Original Article

Association of immune deficiency with prognosis and corticosteroid treatment benefits among patients with acute respiratory distress syndrome

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Background: The role of corticosteroids in acute respiratory distress syndrome (ARDS) remains contentious. This study aims to investigate the prognostic significance of immune deficiency in patients with ARDS and its response to varying doses of corticosteroids.

Methods: This single-center, retrospective cohort study enrolled 657 ARDS patients from January 24, 2008, to September 12, 2022, at Zhongshan Hospital of Fudan University, Shanghai, China. The patients were categorized into a discovery dataset (n=357) and a validation dataset (n=300), based on admission date. Further validation of the results in the validation dataset was used to enhance the credibility of the study conclusions. The study examined the association between immune deficiency and the patients' clinical characteristics, treatment measures, and prognosis. The primary outcome was 28-day mortality post disease onset. Data analysis was conducted from June 15, 2023 to August 15, 2023.

Results: The initial risk factor analysis in the discovery dataset was primarily based on the clinical characteristics, and the results suggested that immune deficiency likely impacted overall survival among patients receiving different doses of corticosteroid treatment. Multivariate analysis identified immune deficiency as an independent prognostic factor for overall survival in both the discovery and validation datasets. The final analysis revealed that patients with mild to moderate ARDS [discovery dataset: hazard ratio (HR) =1.719; 95% confidence interval (CI): 1.229–2.406; log-rank test P=0.001; validation dataset: HR =1.874; 95% CI: 1.238–2.837; log-rank test P=0.002] or severe ARDS (discovery dataset: HR =1.874; 95% CI: 1.007–3.488; log-rank test P=0.04; validation dataset: HR =1.698; 95% CI: 1.042–2.768; log-rank test P=0.03) with immune deficiency exhibited lower overall survival rates. Patients with mild to moderate ARDS and immune deficiency showed greater benefits from low-dose corticosteroid treatment (HR =0.409; 95% CI: 0.249–0.671; P<0.001 for interaction), whereas those with severe ARDS and immune deficiency benefitted from both low and high-dose treatments (low corticosteroid: HR =0.299; 95% CI: 0.136–0.654;

high corticosteroid: HR =0.458; 95% CI: 0.214–0.981; P=0.005 for interaction).

Conclusions: Immune deficiency is an independent risk factor in ARDS. Incorporating it into the disease severity grading system based on the Berlin criteria may enhance personalized treatment approaches for ARDS patients. These findings warrant further validation through prospective, large-scale, multicenter randomized controlled trials (RCTs).

Keywords: Acute respiratory distress syndrome (ARDS); corticosteroid; immune deficiency; overall survival

Submitted Jan 17, 2024. Accepted for publication May 17, 2024. Published online Jul 04, 2024.
doi: 10.21037/jtd-24-109
View this article at: https://dx.doi.org/10.21037/jtd-24-109

Introduction

Acute respiratory distress syndrome (ARDS) is a common clinical syndrome characterized by acute hypoxic respiratory failure and non-cardiogenic lung infiltration (1). ARDS arises from a variety of causes, both infectious and non-infectious. These causes can lead to direct lung damage through local inflammation or indirect damage via systemic inflammation (2). Sepsis from different pathogens are notable causes of ARDS, among which pulmonary sepsis being the predominant source (3). Common non-infectious etiologies include pancreatitis, aspiration of stomach contents, severe traumatic injury with shock, transfusion-related acute lung injury (TRALI), and smoke inhalation or environment conditions, i.e., ARDS commonly seen in workers in coal mines "black lung" or gold mine workers (2). In the LUNG SAFE prospective cohort study, encompassing 459 intensive care units (ICUs) across 50 countries on five continents, 10.4% of ICU patients and 23.4% of those on mechanical ventilation met the Berlin definition criteria, a commonly used tool to assess the severity of ARDS by using respiratory parameters such as partial pressure of oxygen to fraction of inspired oxygen ratio (PaO_2/FiO_2) (3,4). The prevalence of ARDS has notably increased during the coronavirus disease 2019 (COVID-19) pandemic (2). The heterogeneity of ARDS, in terms of pathogenesis, clinical features, and treatment responses, presents challenges for clinical management. Advancements in understanding the epidemiology and risk factors, alongside differential diagnosis and personalized clinical management, are crucial for reducing the disease burden and enhancing patient quality of life.

Biomarkers are instrumental in identifying the main etiology of patients, stratifying risk, and predicting clinical outcomes (5). The discovery and verification of diagnostic or prognostic biomarkers for ARDS aid in screening high-risk populations and phenotypic analysis. Biomarkers used to identify alveolar and bronchiolar damage include surfactant protein D, Krebs von den lungen-6 (KL-6), and soluble receptor for advanced glycation end-products (sRAGEs); endothelial injury and coagulation markers like gelsolin, thrombomodulin, protein C, endocan, plasminogen activator inhibitor-1 (PAI or PAI-1), angiopoietin-2, von Willebrand factor (vWF); and treatment response biomarkers, particularly those related to lung inflammation, infection, C-reactive protein (CRP), and white blood cells (WBCs) (5). As understanding of ARDS deepens, research on biomarkers, particularly those related to pulmonary inflammation, is expanding. Current studies are increasingly focusing on the

Highlight box

Key findings

- Immune deficiency is an independent risk factor in acute respiratory distress syndrome (ARDS) and patients with immune deficiency with varying levels of severity of ARDS may benefit from different doses of corticosteroids.

What is known and what is new?

- The role of corticosteroids in the management of ARDS remains controversial. Many studies primarily focus on the effectiveness and optimal regimen of corticosteroids in treating ARDS patients, without deeply exploring the reasons for these variances.
- This study indicates that immune deficiency is an independent prognostic factor in ARDS. Patients with mild to moderate ARDS and immune deficiency may benefit from low-dose corticosteroid treatment, while those with severe ARDS and immune deficiency may benefit from both low and high-dose corticosteroid therapy.

