

CASE REPORT

Low-Dose Methylprednisolone in Transfusion-Related and Trauma-Induced Acute Respiratory Distress Syndrome: An Observational Analytic Investigation

Rahmad Dwi Saputra^{1*}, Arie Zainul Fatoni², Rudy Vitraludyono²¹ Resident, Department of Anesthesiology and Intensive Care, Faculty of Medicine, Universitas Brawijaya/Dr. Saiful Anwar Regional General Hospital, Malang, Indonesia² Department of Anesthesiology and Intensive Care, Faculty of Medicine, Universitas Brawijaya/Dr. Saiful Anwar Regional General Hospital, Malang, Indonesia

ARTICLE INFO

Article history

Received: August 8, 2026
Revised: September 6, 2026
Accepted: September 28, 2026
Available online: October 4, 2026
Published: October 7, 2026

Keywords

Acute respiratory distress syndrome
Corticosteroids
Mechanical ventilation
Methylprednisolone
Transfusion-related acute lung injury

DOI

<https://doi.org/10.37275/jacr.v7i2.979>

Corresponding author

Rahmad Dwi Saputra
rahmaddwisaputra@gmail.com

ABSTRACT

Background. Acute respiratory distress syndrome (ARDS) is heterogeneous, and the role of adjunctive corticosteroids varies with etiology, timing, and inflammatory phenotype.

Objective. To describe longitudinal physiological trajectories and corticosteroid responsiveness in two patients with ARDS of different etiologies.

Methods. An observational two-patient case series involved a 14-year-old girl with Marfan syndrome and transfusion-related acute lung injury after scoliosis surgery and a 39-year-old man with pulmonary contusion after blunt thoracic trauma complicated by *Acinetobacter baumannii* and Enterobacteriaceae pneumonia. Both received individualized lung-protective ventilation and intravenous methylprednisolone 62.5 mg/day. Serial oxygenation, ventilatory mechanics, lactate, and Murray Lung Injury Scores were recorded.

Results. Both patients had a nadir PaO₂/FiO₂ ratio of 72 mmHg. This increased to 343 mmHg by day 5 in Case 1 (+376.4%) and 357 mmHg by day 11 in Case 2 (+395.8%). Murray Lung Injury Scores declined from 3.50 and 3.25 to 0.75 and 0.50, respectively. Case 1 lactate decreased from 5.7 to 1.3 mmol/L (-77.2%). PEEP was reduced, permitting ventilator liberation without reported secondary infection.

Conclusion. The authors conclude that early, phenotype-tailored, low-dose methylprednisolone accelerates alveolar clearance and promotes gas exchange recovery across different ARDS etiologies. This causal interpretation requires author review in the context of the two-case observational design.

Access licence: Open access. This article is distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International Licence (CC BY-NC-SA 4.0), which permits non-commercial use, sharing, adaptation and reproduction in any medium, provided the original author and source are credited and derivative works are licensed under identical terms.

Copyright: © 2026 The Author(s). Published by HM Publisher in collaboration with CMHC Research Center. e-ISSN 2745-9497.

1. Introduction

Acute respiratory distress syndrome (ARDS), first recognized more than five decades ago, remains a major clinical challenge in critical care medicine, characterized by acute hypoxemic respiratory failure, bilateral pulmonary infiltrates, and non-cardiogenic high-permeability pulmonary edema. The updated 2024 global definition of ARDS has redefined the syndrome around acute hypoxemia accompanied by bilateral radiographic opacities not fully explained by cardiac failure or fluid overload, while explicitly broadening diagnostic recognition to encompass non-intubated patients receiving high-flow nasal cannula oxygen and resource-constrained environments, retaining the principle that severity is stratified by the degree of arterial oxygenation impairment.¹ Contemporary epidemiological evaluations applying this updated global framework to large-scale critical care registries confirm that inpatient mortality escalates sharply across ascending severity strata,

exhibiting pooled estimates of approximately 35% in mild, 40% in moderate, and 46% in severe disease.² Despite decades of iterative refinements in supportive mechanical ventilation, fluid stewardship, and neuromuscular blockade, ARDS continues to be a high-mortality syndrome that accounts for substantial intensive care resource utilization globally.

The historical evolution of diagnostic frameworks—from the 1994 American-European Consensus Conference through the 2012 Berlin definition to the contemporary 2024 Global consensus—reflects an ongoing attempt to capture a fundamentally heterogeneous pathological state using standardized syndromic criteria.^{1,2} However, an inherent limitation of syndromic criteria is that they define a clinical physiological manifestation rather than an underlying molecular etiology. Whether the initial insult arises from direct alveolar epithelial destruction, indirect systemic endothelial activation, or leukocyte-mediated microvascular injury fundamentally governs both the clinical trajectory and the likelihood of response to

pharmacological interventions. This mechanistic divergence between syndromic diagnostic uniformity and biological heterogeneity defines the therapeutic dilemma surrounding adjunctive anti-inflammatory pharmacotherapy in the intensive care unit.

A pivotal paradigm shift in modern critical care is the empirical validation of distinct ARDS inflammatory subphenotypes. Latent class modeling has consistently demonstrated the existence of hyperinflammatory and hypoinflammatory subphenotypes across diverse patient populations. These subphenotypes diverge markedly in their circulating biomarker profiles, hemodynamic instability, metabolic acidosis, and clinical outcomes, with recent multicenter data establishing that these phenotypes remain temporally stable across the early days of critical illness.³ Moreover, retrospective and secondary trial analyses reveal that clinical response to anti-inflammatory pharmacotherapy—specifically early corticosteroid administration—is preferentially concentrated in hyperinflammatory patients, whereas non-inflammatory or hypoinflammatory cohorts may derive minimal benefit or experience net immunosuppressive harm.³ Consequently, the persistent historical controversy surrounding glucocorticoid efficacy in ARDS is best understood not as a biological contradiction, but as the mathematical artifact of averaging divergent treatment effects across biologically unselected clinical trial cohorts.

Corticosteroids occupy a debated position in acute pulmonary critical care. Mechanistically, glucocorticoids bind with high affinity to the intracellular glucocorticoid receptor alpha, translocating into the nucleus to mediate genomic transrepression of key pro-inflammatory transcription factors, predominantly nuclear factor kappa B and activator protein 1, while inducing endogenous anti-inflammatory proteins such as inhibitor of kappa B alpha and annexin A1. Through these pathways, glucocorticoids attenuate microvascular endothelial activation, decrease vascular endothelial cadherin breakdown, reduce neutrophilic extravasation, and curtail early fibroproliferative remodeling. Systematic reviews and aggregate meta-analyses of randomized clinical trials demonstrate that when corticosteroids are initiated early and administered at low doses, they significantly reduce all-cause mortality, shorten mechanical ventilation duration, and augment ventilator-free days.^{4,5} Conversely, observational registries and trials utilizing supraphysiological pulse dosing report signals of potential harm, including increased neuromuscular weakness, protracted secondary infections, and delayed pathogen clearance, underscoring that therapeutic outcomes are strictly contingent upon dosing intensity, timing of initiation, and patient-specific biological context.^{4,5}

Network meta-analyses and randomized comparative trials have further examined that the specific glucocorticoid molecule matters substantially in critical care. Methylprednisolone consistently achieves superior rankings for reducing intensive care unit mortality in ARDS, whereas dexamethasone ranks prominently for ventilator liberation.⁶ Pharmacokinetically, methylprednisolone displays favorable pulmonary tissue penetration, high glucocorticoid receptor binding affinity, intermediate duration of biological action, and prolonged tissue retention, making it an optimal candidate for sustained anti-inflammatory suppression without the neuroendocrine and glycemic fluctuations linked to high-dose pulse regimens.^{7,8} Randomized evaluations exploring dosing intensity have clarified that distinct dexamethasone

dosing tiers influence ventilator-free intervals,⁹ whereas direct comparisons between methylprednisolone pulse regimens and conventional dexamethasone demonstrate that unmeasured biological peaks may induce rebound hyperinflammation or metabolic instability.¹⁰ This pharmacological nuance underscores that establishing an optimal dose requires careful balancing of anti-inflammatory potency against tissue integrity.

