/
Minute ventilation	1.056	1.037-1.075	<0.001	1.056	1.032-1.079	<0.001	1.057	1.023-1.092	0.001
Asthma	0.652	0.452-0.940	0.022	/	/	/	0.359	0.147-0.876	0.024
Sepsis	/	/	/	/	/	/	0.661	0.475-0.920	0.014
Age	/	/	/	1.002	1.000-1.003	0.030	/	/	/

Note: Associations of EOS with 28-day mortality were assessed by Cox regression models using a stepwise backward method with $p < 0.05$. Twelve confounders with a p value <0.10 in the univariate analyses were included in the Cox regression analyses: age, weight, BMI, COPD, asthma, sepsis, SAP II score, WBC, RBC, pH, tidal volume and minute ventilation. Model 1 used all patients included in our study. The p value of the proportional hazards assumption was 0.1465, and the mean VIF=5.17. Model 2 used patients who did not use corticosteroids. The p value of proportional hazards assumption was 0.167, and mean VIF=6.05. Model 3 used patients who used corticosteroids. The p value of the proportional hazards assumption was 0.113, and the mean VIF=5.07.

"/" indicates that the variable was not included into the model.

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; SAPS II, simplified acute physiology score II; WBC, white blood cell; RBC, red blood cell; PLT, platelet; EOS, blood eosinophil count; pH, hydrogen ion concentration; HR, hazard ratio; CI, confidence interval; VIF, variance inflation factor.

Table 4 Comparison of the covariates after propensity score matching

Variables	EOS<2 (n=574)	EOS≥2 (n=574)	P
Age (years)	62.46 (49.74-74.48)	62.01 (50.83-74.55)	0.911
Weight (kg)	84.1 (70.9-101.9)	84.9 (72-100)	0.986
BMI (kg/m^2)	28.81 (24.91-34.62)	29.20 (24.97-34.68)	0.905
COPD, n (%)	85 (14.81)	78 (13.59)	0.554
Asthma, n (%)	40 (6.97)	39 (6.79)	0.907
Sepsis, n (%)	373 (64.98)	381 (66.38)	0.619
SAPS II	43 (34-53)	42 (33-52)	0.545
WBC (*10^9/L)	11.1 (7.6-16.4)	11.2 (7.5-16.1)	0.976
RBC (*10^9/L)	3.45 (2.92-3.91)	3.44 (3.02-3.98)	0.285
pH	7.35 (7.28-7.42)	7.37 (7.29-7.43)	0.179
Tidal volume (mL/kg PBW)	6.40 (5.10-7.89)	6.29 (5.19-7.70)	0.708
Minute ventilation (L/min)	9.72 (8-12.2)	9.5 (7.8-12.1)	0.471
Clinical outcome			
28-day mortality, n (%)	136 (23.69)	105 (18.29)	0.025
ICU mortality, n (%)	118 (20.56)	86 (14.98)	0.013
Hospital mortality, n (%)	142 (24.74)	99 (17.25)	0.002
Length of ICU stay (days)	6.94 (4-13.29)	6.08 (3.46-12.38)	0.042
Length of hospital stay (days)	13.65 (8.33-22.83)	11.67 (7-21.04)	0.013

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; SAPS II, simplified acute physiology score II; WBC, white blood cell; RBC, red blood cell; pH, hydrogen ion concentration; PBW, predicted body weight; ICU, intensive care unit.