What is the implication, and what should change now?

- Incorporating immune deficiency into the disease severity grading system based on the Berlin criteria may enhance personalized treatment approaches for ARDS patients.
- The findings warrant further validation through prospective, large-scale, multicenter randomized controlled trials.

role of immune deficiency in patient prognosis, aligned with the immunopathological mechanisms of ARDS (5,6), such as inflammatory disorder and increased pulmonary endothelial and epithelial permeability (6).

Acute hypoxic respiratory failure is a leading cause for admission of immunocompromised patients to the ICU (7), with ARDS occurring in 35–75% of this population (8). A post hoc analysis of LUNG SAFE data revealed that patients with compromised immune function experienced higher in-hospital mortality compared to those with normal immune function (52.4% *vs.* 36.2%, P<0.001) (9), indicating that immunosuppression may independently predict mortality in ARDS patients (10). Current research primarily focuses on the causes of immune deficiency in ARDS patients and its impact on the efficacy of standard clinical treatments. Immune deficiency can result from a range of conditions, including genetic diseases, acquired diseases like acquired immune deficiency syndrome (AIDS) and hematologic malignancies, as well as treatments such as prolonged corticosteroid or chemotherapy use (11). Additionally, patients with various chronic and critical illnesses also exhibit degrees of immune suppression (11,12). Consequently, some researchers suggest classifying immune suppression based on specific immune system deficits, namely neutropenia, impaired humoral immunity mediated by B lymphocytes, and impaired cellular immunity mediated by T lymphocytes (11). In terms of treatment correlation, while researchers focus on non-invasive ventilation or extracorporeal membrane oxygenation (ECMO), it is argued that immune-compromised status might not independently predict ECMO weaning failure in ARDS patients (13).

Currently, ARDS treatment encompasses ventilation therapy, prone positioning, extracorporeal support, neuromuscular blockade, and corticosteroids (14). However, the role of corticosteroids in ARDS, septic shock, community-acquired pneumonia, and other severe diseases remains controversial (15). A multicenter randomized controlled trial (RCT) in 17 ICUs in Spain found that early dexamethasone administration reduced both the duration of mechanical ventilation (between-group difference 4.8 days, P<0.0001) and overall mortality (between-group difference 15.3%, P=0.005) in patients with moderate-to-severe ARDS (16). Another systematic review of 14 RCTs indicated that low doses (no more than 10 mg/kg/day methylprednisolone) and prolonged courses (more than 7 days) of corticosteroid treatment reduced ARDS mortality [lower dose: relative risk (RR) =0.69; 95% confidence interval (CI): 0.51–0.93; P=0.02; longer-course therapy: RR =0.60; 95% CI: 0.37–0.99; P=0.04] (17). The most common adverse event was hyperglycemia, though no statistical association was established (16). However, another RCT investigating early methylprednisolone use suggested that corticosteroids might increase long-term mortality if initiated 14 days after ARDS onset (18). These studies primarily focus on the effectiveness and optimal regimen of corticosteroids in treating ARDS patients, without deeply exploring the reasons for these variances in mortality associated with initiation of corticosteroids.

This study aims to investigate risk factors that may influence the effectiveness of corticosteroid treatment in ARDS patients through a retrospective cohort design. It further analyzes whether these factors can serve as independent risk factors for ARDS and identify patients who might benefit more from varying doses of corticosteroid treatment. These results could highlight the clinical significance of such risk factors in ARDS, providing a potential prediction system for ARDS prognosis assessment and a reference for personalized treatment of different ARDS subgroups. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-109/rc).

Methods

Study patients and design

This single-center, retrospective cohort study was conducted at Zhongshan Hospital, Fudan University, Shanghai, China. We identified adult ARDS patients admitted between January 24, 2008, and September 12, 2022, according to the American European Consensus Conference (AECC) criteria, which defined the time of onset, imaging characteristics, oxygenation function, and so on (19). Considering the sample size distribution and data characteristics, we selected 2017 as the time node. The discovery dataset included patients admitted after 2017, while the validation dataset comprised those admitted before 2017. The primary source population consisted of patients experiencing respiratory failure during the study period. Eligible patients were 18 years or older, diagnosed with ARDS based on AECC criteria, which include initial clinical symptoms (such as pneumonia, aspiration, sepsis, and pancreatitis) or worsening respiratory symptoms within a week, bilateral lung infiltration on chest imaging, and hypoxemia. Exclusion criteria encompassed pregnancy or

lactation, brain death, severe chronic obstructive pulmonary disease, or congestive heart failure. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Zhongshan Hospital, Fudan University (No. 2021SQCJ2640) and individual consent for this retrospective analysis was waived.

In the discovery dataset, patients were categorized into "no corticosteroid treatment", "low-dose corticosteroid treatment", and "high-dose corticosteroid treatment" groups based on their maximum daily methylprednisolone equivalent. We compared baseline characteristics, clinical treatment courses, and outcomes across these groups and analyzed risk factors affecting the primary outcome. The study then examined the impact of this risk factor on the prognosis of different patient subgroups, with results further validated in the validation dataset. The study also discussed the impact on the efficacy of different corticosteroid doses, aiming to provide a basis for personalized medication in ARDS patients.

Definitions

We classified ARDS patients into different severity categories based on the Berlin criteria (4): mild ARDS as 200 mmHg > PaO_2/FiO_2 ≤300 mmHg, moderate ARDS as 100 mmHg > PaO_2/FiO_2 ≤200 mmHg, and severe ARDS as PaO_2/FiO_2 ≤100 mmHg.

The low-dose corticosteroid treatment group primarily comprised ARDS patients receiving a maximum daily dose of less than 80 mg of methylprednisolone equivalent. Conversely, the high-dose group included ARDS patients with a daily dose exceeding 80 mg. To ensure consistency, doses of various corticosteroids, including cortisone, dexamethasone, prednisone, and hydrocortisone, were converted to their methylprednisolone equivalents, considering that 4 mg of methylprednisolone is equivalent to 0.75 mg dexamethasone, 20 mg hydrocortisone, 25 mg cortisone, or 5 mg prednisone (20).