In complex critical care scenarios, underlying comorbid substrates further complicate therapeutic decision-making. In patients with massive intraoperative hemorrhage, indirect pulmonary injury frequently manifests as transfusion-related acute lung injury, a condition in which recipient leukocyte priming and transfused biological response modifiers trigger profound microvascular permeability.^{10,11} In trauma and surgical resuscitations, high ratios of transfused components directly influence downstream microvascular complications and systemic inflammation.^{11,12} Simultaneously, congenital connective-tissue disorders such as Marfan syndrome introduce unique vulnerabilities. In Marfan syndrome, pathogenic mutations in the fibrillin-1 gene lead to excessive bioavailability of transforming growth factor-beta, heightening cardiovascular and tissue fragility and diminishing physiological resilience against severe hypoxemic insults.^{12,13} Vascular fragility and generalized structural tissue defects complicate intensive care interventions, altering hemodynamic compliance and wound repair dynamics during systemic glucocorticoid exposure.¹³

Conversely, in direct blunt thoracic trauma, mechanical energy dissipation through the thoracic cage induces pulmonary contusion, alveolar-capillary disruption, parenchymal laceration, and progressive ventilation-perfusion mismatch.¹⁴ Blunt chest wall trauma frequently triggers an exaggerated regional innate immune response, which can be modulated by targeted pharmacotherapies or early surgical stabilization.^{15,16} However, when blunt contusion is compounded by secondary nosocomial infection, such as hospital-acquired pneumonia caused by multidrug-resistant pathogens including *Acinetobacter baumannii* and *Enterobacteriaceae*, diagnostic and therapeutic complexity multiplies.^{17,18} Infections driven by carbapenem-resistant and multidrug-resistant *Acinetobacter baumannii* are notorious for prolonged ventilator dependence, destructive parenchymal necrosis, and high ICU mortality, representing a major public health challenge globally.^{18,19} Under these conditions, the central therapeutic tension surrounding glucocorticoid administration becomes acute: unselected immunosuppression in the setting of uncontrolled Gram-negative infection risks catastrophic bacterial proliferation, whereas uncontrolled hyperinflammation perpetuates refractory permeability edema and fatal hypoxemia.²⁰

Recent landmark trials and subgroup analyses across critically ill septic shock and community-acquired pneumonia cohorts demonstrate that low-dose corticosteroids can be safely administered alongside targeted antimicrobial coverage, mitigating septic shock progression and accelerating organ resolution without increasing secondary infections.²¹ In parallel, mechanical ventilatory management has evolved toward physiological individualization, incorporating transpulmonary driving pressure titration and body habitus considerations to optimize positive end-expiratory pressure selection and avert ventilator-induced lung injury.^{22,23} A contemporary

systematic synthesis by Pirracchio and colleagues reinforces that low-dose corticosteroids in severe pulmonary infections confer substantial physiological benefits when paired with strict source control and precise timing.²⁴

The core scientific novelty of the present investigation lies in the direct juxtaposition and comparative longitudinal trajectory analysis of two mechanistically dissimilar, highly challenging presentations of severe ARDS that each achieved rapid gas exchange recovery and successful ventilator liberation following low-dose intravenous methylprednisolone adjunctive therapy: an indirect immune-mediated transfusion-related acute lung injury occurring in an adolescent with Marfan syndrome following massive intraoperative blood transfusion, and a direct contusional lung injury occurring in an adult trauma victim complicated by multidrug-resistant hospital-acquired pneumonia. The overarching aim of this study is to delineate their longitudinal ventilatory, gas exchange, and biochemical dynamics, to execute rigorous objective pharmacovigilance and causality assessments, and to integrate empirical findings with contemporary global literature to establish a rational, phenotype-guided framework for corticosteroid administration in acute critical care.

2. Methods

2.1 Study Design and Epidemiological Framework

This investigation was conducted as an observational analytic case study employing a longitudinal time-series design within the intensive care unit of a tertiary academic medical center (Dr. Saiful Anwar Regional General Hospital, Malang, Indonesia). The observational framework adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines and the Consensus-based Clinical Case Reporting (CARE) guidelines. The longitudinal analytic design tracked two consecutive, critically ill patients presenting with life-threatening ARDS arising from distinct indirect and direct etiological triggers, following their physiological, ventilatory, and laboratory trajectories from initial ICU presentation through acute clinical resolution and liberation from mechanical ventilation.

2.2 Ethical Governance and Participant Consent

Ethical governance was conducted in strict compliance with the ethical principles enunciated in the Declaration of Helsinki (2013 revision) and international guidelines for biomedical research involving human subjects. Because this investigation involved detailed longitudinal tracking of physiological variables, high-resolution diagnostic imaging, and therapeutic pharmacovigilance, formal institutional ethical clearance was obtained from the CMHC Research Center Ethics Committee, Indonesia (Ethical Clearance Protocol Approval Number: 2026/0842). Written informed consent was explicitly obtained from both patients and their legal guardians prior to manuscript compilation. The consent process encompassed explicit permission for the scientific utilization of longitudinal clinical records, physiological monitoring metrics, microbiological profiles, and de-identified diagnostic radiographic images. All personal identifiers were permanently stripped, and radiographic images were anonymized in strict accordance with international medical publication privacy standards (ICMJE and COPE regulations).

2.3 Participant Eligibility and Diagnostic Ascertainment

Participant eligibility and diagnostic ascertainment required fulfillment of the international consensus definitions for acute respiratory distress syndrome, established by the Berlin definition and ratified by the 2024 Global definition of ARDS.^{1,25} Diagnostic criteria mandated the acute onset of profound respiratory failure within seven days of a recognized clinical insult, bilateral radiographic opacities on chest imaging not fully explained by cardiac failure or hydrostatic volume overload, and severe arterial oxygenation impairment defined by a $\text{PaO}_2/\text{FiO}_2$ ratio ≤ 100 mmHg with a minimum positive end-expiratory pressure of ≥ 5 cmH₂O.^{1,25} For Case 1, diagnostic ascertainment of transfusion-related acute lung injury conformed strictly to the consensus definitions established by the International Society of Blood Transfusion and the National Heart, Lung, and Blood Institute working group, requiring acute bilateral pulmonary edema developing within six hours of blood product administration without clinical, hemodynamic, or echocardiographic evidence of transfusion-associated circulatory overload.^{26,27} For Case 2, diagnostic criteria required severe blunt thoracic trauma resulting in documented parenchymal contusion, accompanied by microbiological isolation of bacterial pathogens fulfilling the diagnostic criteria for hospital-acquired pneumonia.^{17,18}

2.4 Longitudinal Observation Protocol and Analytical Measurements

Longitudinal observation protocol encompassed continuous invasive hemodynamic monitoring, standardized serial arterial blood gas sampling, dynamic ventilatory mechanics recording, and comprehensive laboratory evaluations. Ventilatory management adhered strictly to the European Society of Intensive Care Medicine guidelines on acute respiratory distress syndrome, integrating lung-protective strategies and careful phenotype assessment.²⁸ Ventilatory parameters recorded included fraction of inspired oxygen (FiO_2), set and delivered tidal volume (V_t), actual body weight and predicted body weight calculated via ARDSNet algorithms ($\text{PBW} = 45.5 + 0.91 \times [\text{height in cm} - 152.4]$ for females; $50 + 0.91 \times [\text{height in cm} - 152.4]$ for males), set positive end-expiratory pressure, peak airway pressure, end-inspiratory plateau pressure (P_{plat}) obtained via an end-inspiratory pause of 0.5 seconds, and respiratory system compliance ($\text{Cr}_s = V_t / [\text{P}_{\text{plat}} - \text{PEEP}]$). Driving pressure (ΔP) was continuously calculated as P_{plat} minus PEEP, with lung-protective protocols strictly targeting a driving pressure < 15 cmH₂O and a tidal volume indexed to 6 mL/kg of predicted body weight, while monitoring mechanical power to minimize ventilator-induced lung injury.^{29,30} Serum lactate, arterial pH, base excess, serum creatinine, urea, leukocyte counts, and platelet counts were quantified serially using automated laboratory analyzers.