Figures

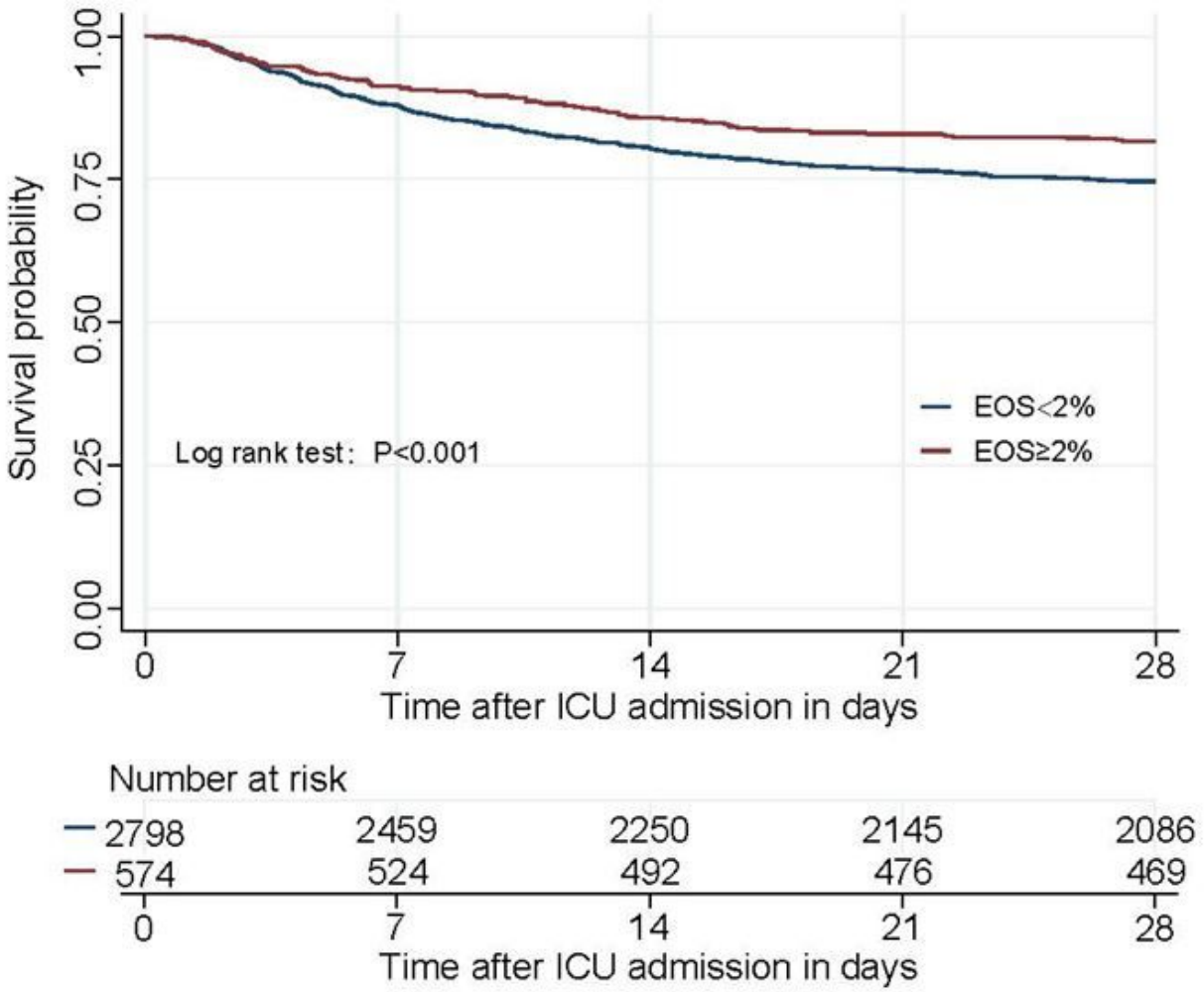

Figure 1

Kaplan-Meier survival curve of the study population. Abbreviations: EOS, eosinophil count; ICU, intensive care unit.

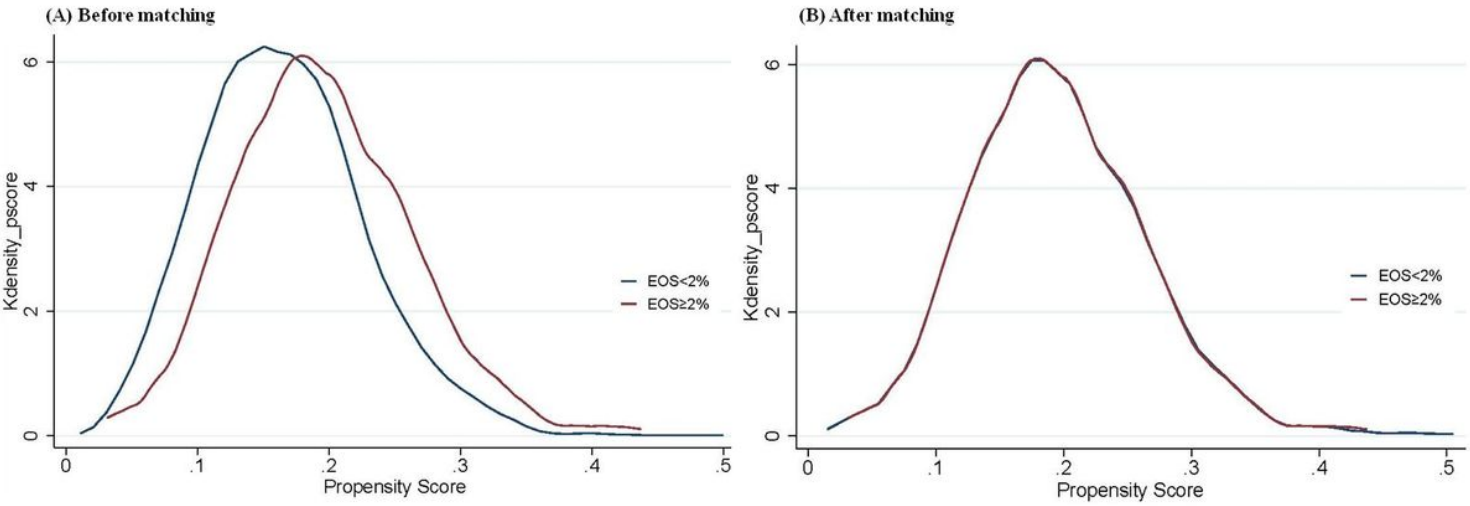

Figure 2

Kernel density plots of p-score before and after propensity score matching. Abbreviations: EOS, eosinophil count.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- STROBEchecklistv4combined.docx