Patients classified as having immune deficiency included those on long-term (>3 months) or high-dose (>0.5 mg/kg/day) steroid therapy or other immunosuppressants, recipients of solid organ transplants, patients with solid tumors or hematological malignancies undergoing chemotherapy within the past 5 years, and those with primary immune deficiencies (i.e., X-linked agammaglobulinemia, DiGeorge syndrome, etc.), regardless of the time since diagnosis and treatment (21).

Data collection

Data were extracted and compiled from the medical record system, including: (I) basic demographic characteristics: age, sex, smoking status, immune deficiency status, pathogenesis, comorbidities, experimental examination results, and Acute Physiologic and Chronic Health Evaluation (APACHE) II score; (II) corticosteroid usage, administered intravenously (including cortisone, methylprednisolone, dexamethasone, prednisone, and hydrocortisone), with dosages converted to methylprednisolone equivalents, and duration of treatment for each patient; (III) respiratory support methods: noninvasive mechanical ventilation, invasive mechanical ventilation, and ECMO; and (IV) outcome measures: primary outcome was 28-day mortality post disease onset, with secondary outcomes including in-hospital mortality and hospitalization duration.

Statistical analysis

Statistical analysis was performed using Stata, version 17.0, with continuous variables grouped using X-tile, version 3.6.1. Categorical variables were expressed as percentages. Baseline characteristics, interventions, and outcomes between different corticosteroid dose groups, and between patients with or without immune deficiency, were compared using Pearson chi-squared test or Fisher's exact test. Continuous variables were presented as median and interquartile ranges. One-way analysis of variance (ANOVA) or Kruskal-Wallis tests were employed to compare groups receiving different corticosteroid doses, while unpaired, two-tailed Student's *t*-test or Mann-Whitney *U* test were used for comparisons between groups with or without immune deficiency. Kaplan-Meier curves and log-rank tests assessed survival outcomes across different severity subgroup multivariate Cox regression analyzed risk factors impacting patient survival and the effect of immune deficiency on corticosteroid treatment efficacy in various severity groups. All statistical analyses were two-sided, with a $P<0.05$ considered statistically significant.

Results

Risk factors associated with survival across different corticosteroid dose groups

In the discovery dataset, we compared basic characteristics, clinical treatments, pathological parameters, and prognoses among groups receiving various corticosteroid

doses, as detailed in Table S1. Risk factors potentially influencing survival in these groups were analyzed using chi-squared test or Fisher's exact test (Table S2). This analysis revealed associations between PaO_2/FiO_2, immune deficiency, neutrophil and lymphocyte counts, and overall and subgroup outcomes, suggesting these factors might influence the efficacy of corticosteroid treatment. Subsequently, multivariate Cox regression analysis was utilized to examine the relationship between potential risk factors and survival (Table S3), encompassing age, sex, smoking status, PaO_2/FiO_2, disease etiology, comorbidities, immune deficiency, platelet count (PLT), procalcitonin (PCT), prothrombin time (PT), and CRP. The findings indicated that immune deficiency could be a significant risk factor affecting therapeutic outcomes at different dosages.

Baseline patient characteristics

The study flow is depicted in *Figure 1*. We screened 6,110 patients with respiratory failure for ARDS, ultimately including 657 ARDS patients in the discovery and validation datasets. In the discovery dataset (n=357), 244 (68.35%) patients were male, with a median age of 67 [57–75] years. Of these, 160 (44.82%) had immune deficiencies, and 197 (55.18%) did not. The validation dataset (n=300) comprised 196 (65.33%) male patients with a median age of 63 [50–73] years, including 101 (33.67%) with immune deficiencies and 199 (66.33%) without (*Table 1*). Within the discovery dataset, 193 (54.06%) patients died within 28 days, and 219 (61.34%) died in-hospital. In the validation dataset, these outcomes were observed in 161 (53.67%) and 192 (64.00%) patients, respectively (*Table 2*).

Additional comprehensive characteristics and clinicopathological indicators are presented in *Table 1* and *Figure 2*. Age distribution differed significantly between groups in the discovery dataset (P=0.009). In the validation dataset, except for smoking status, PaO_2/FiO_2 and comorbidities, all other parameters showed significant differences between groups. Both datasets showed notable differences in PT and interleukin (IL)-10.

Independent risk factors for mortality in ARDS

After verifying the proportional hazards assumption, we conducted a multivariate Cox regression analysis (*Figure 3*), incorporating variables such as age, sex, smoking status, immune deficiency, disease severity, comorbidities (diabetes and chronic liver disease), and select physiological parameters (PLT, PCT, PT, CRP). IL-6 and IL-10 were excluded due to multicollinearity or significant data loss. The analysis identified immune deficiency [discovery dataset: hazard ratio (HR) =1.677; 95% CI: 1.192–2.359; P=0.003; validation dataset: HR =1.856; 95% CI: 1.266–2.721; P=0.002] and severe disease severity (discovery dataset: HR =1.551; 95% CI: 1.024–2.349; P=0.04; validation dataset: HR =3.104; 95% CI: 1.315–7.327; P=0.01) as independent risk factors for overall survival. Additionally, increased age in the discovery dataset (HR =1.013; 95% CI: 1.000–1.025; P=0.045) and elevated PCT in the validation dataset (HR =1.036; 95% CI: 1.013–1.059; P=0.002) were identified as potential, albeit weaker, risk factors for overall survival.

Relationship between immune deficiency and prognosis in patients with different severities of ARDS

To assess the impact of immune deficiency on the prognosis of ARDS patients of varying severities, Kaplan-Meier survival analysis was employed (*Figure 4*). In both the discovery (HR =1.638; 95% CI: 1.233–2.174) and validation datasets (HR =1.830; 95% CI: 1.334–2.510), non-immune deficiency patients exhibited significantly better overall survival compared to their immune-deficient counterparts, with the log-rank test results of both were P<0.001. These findings indicate that immune deficiency is potentially clinically significant for the survival outcome of ARDS patients.