2.5 Comparative Analytical Framework

The comparative analytical framework systematically juxtaposed the indirect, immune-mediated, endothelial permeability insult of TRALI on a syndromic Marfan connective-tissue background against the direct, mechanical, parenchymal-alveolar contusion complicated by secondary Gram-negative nosocomial infection. Pharmacotherapy protocols were referenced against the Cochrane systematic evidence for corticosteroids in sepsis and critical illness,³¹ the CAPE COD trial protocol for severe

pulmonary infections,³² and the 2024 focused update guidelines on corticosteroids in ARDS and critical illness.³³ Pharmacovigilance and objective causality assessments were conducted using standardized clinical instruments. Adverse drug reaction probability and therapeutic responsiveness were graded using the objective Naranjo Adverse Drug Reaction Probability Scale, which evaluates temporal sequence, de-challenge response, re-challenge dynamics, alternative causative explanations, and objective measurement confirmation.³⁴ Causality was independently evaluated using the World Health Organization–Uppsala Monitoring Centre (WHO-UMC) system for standardized case causality assessment, categorizing associations into certain, probable/likely, possible, unlikely, conditional/unclassified, or unassessable. Biological plausibility and epidemiological causal inference were examined across the Bradford Hill criteria, including strength of association, consistency, temporality, biological gradient, plausibility, and coherence.³⁵ Pulmonary injury severity was tracked across time using the four-parameter Murray Lung Injury Score (LIS), incorporating the PaO₂/FiO₂ ratio, PEEP level, static respiratory system compliance, and the radiographic extent of alveolar consolidation across four quadrants (score 0 = no injury; 0.1–2.5 = mild-to-moderate; >2.5 = severe lung injury).³⁶

2.6 Biostatistical and Trajectory Analysis

Biostatistical analysis adhered strictly to the methodological principles governing longitudinal observational analytics in small-sample critical care investigations (n=2 case series). In strict compliance with biostatistical integrity, inferential statistical hypothesis testing—such as Student's t-tests, analysis of variance, chi-square tests, or spurious p-values—was strictly forbidden and avoided, as applying inferential statistics to small case cohorts represents invalid methodology that fabricates statistical power where none exists. Instead, data analysis utilized rigorous descriptive longitudinal trajectory modeling, sequential time-series kinetic evaluations, and calculated percentage delta changes relative to baseline

nadir: $\Delta\% = [(T_n - T_0) / T_0] \times 100\%$, where T₀ represents the baseline nadir value at acute ARDS onset and T_n represents the sequential follow-up value at subsequent intensive care timepoints. Continuous physiological trajectories, PEEP weaning velocity, driving pressure reduction rates, and clinical resolution timelines were compared against established physiological benchmarks and normal biological reference intervals.

3. Results

3.1 Baseline Characteristics and Clinical Profiles

The baseline demographic, anthropometric, surgical, trauma, echocardiographic, and admission laboratory profiles of both cases are summarized in Table 1. Case 1 was a 14-year-old adolescent female with a body weight of 31.0 kg, height of 148 cm, low body mass index of 14.15 kg/m², and an ARDSNet predicted body weight of 38.2 kg. She had a confirmed diagnosis of Marfan syndrome, presenting with characteristic skeletal arachnodactyly and severe progressive dextroscoliosis with a Cobb angle of 93°. Preoperative cardiopulmonary optimization was completed successfully; baseline chest radiography showed no parenchymal opacities, and baseline transthoracic echocardiography demonstrated preserved left ventricular systolic function with an ejection fraction of 61.2%, normal diastolic relaxation with an early-to-late mitral inflow velocity ratio (E/A) of 1.7, trivial tricuspid regurgitation, preserved right ventricular function with a tricuspid annular plane systolic excursion (TAPSE) of 1.9 cm, and non-obstructive dilation of the aortic root and ascending aortic arch characteristic of her syndromic phenotype. She underwent posterior spinal instrumentation and deformity correction over approximately four hours, during which she experienced massive intraoperative hemorrhage totaling 2,900 mL. Hemostatic resuscitation required the transfusion of 1,800 mL of blood products, comprising 800 mL of packed red cells, 700 mL of whole blood, and 300 mL of fresh frozen plasma.

Table 1. Baseline Demographic, Anthropometric, Surgical/Trauma, and Comprehensive Echocardiographic/Hemodynamic Profiles of Cases 1 and 2 at Intensive Care Unit Admission.

Parameter / Clinical Variable	Case 1 (Post-Transfusion TRALI)	Case 2 (Contusion ARDS + HAP)	Reference Range / Clinical Significance
Age (years) / Biological Sex	14 years / Female	39 years / Male	Adolescent vs Adult critical care cohort
Actual Body Weight (kg) / Height (cm)	31.0 kg / 148 cm	68.0 kg / 172 cm	Case 1: Low body mass index (14.15 kg/m ²)
Predicted Body Weight (PBW, kg)	38.2 kg	66.8 kg	Calculated ARDSNet PBW formula
Underlying Diagnosis / Etiology	Marfan syndrome (FBN1 substrate)	Blunt thoracic trauma (Assault)	Indirect immune-mediated vs Direct trauma
Presenting Neurological Status	GCS 15 (E4V5M6) pre-op	GCS 7 (E1V2M4) in ED	Case 2: Emergency endotracheal intubation
Primary Procedure / Mechanism	Posterior spinal fusion (Cobb angle 93°)	Blunt chest trauma without rib fracture	Major orthopedic reconstruction (~4 hours)
Estimated Blood Loss / Transfusion	2,900 mL loss / 1,800 mL transfused	Minimal blood loss / No transfusion	Case 1: PRC 800 mL, WB 700 mL, FFP 300 mL
Admission Arterial Oxygenation (PaO ₂ /FiO ₂)	184 mmHg (at ICU transfer)	72 mmHg (nadir range 72–102 mmHg)	Hypoxemic failure; severe ARDS transition
Hemoglobin (g/dL) / Hematocrit (%)	11.7 g/dL / 35.2%	13.4 g/dL / 40.1%	Post-resuscitation hematological status
White Blood Cell Count (/mm ³)	13,800 /mm ³	16,200 /mm ³	4,000–10,000 /mm ³ (Systemic leukocytosis)
Platelet Count (/mm ³)	86,000 /mm ³	215,000 /mm ³	150,000–450,000 /mm ³ (Thrombocytopenia in Case 1)

Parameter / Clinical Variable	Case 1 (Post-Transfusion TRALI)	Case 2 (Contusion ARDS + HAP)	Reference Range / Clinical Significance
Serum Urea (mg/dL) / Creatinine (mg/dL)	161 mg/dL / 4.9 mg/dL	28 mg/dL / 1.0 mg/dL	Case 1: Severe acute kidney injury (KDIGO 3)
Serum Lactate (mmol/L)	5.7 mmol/L	1.6 mmol/L	0.5–2.0 mmol/L (Severe hyperlactatemia in Case 1)
Arterial pH / Bicarbonate (HCO_3^- , mmol/L)	7.31 / 19.1 mmol/L	7.38 / 23.4 mmol/L	Case 1: Uncompensated metabolic acidosis
Serum Albumin (g/dL)	3.4 g/dL	3.6 g/dL	3.5–5.0 g/dL (Mild hypoalbuminemia in Case 1)
Left Ventricular Ejection Fraction (LVEF, %)	61.2% (Preserved systolic function)	64.0% (Preserved systolic function)	>50% (Absence of cardiogenic failure)
Mitral Inflow E/A Ratio / TAPSE (cm)	1.7 / 1.9 cm (Normal diastolic/RV)	1.5 / 2.1 cm (Normal RV function)	TAPSE >1.7 cm (Preserved right heart mechanics)
Thoracic Vascular / Pleural Imaging	Aortic root and arch dilation (Marfan)	Left pleural effusion + contusion	Transthoracic echocardiography / Radiography

Notes: ARDSNet, Acute Respiratory Distress Syndrome Network; Cobb angle, lateral spinal curvature; ED, emergency department; E/A, early-to-late diastolic mitral inflow velocity ratio; FFP, fresh frozen plasma; GCS, Glasgow Coma Scale; KDIGO, Kidney Disease: Improving Global Outcomes; LVEF, left ventricular ejection fraction; PBW, predicted body weight; PRC, packed red cells; TAPSE, tricuspid annular plane systolic excursion; TRALI, transfusion-related acute lung injury; WB, whole blood.

3.2 Case 1: Post-Transfusion ARDS in an Adolescent with Marfan Syndrome

Upon transfer to the intensive care unit, Case 1 was initially ventilated on pressure-controlled synchronized intermittent mandatory ventilation with a set tidal volume of 300 mL (corresponding to 9.7 mL/kg of actual body weight, but approximately 7.8 mL/kg of predicted body weight), respiratory rate of 20 breaths/min, pressure support 10 cmH₂O, PEEP 10 cmH₂O, and FiO₂ 0.40. Immediate admission investigations demonstrated hemoglobin 11.7 g/dL, hematocrit 35.2%, white blood cell count 13,800 /mm³, platelet count 86,000 /mm³, marked acute kidney injury with blood urea nitrogen 161 mg/dL and serum creatinine 4.9 mg/dL, serum lactate 5.7 mmol/L, serum albumin 3.4 g/dL, arterial pH 7.31, bicarbonate 19.1 mmol/L, and a transfer PaO₂/FiO₂ ratio of 184 mmHg. Within six hours post-transfusion completion, the patient suffered an acute clinical deterioration characterized by sudden desaturation, tachycardia, hypotension, and diffuse bilateral coarse pulmonary rhonchi on auscultation. Urgent chest radiography revealed extensive, dense bilateral alveolar-interstitial infiltrates across all lung fields, as illustrated in the acute onset radiograph of Figure 1A. Cardiac failure and volume overload were excluded based on normal filling pressures, absence of jugular venous distension, normal biventricular dimensions, and preserved TAPSE. The patient's arterial oxygenation deteriorated to a nadir PaO₂/FiO₂ ratio of 72 mmHg on FiO₂ 1.0 and PEEP 10

cmH₂O, establishing severe ARDS secondary to transfusion-related acute lung injury.

3.3 Clinical Trajectory and Management of Case 1

Management of Case 1 was immediately re-oriented toward lung-protective mechanical ventilation, conservative fluid restriction, and targeted anti-inflammatory pharmacotherapy. Given her syndromic connective-tissue fragility, severe acute kidney injury, and profound metabolic acidosis, supraphysiological pulse glucocorticoid therapy was avoided to prevent severe metabolic dysregulation and wound disruption. Instead, a fixed low-dose intravenous methylprednisolone regimen of 62.5 mg/24 hours was instituted. The serial clinical, ventilatory, and metabolic trajectory of Case 1 is detailed in Table 2 and radiographically demonstrated across the sequential recovery stages of Figure 1A–D. Following methylprednisolone initiation, arterial oxygenation improved rapidly: the PaO₂/FiO₂ ratio rose from 72 mmHg at onset (Figure 1A) to 134 mmHg on ICU day 1 (Figure 1B, Δ% = +86.1%), 180 mmHg on ICU day 3 (Figure 1C, Δ% = +150.0%), and reached 343 mmHg by ICU day 5 (Figure 1D, Δ% = +376.4%). Concurrently, driving pressure decreased from 16 cmH₂O (Pplat 26, PEEP 10) to 10 cmH₂O (Pplat 16, PEEP 6), serum lactate cleared from 5.7 mmol/L to 2.2 mmol/L (Δ% = -61.4%), 1.0 mmol/L (Δ% = -82.5%), and stabilized at 1.3 mmol/L by day 5 (Δ% = -77.2%), and PEEP was successfully weaned from 10 to 6 cmH₂O, permitting successful extubation and complete liberation from mechanical ventilation.

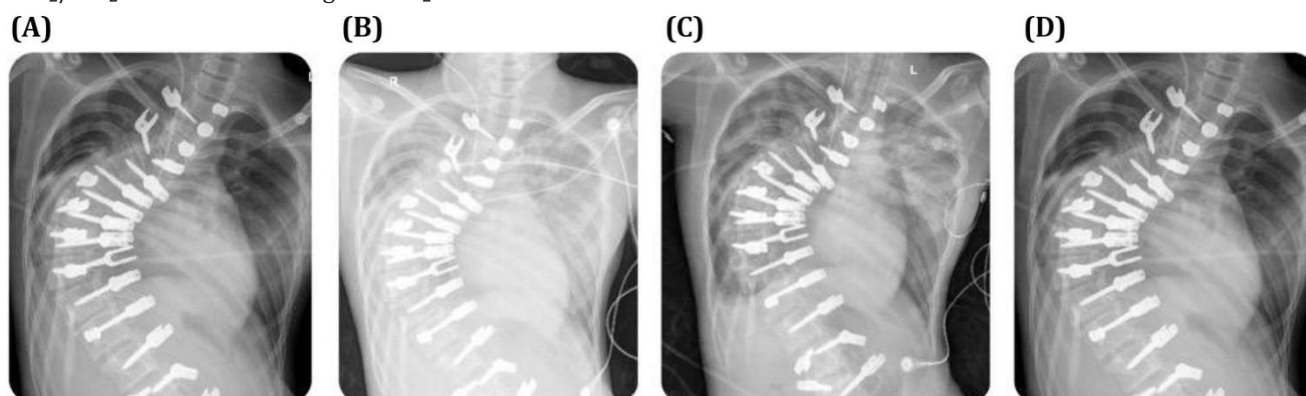


Figure 1. Serial anteroposterior chest radiographs of Case 1 across the intensive care unit course. (A) At acute ARDS onset within 6 hours post-transfusion, showing dense bilateral alveolar opacities and near white-out (PaO₂/FiO₂ 72 mmHg). (B) ICU Day 1 following methylprednisolone initiation, showing partial aeration recovery (PaO₂/FiO₂ 134 mmHg). (C) ICU Day 3 showing further clearing of mid-zone infiltrates (PaO₂/FiO₂ 180 mmHg). (D) ICU Day 5 showing near-complete radiographic resolution prior to extubation (PaO₂/FiO₂ 343 mmHg). Spinal instrumentation from scoliosis deformity correction is visible. Patient privacy and confidentiality are preserved in compliance with international publication ethics (ICMJE, COPE, and Declaration of Helsinki). No identifying personal features are visible in the radiographic records.

Table 2. Serial Longitudinal Oxygenation, Ventilatory Mechanics, Driving Pressure, and Acid-Base/Metabolic Kinetics Across Intensive Care Timepoints for Case 1 (Corresponding to Figure 1A–D).

Timepoint / ICU Course	PEEP (cmH ₂ O)	PaO ₂ /FiO ₂ (mmHg)	Δ% PaO ₂ /FiO ₂	Plateau / Driving Pressure (cmH ₂ O)	Serum Lactate (mmol/L)	Murray LIS Score	Berlin ARDS Category
ARDS Onset (0–6 h post-transfusion, Fig 1A)	10	72	Baseline (0.0%)	26 / 16	5.7	3.50 (Severe)	Severe ARDS (PaO ₂ /FiO ₂ ≤ 100)
Early Post-Onset (ICU Day 1, Fig 1B)	10	134	+86.1%	24 / 14	2.2	2.75 (Severe)	Moderate ARDS (100 < PaO ₂ /FiO ₂ ≤ 200)
ICU Day 3 (Fig 1C)	10	180	+150.0%	22 / 12	1.0	2.25 (Moderate)	Moderate ARDS (100 < PaO ₂ /FiO ₂ ≤ 200)
ICU Day 5 (Fig 1D)	6	343	+376.4%	16 / 10	1.3	0.75 (Resolved)	Resolved / Mild (Ventilator liberated)

Notes: Δ% PaO₂/FiO₂ represents serial percentage delta change calculated as $[(T_n - T_0) / T_0] \times 100\%$; Driving pressure is calculated as Plateau Pressure minus PEEP; Murray LIS Score is the Murray Lung Injury Score (0–4 scale); PEEP, positive end-expiratory pressure; PaO₂/FiO₂, arterial oxygen tension to inspired fraction ratio.