We then categorized patients into mild-to-moderate and severe disease subgroups. Among those with mild-to-moderate ARDS, immune-deficient patients showed poorer survival in both the discovery (HR =1.719; 95% CI: 1.229–2.406; log-rank test P=0.001) and validation datasets (HR =1.874; 95% CI: 1.238–2.837; log-rank test P=0.002). Similar trends were observed in patients with severe ARDS (discovery dataset: HR =1.874; 95% CI: 1.007–3.488; log-rank test P=0.04; validation dataset: HR =1.698; 95% CI: 1.042–2.768; log-rank test P=0.03).

Relationship between immune deficiency and corticosteroid treatment benefits in patients with different severities of ARDS

Furthermore, we explored whether ARDS patients with immune deficiency could benefit from corticosteroid treatment. For immune-deficient ARDS patients, a relationship was noted between corticosteroid use and

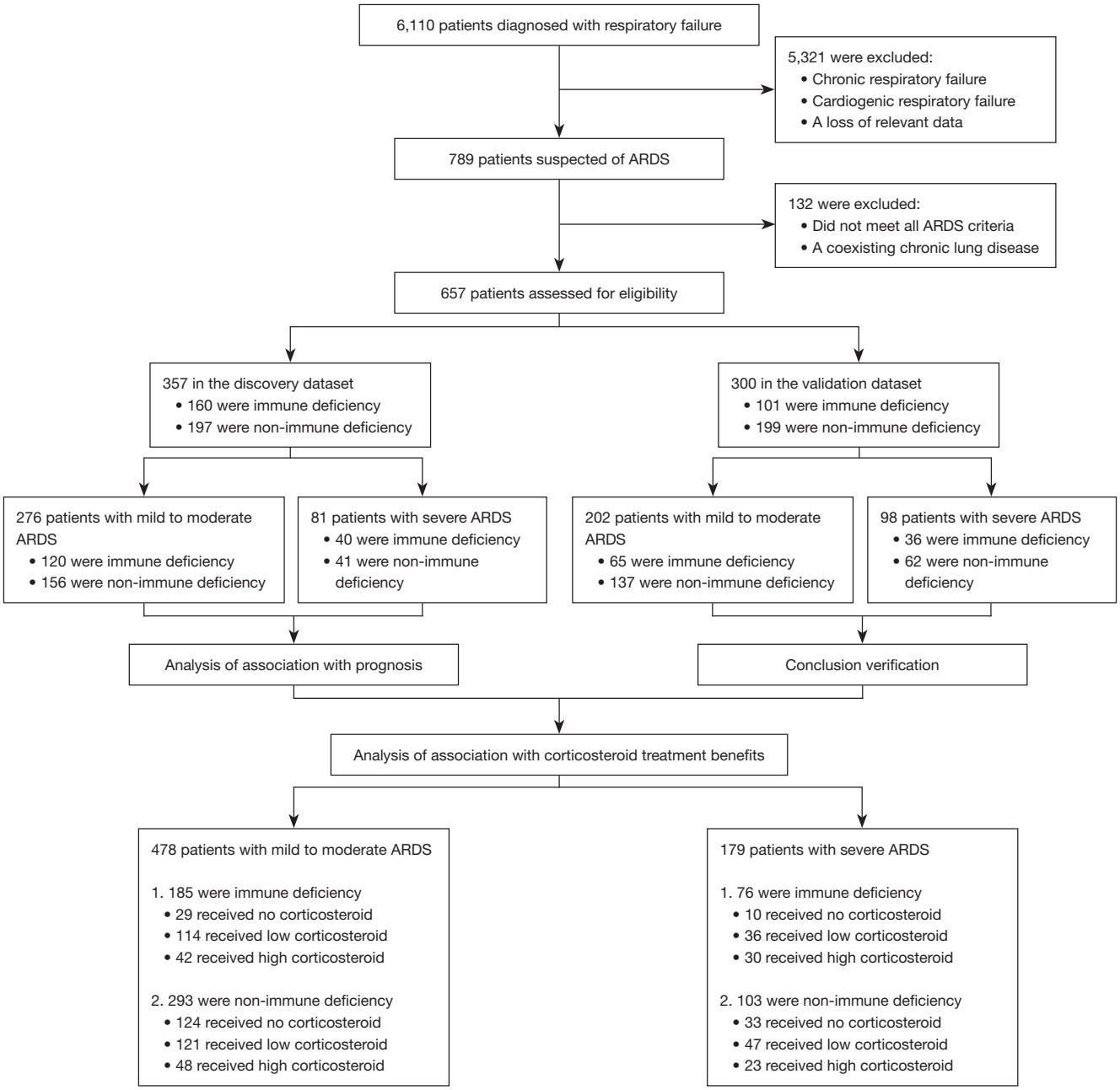

Figure 1 Study design. In this study, 657 patients with ARDS were identified from 6,110 patients with respiratory failure. The association between the presence of immune deficiency and overall survival was studied in two randomly assigned patient datasets: a discovery dataset (n=357) and a validation dataset (n=300). The association between the presence of immune deficiency and the benefit of different doses of corticosteroid treatment was tested in a pooled database of 478 patients with mild to moderate ARDS and 179 patients with severe ARDS in two datasets. ARDS, acute respiratory distress syndrome.

Table 1 Baseline characteristics of ARDS patients with or without immune deficiency in discovery dataset and validation dataset

Variables	Discovery dataset				Validation dataset			
	All patients (n=357)	Immune deficiency (n=160)	Non-immune deficiency (n=197)	P value	All patients (n=300)	Immune deficiency (n=101)	Non-immune deficiency (n=199)	P value
Age (years)	67 [57–75]	64 [56–73]	68 [59–78]	0.009	63 [50–73]	60 [42–69]	64 [53–76]	0.002
Sex, male	244 (68.35)	104 (65.00)	140 (71.07)	0.22	196 (65.33)	55 (54.46)	141 (70.85)	0.005
Smoking	101 (28.29)	53 (33.13)	48 (24.37)	0.07	53 (17.67)	15 (14.85)	38 (19.10)	0.36
PaO_2/FiO_2	189.5 [111–259]	165 [102–248]	198 [117–266]	0.06	121.5 [93–155.5]	126 [82–165]	116 [94–150]	0.90
APACHE II score	19 [11–28]	22.5 [14–31]	17 [11–27]	0.11	16 [11–21]	18 [13–23]	15 [11–20]	<0.001
Cause of ARDS								
Pneumonia	265 (74.23)	130 (81.25)	135 (68.53)	0.006	163 (54.33)	65 (64.36)	98 (49.25)	0.01
Sepsis	17 (4.76)	5 (3.13)	12 (6.09)	0.19	52 (17.33)	22 (21.78)	30 (15.08)	0.15
Aspiration	12 (3.36)	4 (2.50)	8 (4.06)	0.42	52 (17.33)	11 (10.89)	41 (20.60)	0.04
Trauma	10 (2.80)	4 (2.50)	6 (3.05)	>0.99	36 (12.00)	6 (5.94)	30 (15.08)	0.02
Others	53 (14.85)	17 (10.63)	36 (18.27)	0.04	–	–	–	–
Any comorbidity								
Diabetes	77 (21.57)	31 (19.38)	46 (23.35)	0.36	37 (12.33)	11 (10.89)	26 (13.07)	0.59
Hypertension	144 (40.34)	61 (38.13)	83 (42.13)	0.44	115 (38.33)	38 (37.62)	77 (38.69)	0.86
Chronic liver disease	41 (11.48)	20 (12.50)	21 (10.66)	0.59	11 (3.67)	4 (3.96)	7 (3.52)	>0.99
Respiratory support								
NIMV	281 (78.71)	124 (77.50)	157 (79.70)	0.61	157 (52.33)	41 (40.59)	116 (58.29)	0.004
IMV	184 (51.54)	82 (51.25)	102 (51.78)	0.92	173 (57.67)	47 (46.53)	126 (63.32)	0.005
ECMO	19 (5.32)	11 (6.88)	8 (4.06)	0.24	–	–	–	–

Data are presented as n (%) or median [IQR]. For continuous variables, *t*-test or Mann-Whitney *U* test was used to calculate the P value unless otherwise noted. For categorical variables, chi-square test was used to calculate the P value unless otherwise noted. In the discovery dataset, most of the baseline characteristics were comparable between the immune deficient and non-immune deficient groups, whereas in the validation dataset, a greater number of baseline characteristics were unevenly distributed between the two groups. ARDS, acute respiratory distress syndrome; PaO_2, partial pressure of oxygen; FiO_2, fraction of inspired oxygen; APACHE II, Acute Physiologic and Chronic Health Evaluation II; NIMV, noninvasive mechanical ventilation; IMV, invasive mechanical ventilation; ECMO, extracorporeal membrane oxygenation; IQR, interquartile range.

Table 2 Clinical outcomes of ARDS patients with or without immune deficiency in discovery dataset and validation dataset

Outcomes	Discovery dataset				Validation dataset			
	All patients (n=357)	Immune deficiency (n=160)	Non-immune deficiency (n=197)	P value	All patients (n=300)	Immune deficiency (n=101)	Non-immune deficiency (n=199)	P value
28-day mortality	193 (54.06)	102 (63.75)	91 (46.19)	0.001	161 (53.67)	71 (70.30)	90 (45.23)	<0.001
In-hospital mortality	219 (61.34)	115 (71.88)	104 (52.79)	<0.001	192 (64.00)	83 (82.18)	109 (54.77)	<0.001
Length of hospitalization (days)	14 [7–24]	15 [7–25]	13 [7–20.5]	0.16	14 [7–24]	11 [5–22]	15 [9–25]	0.04

Data are presented as n (%) or median [IQR]. For continuous variables, *t*-test or Mann-Whitney *U* test was used to calculate the P value unless otherwise noted. For categorical variables, chi-square test was used to calculate the P value unless otherwise noted. In the discovery dataset, the proportion of 28-day mortality and in-hospital mortality was different between the immune deficient and non-immune deficient groups. In the validation dataset, there are also differences in the distribution of length of hospitalization. ARDS, acute respiratory distress syndrome; IQR, interquartile range.