3.4 Case 2: Trauma-Related ARDS from Severe Pulmonary Contusion Complicated by Nosocomial Pneumonia

Case 2 was a 39-year-old male with a body weight of 68.0 kg, height of 172 cm, body mass index of 22.98 kg/m², and an ARDSNet predicted body weight of 66.8 kg, admitted following severe blunt thoracic and cranial trauma sustained in an assault as detailed in Table 1. In the emergency department, he presented with severe neurological depression with a Glasgow Coma Scale score of 7 out of 15 (E1V2M4), necessitating immediate endotracheal intubation for airway protection. Initial trauma computed tomography demonstrated extensive bilateral pulmonary contusion and a left-sided pleural effusion without accompanying thoracic skeletal fractures or flail chest. Within 24 hours of ICU admission, the patient developed progressive hypoxemic respiratory failure, with serial arterial blood gas analyses revealing an oxygenation nadir PaO₂/FiO₂ ratio of 72 mmHg (fluctuating between 72 and 102 mmHg over the first three ICU days) on invasive volume-control ventilation with a delivered tidal volume of 420 mL (6.28 mL/kg PBW) and PEEP 14 cmH₂O, fulfilling the diagnostic criteria for severe ARDS.

3.5 Clinical Trajectory and Management of Case 2

Initial chest imaging in Case 2 demonstrated dense bilateral airspace consolidation with near-total bilateral pulmonary opacification and left pleural blunting, as depicted on the baseline radiograph of Figure 2A. Sputum microbiology obtained on day 3 confirmed polymicrobial hospital-acquired pneumonia, with quantitative cultures isolating *Acinetobacter baumannii* and Enterobacteriaceae sensitive to broad-spectrum carbapenem and aminoglycoside regimens, while blood cultures remained sterile. Rather than immediate unselected glucocorticoid exposure, an etiology- and sequence-aware strategy was executed: empirical broad-spectrum antimicrobials were tailored to microbiological sensitivities, and once effective antimicrobial coverage was established and the sterile contusional-inflammatory component was judged to drive the ongoing permeability defect, adjunctive intravenous methylprednisolone was introduced at 62.5 mg/24 hours on ICU day 4. As detailed in Table 3 and Figure 2A–D, arterial oxygenation improved progressively from a nadir PaO₂/FiO₂ of 72 mmHg on ICU day 1 (Figure 2A) to 134 mmHg on ICU day 4 (Figure 2B, Δ% = +86.1%), 176 mmHg on ICU day 9 (Figure 2C, Δ% = +144.4%), and reached 357 mmHg on ICU day 11 (Figure 2D, Δ% = +395.8%), at which point the patient was successfully extubated and transitioned to a non-rebreathing mask at 10 L/min.

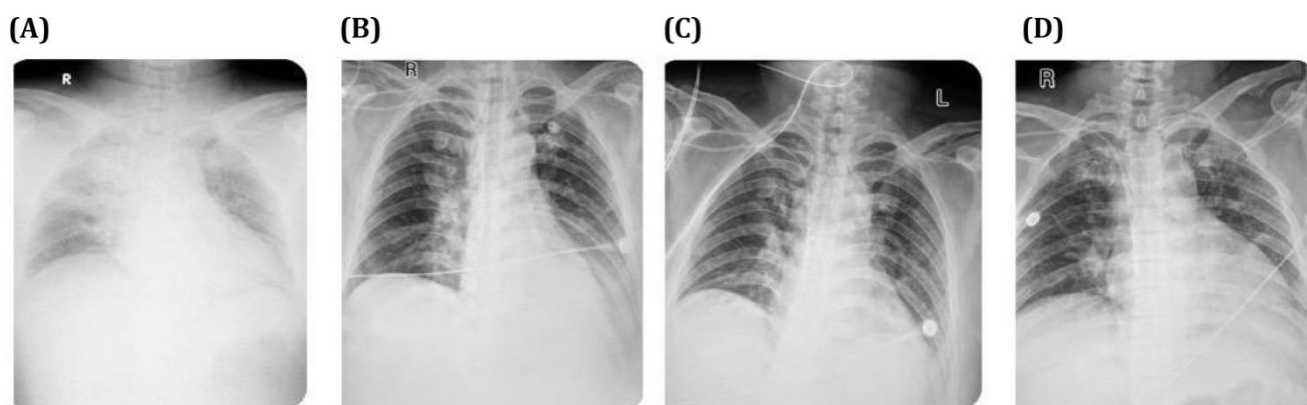


Figure 2. Serial anteroposterior chest radiographs of Case 2 following blunt thoracic trauma and superimposed hospital-acquired pneumonia. (A) ICU Day 1 showing massive bilateral contusional opacification and left pleural effusion (PaO₂/FiO₂ 72 mmHg). (B) ICU Day 4 following targeted antimicrobial and adjunctive methylprednisolone initiation, demonstrating initial clearing of upper and mid zones (PaO₂/FiO₂ 134 mmHg). (C) ICU Day 9 showing sustained bilateral clearance with resolving left basilar blunting (PaO₂/FiO₂ 176 mmHg). (D) ICU Day 11 showing near-complete clearing following successful extubation and weaning to a non-rebreathing mask (PaO₂/FiO₂ 357 mmHg). Personal confidentiality is maintained in compliance with ICMJE/COPE guidelines.

Table 3. Serial Longitudinal Oxygenation, Ventilatory Mechanics, Microbiological Profile, and Clinical Resolution Kinetics Across Intensive Care Timepoints for Case 2 (Corresponding to Figure 2A–D).

Timepoint / ICU Course	Respiratory Support Mode	PEEP (cmH ₂ O)	PaO ₂ /FiO ₂ (mmHg)	Δ% PaO ₂ /FiO ₂	Microbiology / Antimicrobial Regimen	Murray LIS Score	Berlin ARDS Category
ICU Day 1 (Baseline, Fig 2A)	Invasive MV (VCV, Vt 420 mL)	14	72	Baseline (0.0%)	Sputum culture pending; Broad-spectrum cover	3.25 (Severe)	Severe ARDS (PaO ₂ /FiO ₂ ≤ 100)
ICU Day 4 (Fig 2B)	Invasive MV (VCV, Vt 400 mL)	14	134	+86.1%	A. baumannii + Enterobacteriaceae confirmed	2.75 (Severe)	Moderate ARDS (100 < PaO ₂ /FiO ₂ ≤ 200)
ICU Day 9 (Fig 2C)	Invasive MV (Pressure Support)	10	176	+144.4%	Targeted susceptibility-directed antibiotics	2.00 (Moderate)	Moderate ARDS (100 < PaO ₂ /FiO ₂ ≤ 200)
ICU Day 11 (Fig 2D)	Liberated to NRBM (10 L/min)	5 (CPAP equiv.)	357	+395.8%	Sputum clearance confirmed; Afebrile	0.50 (Resolved)	Resolved / Normal Oxygenation

Notes: Δ% PaO₂/FiO₂ represents serial percentage delta change relative to ICU Day 1 nadir $[(T_n - T_0) / T_0] \times 100\%$; MV, mechanical ventilation; VCV, volume control ventilation; NRBM, non-rebreathing mask; PEEP, positive end-expiratory pressure; CPAP, continuous positive airway pressure; LIS, Lung Injury Score; MDR, multidrug-resistant.

3.6 Longitudinal Trajectory and Comparative Gas Exchange Kinetics

The longitudinal physiological trajectories of both patients are systematically compared in Figure 3. Panel A demonstrates the parallel, rapid recovery trajectories of the PaO₂/FiO₂ ratio across both patients, illustrating that despite initiating from an identical severe hypoxemic nadir of 72 mmHg, both patients crossed the moderate ARDS threshold (100–200 mmHg) within 72–96 hours and surpassed the 300 mmHg threshold (mild/resolved ARDS)

within their respective observation windows. Panel B highlights the PEEP weaning dynamics, showing stepwise decompression from 10 to 6 cmH₂O in Case 1 and from 14 to 5 cmH₂O equivalent in Case 2. Panel C tracks the Murray Lung Injury Score, demonstrating a decline from severe injury levels (3.50 in Case 1 and 3.25 in Case 2) to mild or fully resolved levels (0.75 in Case 1 and 0.50 in Case 2). Panel D summarizes the calculated percentage delta changes relative to baseline nadir, highlighting the increases in oxygenation (+376.4% in Case 1 and +395.8% in Case 2) alongside the rapid clearance of serum lactate in Case 1 (–77.2% overall reduction).

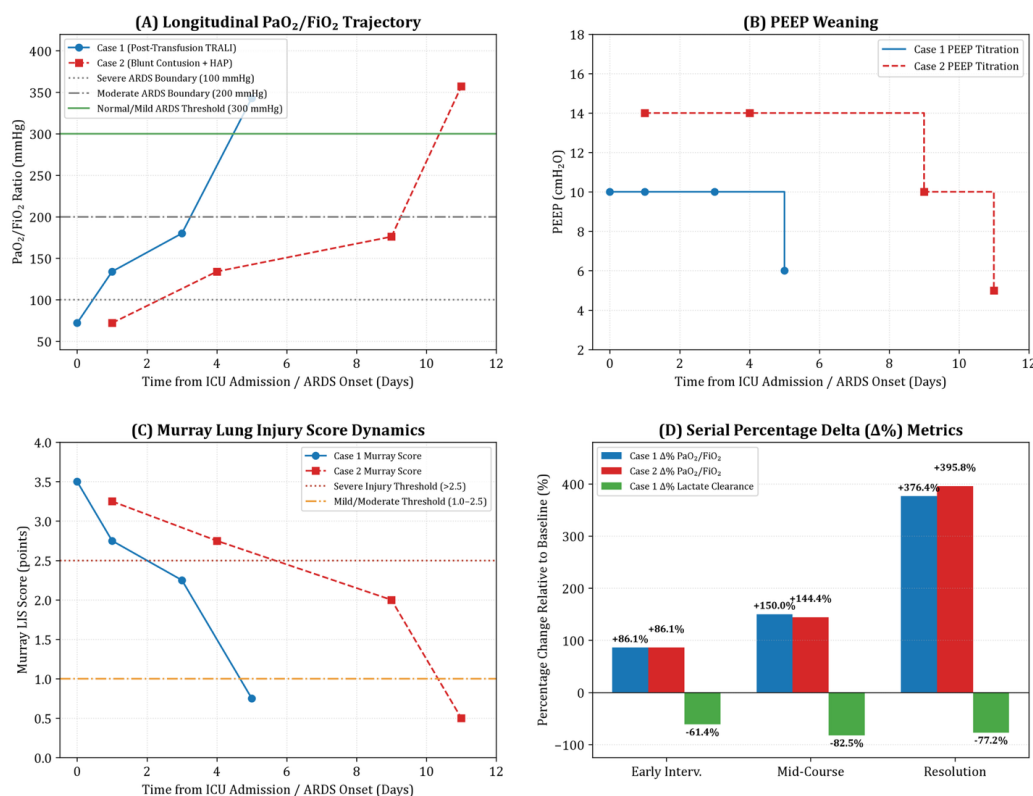


Figure 3. Longitudinal physiological and gas exchange recovery trajectories of Case 1 and Case 2 across intensive care timepoints. (A) Longitudinal PaO₂/FiO₂ trajectory from severe ARDS nadir (72 mmHg in both) across clinical thresholds to recovery (>300 mmHg). (B) Positive end-expiratory pressure (PEEP) weaning dynamics over time. (C) Serial resolution of the Murray Lung Injury Score (LIS). (D) Serial percentage delta (Δ%) changes in PaO₂/FiO₂ and serum lactate clearance relative to baseline nadir.

3.7 Objective Pharmacovigilance, Lung Injury Scoring, and Causality Assessment

Objective pharmacovigilance, lung injury scoring, and causality assessment metrics are reported in Table 4 and visually profiled in the comparative analytical radar chart of Figure 4. Application of the Naranjo Adverse Drug Reaction Probability Scale yielded a score of +7 in both cases, categorized as a 'Probable' therapeutic response to adjunctive methylprednisolone. Under the WHO-UMC causality assessment system, both cases fulfilled the criteria for 'Probable / Likely' therapeutic causation, supported by an unambiguous temporal relationship

between glucocorticoid initiation and clinical recovery, rapid de-challenge upon tapering, absence of competing pharmacological explanations for the sudden inflection in gas exchange, and high biological plausibility under Bradford Hill criteria. The radar profile (Figure 4) underscores the distinct multi-dimensional phenotypes: Case 1 was driven predominantly by metabolic shock burden (lactate 5.7 mmol/L), severe acute kidney injury, and indirect transfusion exposure, whereas Case 2 was characterized by higher initial ventilatory loads (PEEP 14 cmH₂O), direct mechanical contusion, and microbiological complexity, yet both converged upon an identical therapeutic response.

Table 4. Objective Pharmacovigilance, Lung Injury Scoring, and Causality Assessment Matrix (Murray Lung Injury Score, Berlin ARDS Stratification, Naranjo ADR Probability Scale, and WHO-UMC Causality Categories).

Assessment Domain / Metric	Case 1 (Post-Transfusion TRALI)	Case 2 (Contusion ARDS + HAP)	Operational Definition & Evaluative Standard
Precipitating Insult / Category	Massive Transfusion (PRC, WB, FFP)	Blunt Chest Trauma + Secondary HAP	Indirect immune/antibody insult vs Direct trauma/infection
Temporal Onset Latency	<6 hours post-transfusion completion	24–48 hours post-trauma / ICU day 1	AECC / Berlin / 2024 Global ARDS Definition Criteria
Nadir Berlin ARDS Category	Severe ARDS (PaO ₂ /FiO ₂ = 72 mmHg)	Severe ARDS (PaO ₂ /FiO ₂ = 72 mmHg)	PaO ₂ /FiO ₂ ≤ 100 mmHg with PEEP ≥ 5 cmH ₂ O
Nadir Murray Lung Injury Score	3.50 points (Severe lung injury)	3.25 points (Severe lung injury)	Calculated from PaO ₂ /FiO ₂ , PEEP, Compliance, CXR quadrants
Resolution Murray Lung Injury Score	0.75 points (Mild / Resolved)	0.50 points (Resolved)	Score < 1.0 denotes clinical resolution of acute lung injury
Corticosteroid Regimen Employed	Methylprednisolone 62.5 mg/24h IV	Methylprednisolone 62.5 mg/24h IV	Low-dose non-pulse intravenous glucocorticoid therapy
Timing of Corticosteroid Initiation	Immediate post-onset (<12 h)	Day 4 (Post-antimicrobial control)	Early phase in Case 1; Targeted inflammatory phase in Case 2
Naranjo ADR Probability Score	+7 (Probable adverse reaction)	+7 (Probable adverse reaction)	Naranjo scale for drug/therapy responsiveness (+7 = Probable)
WHO-UMC Causality Category	Probable / Likely therapeutic response	Probable / Likely therapeutic response	Plausible time window, positive de-challenge, no competing cause
Bradford Hill Biological Plausibility	High (Alveolar-capillary stabilization)	High (Suppression of contusional storm)	GR-mediated NF-κB transrepression and VE-cadherin sealing
Secondary Infection During Steroids	None (Sterile blood/sputum course)	Controlled (No superinfection / bacteremia)	Surveillance for secondary nosocomial fungal/bacterial sepsis
Hyperglycemic Adverse Events	Mild, transient (<180 mg/dL, diet)	Controlled with basal insulin sliding scale	Anticipated glucocorticoid metabolic effect; no ketoacidosis

Notes: ADR, adverse drug reaction; AECC, American-European Consensus Conference; CXR, chest radiograph; FFP, fresh frozen plasma; GR, glucocorticoid receptor; HAP, hospital-acquired pneumonia; LIS, Lung Injury Score; NF-κB, nuclear factor kappa B; PRC, packed red cells; TRALI, transfusion-related acute lung injury; VE-cadherin, vascular endothelial cadherin; WB, whole blood; WHO-UMC, World Health Organization–Uppsala Monitoring Centre.