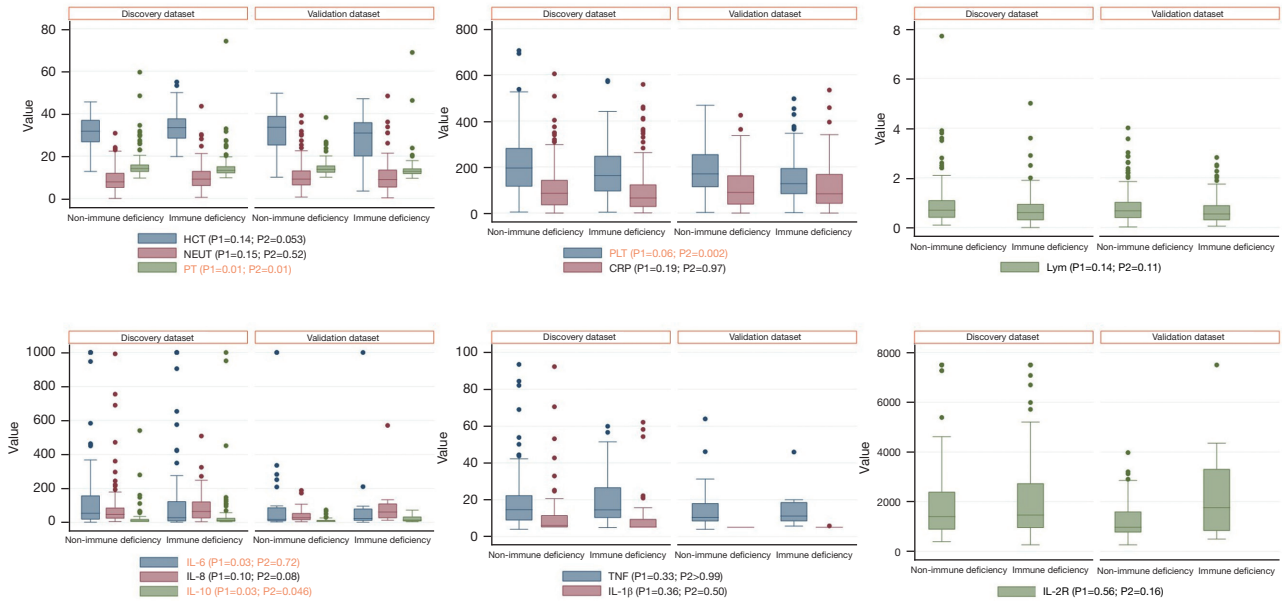

Figure 2 Distribution of physiological parameters and comparison between groups in discovery dataset and validation dataset. The *t*-test or Mann-Whitney *U* test was used to compare any of the above physiological parameters between immune deficiency and non-immune deficiency groups. P1 and P2 represent the statistical test results of discovery dataset and validation dataset, respectively. The distributions of PT and IL-10 were different in both discovery and validation datasets. The difference in PLT between the two groups was only in the validation dataset, and the difference in IL-6 between the two groups was only in the discovery dataset. HCT, hematocrit; NEUT, neutrophil count; PT, prothrombin time; PLT, platelet count; CRP, C-reactive protein; Lym, lymphocyte count; IL, interleukin; TNF, tumor necrosis factor; IL-2R interleukin 2 receptor.

mortality risk. Compared to patients not receiving corticosteroids or those on high-dose treatment, those on low-dose corticosteroid therapy exhibited a lower mortality risk. This trend was consistent across both mild-to-moderate and severe ARDS patients (*Table 3*).

Further analysis revealed that immune deficiency and corticosteroid treatment may interactively affect overall patient survival. The interaction term statistics were lower than 0.001 and 0.005 for patients with mild-to-moderate and severe ARDS, respectively (*Table 4*). Considering these interactions, it was observed that patients with mild-to-moderate ARDS and immune deficiency could benefit from low-dose corticosteroid treatment (HR =0.409; 95% CI: 0.249–0.671). Similarly, patients with severe ARDS and immune deficiency might benefit from both low-dose (HR =0.299; 95% CI: 0.136–0.654) and high-dose corticosteroid treatments (HR =0.458; 95% CI: 0.214–0.981).

Discussion

This study initially analyzed risk factors affecting the prognosis of ARDS patients undergoing varying doses of corticosteroid treatment. Immune deficiency was found to influence the 28-day mortality and in-hospital mortality of these patients, demonstrating a beneficial response to different corticosteroid dosages. Additionally, subgroup analysis evaluating the severity of ARDS based on the Berlin criteria (PaO_2/FiO_2) indicated that immune deficiency acted as an independent risk factor for overall survival. Mild to moderate ARDS patients with immune deficiency benefited from low-dose corticosteroid treatment, while severe ARDS patients with immune deficiency benefited from both low and high doses.

Comparing immune-deficient and non-immune-deficient patients revealed that the former had a lower average age (discovery dataset: P=0.009; validation dataset: P=0.002), aligning with findings from Cortegiani *et al.* (9). ARDS patients with immune deficiency were more commonly affected by pulmonary inflammation (discovery dataset: 81.25% *vs.* 68.53%, P=0.006; validation dataset: 64.36% *vs.* 49.25%, P=0.01), and exhibited higher levels of PLT, PT, IL-6, and IL-10. These findings align with the conclusions

Variables	Discovery dataset			Validation dataset		
	Forest plot	HR (95% CI)	P value	Forest plot	HR (95% CI)	P value
Age		1.013 (1.000–1.025)	0.045		1.011 (0.999–1.022)	0.07
Sex, male		0.835 (0.557–1.251)	0.38		1.131 (0.756–1.693)	0.55
Smoking		0.942 (0.620–1.431)	0.78		0.710 (0.401–1.258)	0.24
Immune deficiency		1.677 (1.192–2.359)	0.003		1.856 (1.266–2.721)	0.002
Moderate (100 mmHg < PaO_2/FiO_2 ≤200 mmHg)		1.133 (0.754–1.702)	0.55		1.892 (0.811–4.416)	0.14
Severe (PaO_2/FiO_2 ≤100 mmHg)		1.551 (1.024–2.349)	0.04		3.104 (1.315–7.327)	0.01
Diabetes		0.864 (0.573–1.302)	0.49		0.850 (0.483–1.497)	0.57
Chronic liver disease		1.456 (0.875–2.425)	0.15		1.255 (0.504–3.124)	0.63
PLT		0.999 (0.997–1.000)	0.09		0.999 (0.997–1.001)	0.18
PCT		1.008 (0.999–1.017)	0.07		1.036 (1.013–1.059)	0.002
PT		1.001 (0.990–1.011)	0.88		0.999 (0.996–1.002)	0.66
CRP		1.000 (0.999–1.002)	0.83		1.000 (0.998–1.001)	0.94

Figure 3 Multivariate cox regression analysis for overall survival and the corresponding forest plots. Multivariate cox regression analysis and forest plots were used to explore the association between possible risk factors and overall survival. Patients with immune deficiency and severe illness were risk factors for survival, both in discovery and validation datasets. Age may be related to survival in discovery dataset and PCT may be related to survival in validation dataset with weak association. HR, hazard ratio; CI, confidence interval; PaO_2, partial pressure of oxygen; FiO_2, fraction of inspired oxygen; PLT, platelet count; PCT, procalcitonin; PT, prothrombin time; CRP, C-reactive protein.

of most current studies (9,10,13,22). However, Rilinger *et al.* (10) observed lower WBC, PLT, hemoglobin (HB), and hematocrit (HCT) levels in the immune-deficient group, speculating these as potential causes for increased mortality risk in these patients. Their study, however, only analyzed the impact of immune deficiency on patients with severe ARDS. The in-hospital mortality among our immune-compromised ARDS patients was higher than that in a post hoc analysis of LUNG SAFE data by Cortegiani *et al.* (9), where 584 (20.8%) of 2,813 ARDS patients were immune deficient.