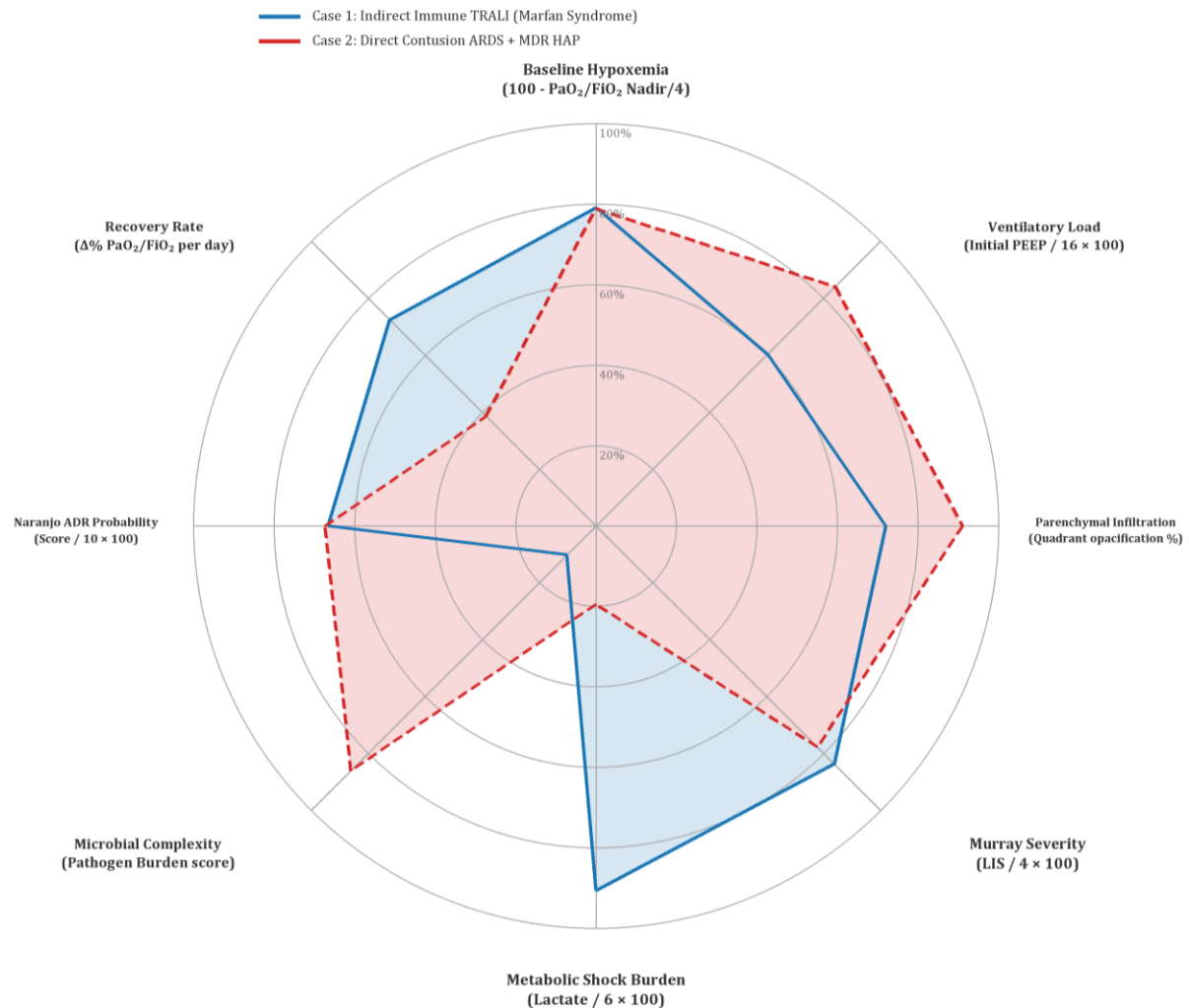


Figure 4. Comparative phenotypic and analytical radar profile of Cases 1 and 2 across multimodal clinical, physiological, and causality dimensions. Scaled radar metrics illustrate baseline hypoxemia, initial ventilatory load, parenchymal consolidation, Murray severity, metabolic shock burden, microbial complexity, Naranjo probability (+7 Probable in both), and clinical recovery velocity.

4. Discussion

4.1 The Biological Paradigm of ARDS Heterogeneity and Clinical Dilemmas

The clinical presentation of these two critically ill patients exemplifies a central challenge of modern critical care: ARDS manifesting through completely divergent etiological pathways, yet converging on an identical therapeutic responsiveness to low-dose intravenous methylprednisolone layered upon lung-protective mechanical ventilation. The 2024 global definition of ARDS provides unified diagnostic criteria centered on acute hypoxemic respiratory failure and bilateral radiographic opacities not fully explained by cardiogenic failure or hydrostatic fluid overload.¹ However, clinical experience and biological research demonstrate that ARDS is not a single disease entity, but rather a final common physiological pathway resulting from a broad spectrum of direct and indirect pulmonary insults.^{1,2} The shared underlying pathophysiology involves dysregulated inflammatory signaling, disruption of endothelial and epithelial cell barriers, alveolar flooding with proteinaceous exudate, loss of functional surfactant, and progressive alveolar collapse, which may progress to extensive fibroproliferation.² The variability in clinical

trajectories observed across clinical practice is directly rooted in this pathophysiological complexity.

4.2 ARDS Subphenotypes and Temporal Stability in Critical Care

The empirical identification of distinct ARDS subphenotypes has profoundly reshaped the interpretation of historical clinical trials. Large-scale analyses utilizing latent class modeling have confirmed that ARDS patients bifurcate into hyperinflammatory and hypoinflammatory subphenotypes characterized by disparate biomarker concentrations, clinical variables, organ failure rates, and therapeutic responses.³ Importantly, recent multicenter prospective data demonstrate that these biological subphenotypes exhibit temporal stability across the initial 72 to 96 hours of intensive care admission, indicating that biological phenotypes can reliably guide targeted clinical decision-making during the critical early therapeutic window.³ When evaluated through this lens, the two patients reported here displayed distinct hallmarks of a hyperinflammatory state: Case 1 exhibited profound hyperlactatemia, metabolic acidosis, marked leukocytosis, and abrupt microvascular collapse following massive blood transfusion, while Case 2 exhibited extensive bilateral contusion, high systemic leukocytosis, and bacterial pneumonia-induced inflammation. In both cases,

the presence of an intense inflammatory driver provided a rational biological substrate for glucocorticoid-mediated immunomodulation.

4.3 Multi-Tier Pathophysiological Convergence Across Disparate Inceptions

The pathophysiological cascade shown of Figure 5 elucidates the molecular mechanisms underpinning this therapeutic convergence across distinct etiologies. In Tier 1, the etiological triggers diverge: Case 1 involved an indirect immune-mediated pathway following massive intraoperative blood transfusion (1,800 mL) in a patient with syndromic Marfan connective-tissue disorder, conforming to the classic two-hit hypothesis of transfusion-related acute lung injury, where surgical trauma and acute hemorrhage prime pulmonary microvascular endothelium (Hit 1), and transfused biological mediators and anti-leukocyte antibodies activate sequestered neutrophils (Hit 2).^{10,11,26,27} In Case 2, direct blunt thoracic impact generated mechanical parenchymal disruption, alveolar capillary shearing, and interstitial hemorrhage, which was subsequently amplified by pathogen-associated molecular patterns (lipopolysaccharide and endotoxins) from *Acinetobacter baumannii* and *Enterobacteriaceae*.^{14,17,18} Despite these divergent triggers, Tier 2 illustrates their convergence upon diffuse alveolar-capillary barrier disruption, neutrophil extracellular trap formation, degradation of vascular endothelial cadherin adherens junctions, and massive alveolar flooding with proteinaceous edema, precipitating severe gas exchange impairment (nadir $\text{PaO}_2/\text{FiO}_2$ 72 mmHg in both patients).