The body's immune defense mechanism plays a crucial role in the development of ARDS. Proinflammatory structural components and endogenous molecules related to cell damage can attach to Toll-like receptors on lung epithelial cells and alveolar macrophages, activating the innate immune system (23). The ensuing formation of neutrophil extracellular traps and release of histone proteins aid in capturing pathogenic microorganisms (24), along with the generation of reactive oxygen species, leukocyte proteases, chemokines, and cytokines to neutralize pathogens (25). However, while these mechanisms inhibit inflammation, they may also exacerbate lung injury. Thus, balancing their anti-infective effects and potential for alveolar damage is vital. Corticosteroids, widely used in ARDS since their inception (26,27), are linked to significant improvements in alveolar-capillary membrane permeability and the regulation of inflammation and tissue repair mediators (28). Ameliorating inflammation is fundamental to restoring homeostasis in ARDS patients (29). Variations in inflammation-related factors among immune-deficient patients may influence their prognosis and response to

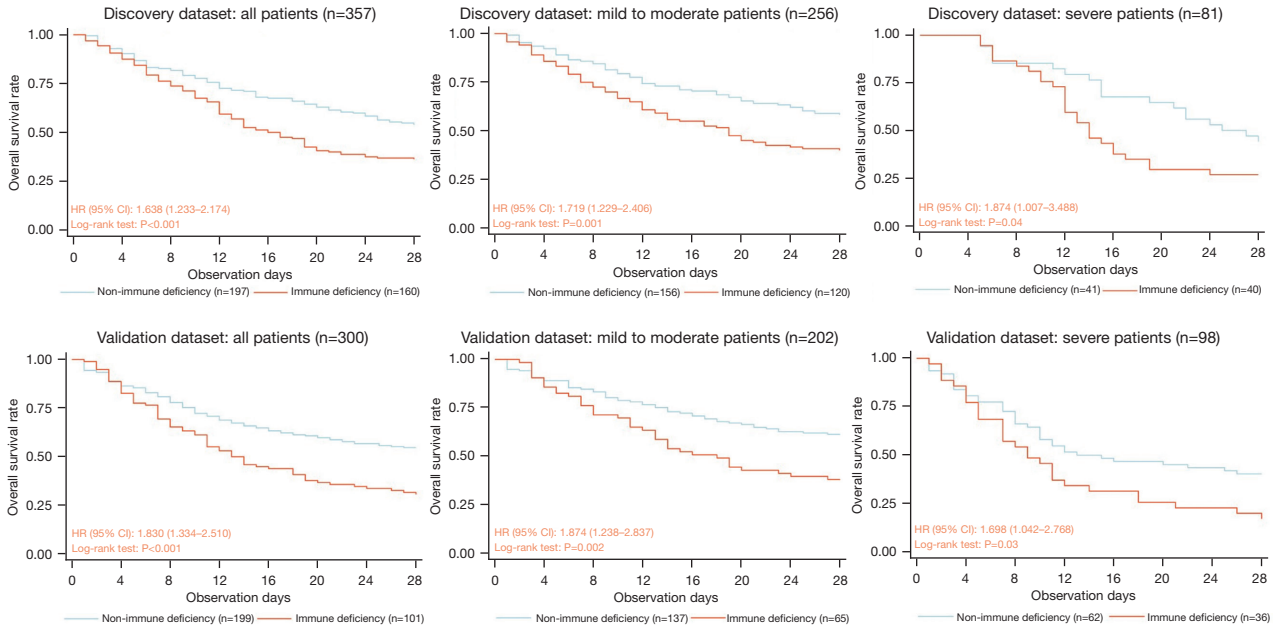

Figure 4 Kaplan-Meier survival curves and log-rank test to evaluate the prognostic value of immune deficiency in discovery dataset and validation dataset. In the two datasets, stratified according to disease severity, survival curves, and log-rank test results were used to analyze the impact of immune deficiency on patient prognosis. For general and mild to moderate ARDS patients, the overall risk of death was higher in immune deficiency patients, and the difference was statistically significant. For patients with severe ARDS in discovery dataset, due to the existence of unknown confounding, "survival time >5 days" was included as a restriction in the analysis model for correction, and the results were consistent. HR, hazard ratio; CI, confidence interval; ARDS, acute respiratory distress syndrome.

Table 3 Effect of corticosteroid therapy on different subgroups of patients

Patients	28-day mortality, n/total (%)			P value			
	No corticosteroid	Low corticosteroid	High corticosteroid	Total	No *vs.* low	No *vs.* high	Low *vs.* high
Patients with mild to moderate ARDS (n=478)							
Immune deficiency (n=185)	24/29 (82.76)	57/114 (50.00)	32/42 (76.19)	<0.001	0.001	0.51	0.003
Non-Immune deficiency (n=293)	46/124 (37.10)	49/121 (40.50)	23/48 (47.92)	0.43	0.59	0.19	0.38
Patients with severe ARDS (n=179)							
Immune deficiency (n=76)	10/10 (100.00)	23/36 (63.89)	27/30 (90.00)	0.007	0.04	0.56	0.01
Non-Immune deficiency (n=103)	17/33 (51.52)	30/47 (63.83)	16/23 (69.57)	0.35	0.27	0.18	0.64

The efficacy of corticosteroid was analyzed by chi-square test among different subgroups. For ARDS patients with immune deficiency, the probability of death was lower when low-dose glucocorticoids were used than no corticosteroid, but the probability was increased when high-dose corticosteroid were used compared with low-dose corticosteroid, and this conclusion was independent of the severity of the disease. ARDS, acute respiratory distress syndrome.

corticosteroid therapy.

Previous research indicates that certain cytokine levels are elevated in immune-deficient ARDS patients, yet levels of C-C motif chemokine ligand 22 (CCL22) are low (30). CCL22 recruits immunosuppressive regulatory T cells (Tregs) to modulate the local immune response (31,32), and diminished Treg levels may increase the likelihood of T lymphocyte dysregulation, potentially explaining the higher

Table 4 Corticosteroid treatment interaction with immune deficiency for overall survival

Patients	Patients with mild to moderate ARDS (n=478)					Patients with severe ARDS (n=179)				
	P value†	Low corticosteroid		High corticosteroid		P value†	Low corticosteroid		High corticosteroid	
		HR (95% CI)	P value	HR (95% CI)	P value		HR (95% CI)	P value	HR (95% CI)	P value
Immune deficiency	<0.001	0.409 (0.249–0.671)	<0.001	0.730 (0.424–1.258)	0.26	0.005	0.299 (0.136–0.654)	0.002	0.458 (0.214–0.981)	0.04
Non-immune deficiency		1.089 (0.728–1.628)	0.68	1.334 (0.809–2.202)	0.26		1.171 (0.645–2.125)	0.60	1.507 (0.760–2.989)	0.24

The effect of immune deficiency on the efficacy of corticosteroid was analyzed by multivariate Cox regression. For mild to moderate ARDS patients, the benefit of low dose corticosteroid was more obvious in immune deficiency patients. However, for patients with severe ARDS, both low-dose and high-dose corticosteroid benefit significantly in immune deficiency patients. †, the interaction between immune deficiency and glucocorticoid treatment. ARDS, acute respiratory distress syndrome; HR, hazard ratio; CI, confidence interval.

mortality in these patients. Additionally, considering the role of neutrophils in both ARDS pathogenesis and immune deficiency (1,33-35), changes in various biomarkers, pro-inflammatory cytokines, and chemokines in neutropenic patients are also noteworthy.

Most current studies have focused on the relationship between immune deficiency and non-pharmacological treatments, such as ventilation strategies, with less exploration into the response of immune-deficient patients to corticosteroid treatment. Our study integrated immune deficiency with disease severity to more accurately predict patient outcomes. Moreover, in analyzing the response to corticosteroids, we accounted for different dosages, potentially advancing personalized management of ARDS.

The study has several limitations. First, as a single-center retrospective cohort study, there are inherent risks of selection and reporting biases, and the potential for unknown confounders affecting the analysis. To mitigate this, patients were divided into discovery and validation datasets to enhance the reliability of the conclusions. Second, the study did not use the widely accepted Berlin definition to enroll ARDS patients, primarily due to limitations of the Berlin definition and the prolonged enrollment period, during which some patients in the validation cohort were diagnosed with ARDS prior to the introduction of the Berlin definition. Third, the classification of the immune-deficient population within the ARDS cohort was solely based on the definition and baseline characteristics of patients. Aside from malignancies and long-term corticosteroid use, current data struggle to accurately differentiate between immune-deficient and non-immune-deficient patients, potentially leading to misclassification bias. Fourth, the study did not consider the use of pharmacological and non-pharmacological treatments other than corticosteroids. However, the prognosis of patients with immune deficiency may depend on the nature of the underlying disease and associated treatments. The exclusion of these factors could limit the generalizability of our findings. Therefore, while our results may offer a foundation for personalized treatment of ARDS patients, due to the retrospective design of our study, the findings require validation through large-scale, multicenter, prospective studies.

Conclusions

This study showed that immune deficiency is an independent risk factor for mortality in ARDS. Patients with mild to moderate ARDS and immune deficiency may benefit from low-dose glucocorticoid treatment, while those with severe ARDS and immune deficiency may benefit from both low and high-dose glucocorticoid therapy, providing a basis for personalized medication in ARDS management.

Acknowledgments

Funding: This study was supported by the Shanghai Municipal Science and Technology Major Project (No. ZD2021CY001), the National Natural Science Foundation of China (Nos. 82130001, 82200090, and 82272243), the Science and Technology Commission of Shanghai Municipality (Nos. 20Z11901000, 20DZ2261200, 20XD1401200, and 22Y11900800), the Clinical Research Plan of SHDC (No. SHDC2020CR5010-002), the Shanghai Municipal Key Clinical Specialty (No. shslczdzk02201), and the Shanghai Municipal Health Commission and Shanghai

Municipal Administrator of Traditional Chinese Medicine [No. ZY(2021-2023)-0207-01].

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-109/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-109/dss

Peer Review File: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-109/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-109/coif). Y.W. reports that this study was supported by the National Natural Science Foundation of China (No. 82200090). Y.S. reports that this study was supported by the Shanghai Municipal Science and Technology Major Project (No. ZD2021CY001), the National Natural Science Foundation of China (Nos. 82130001 and 82272243), the Science and Technology Commission of Shanghai Municipality (Nos. 20Z11901000, 20DZ2261200, 20XD1401200, and 22Y11900800), the Clinical Research Plan of SHDC (No. SHDC2020CR5010-002), the Shanghai Municipal Key Clinical Specialty (No. shslczdzk02201), and the Shanghai Municipal Health Commission and Shanghai Municipal Administrator of Traditional Chinese Medicine [No. ZY(2021-2023)-0207-01]. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Zhongshan Hospital, Fudan University (No. 2021SQCJ2640) and individual consent for this retrospective analysis was waived.

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Cite this article as: Zhou Y, Hou D, Chen C, Yang Y, Wang Y, Song Y. Association of immune deficiency with prognosis and corticosteroid treatment benefits among patients with acute respiratory distress syndrome. J Thorac Dis 2024;16(7):4250-4262. doi: 10.21037/jtd-24-109