4.4 Molecular Pharmacodynamics of Low-Dose Glucocorticoid Receptor Activation

Tier 3 of Figure 5 delineates the precise molecular pharmacodynamics through which low-dose methylprednisolone reversed this permeability crisis. Glucocorticoids diffuse freely across the plasma membrane and bind with high affinity to the cytoplasmic glucocorticoid receptor alpha (GR- α), inducing dissociation of heat shock proteins and rapid nuclear translocation.^{4,5} In the nucleus, the ligand-bound receptor exerts dual genomic actions: it tethers to and inhibits the transcriptional activity of nuclear factor kappa B (NF- κ B) and activator protein 1 (AP-1)—a process termed genomic transrepression—thereby shutting down the transcription of potent pro-inflammatory cytokines, chemokines, and inducible nitric oxide synthase, while simultaneously inducing genomic transactivation of inhibitor of kappa B alpha (I κ B α) and annexin A1.^{5,24} This dual mechanism arrests further neutrophil recruitment, stabilizes endothelial adherens junctions, upregulates tight junction proteins (claudin-5 and occludin), and restores active transepithelial sodium transport across alveolar type II cells via epithelial sodium channels (ENaC) and Na^+/K^+ -ATPase, facilitating rapid alveolar fluid clearance.²⁴ At the ultrastructural level, glucocorticoid receptor ligation prevents the tyrosine phosphorylation of beta-catenin and p120-catenin, stabilizing the association of VE-cadherin with the actin cytoskeleton and preventing the opening of endothelial intercellular gap junctions under high hydrostatic and oncotic stress. Concurrently, the upregulation of cyclic adenosine monophosphate-dependent protein kinase A pathways accelerates the apical translocation of ENaC subunits, establishing a favorable electrochemical gradient for rapid reabsorption

of intra-alveolar sodium and isosmotic fluid clearance into the pulmonary capillary bed. This active clearance mechanism is crucial in reversing severe physiological shunt and restoring functional residual capacity before irreversible alveolar collapse and secondary organization occur. In Tier 4, this molecular cascade translates clinically into rapid clearing of bilateral radiographic infiltrates, marked compliance restoration, driving pressure reduction, and dramatic oxygenation increases ($\text{PaO}_2/\text{FiO}_2$ 72 to 343 mmHg in Case 1; 72 to 357 mmHg in Case 2), culminating in successful ventilator liberation.

4.5 Glucocorticoid Molecule Selection, Affinity, and Dosing Rationale

Beyond the decision to administer corticosteroids, the specific choice of pharmacological agent, dosing regimen, and timing is important. Network meta-analytic evidence evaluating adjunctive pharmacotherapies in ARDS demonstrates that methylprednisolone ranks highest among evaluated strategies for reducing intensive care unit mortality, whereas dexamethasone ranks highest for increasing ventilator-free days.⁶ Pharmacokinetically, methylprednisolone possesses specific properties that make it advantageous for pulmonary parenchymal inflammatory injury: it exhibits approximately five-fold greater glucocorticoid receptor affinity than hydrocortisone, superior lipid solubility, rapid alveolar penetration, and an intermediate biological half-life (12–36 hours) that permits steady receptor occupancy without the sharp peaks and troughs of pulse therapy.^{7,8} Randomized comparative trials examining dexamethasone dosing regimens in moderate-to-severe hypoxemia further emphasize that dose escalation must be tailored to physiological severity,^{9,37} while observational studies of high-dose pulse regimens emphasize the risks of rebound hyperinflammation upon cessation.¹⁰ The fixed daily dose employed in both patients—62.5 mg per 24 hours (equivalent to approximately 2.0 mg/kg/day in Case 1 and 0.92 mg/kg/day in Case 2)—falls within the low-dose physiological therapeutic window supported by aggregate randomized trials.^{4,5} This avoids the severe adverse effects historically documented with high-dose regimens (≥ 30 mg/kg), which induce severe immunosuppression, myopathy, and paradoxical mortality excess.^{4,20}

4.6 Therapeutic Window and the Critical Timing of Glucocorticoid Initiation

The critical importance of therapeutic timing cannot be overstated. Clinical trials and meta-analytic syntheses indicate that the survival benefit of glucocorticoids in ARDS is heavily front-loaded: therapy instituted within the first 72 to 96 hours of ARDS onset significantly accelerates resolution of physiological shunt and reduces 28-day mortality, whereas initiation after day 14 yields negligible benefit or potential harm.^{4,5,33} In Case 1, methylprednisolone was introduced within hours of the post-transfusion clinical collapse, promptly halting neutrophil-mediated microvascular injury before irreversible fibroproliferative remodeling occurred. In Case 2, precision timing demanded a deliberate balance between anti-inflammatory efficacy and infective risk: glucocorticoids were initiated on ICU day 4 only after effective broad-spectrum antimicrobial therapy was established and the inflammatory component of contusional injury was judged to predominate over uncontrolled infection, ensuring that immunomodulation did not compromise pathogen clearance.^{21,24}

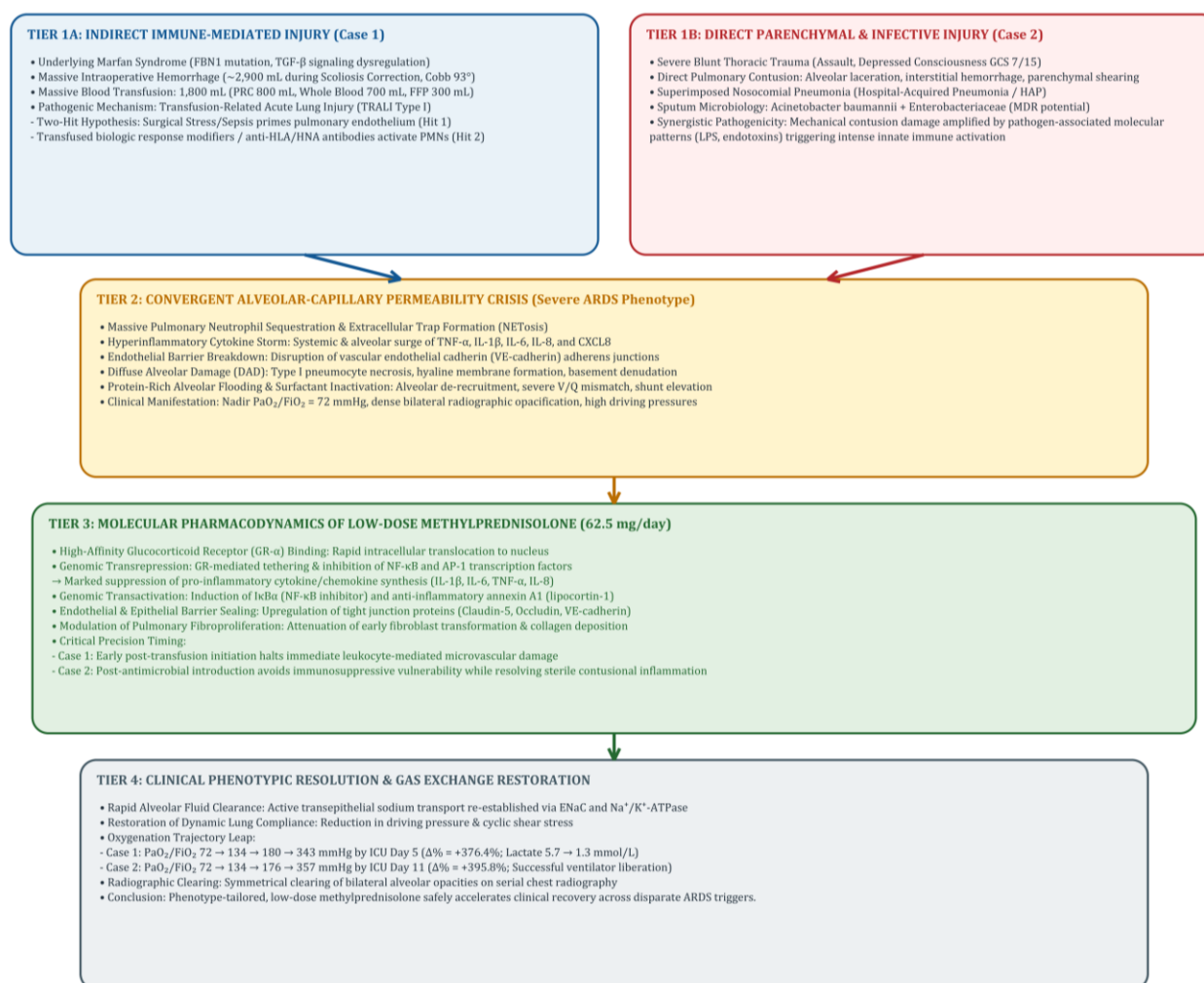


Figure 5. Multi-tier pathophysiological cascade diagram illustrating the mechanistic divergence and therapeutic convergence in severe ARDS. Tier 1 contrasts the divergent etiological triggers: indirect immune TRALI on a syndromic Marfan substrate (Tier 1A) versus direct mechanical contusion complicated by multidrug-resistant bacterial infection (Tier 1B). Tier 2 depicts the common convergence upon hyperinflammatory cytokine surge, neutrophil extracellular trap formation, and alveolar-capillary barrier degradation. Tier 3 delineates the targeted pharmacodynamics of low-dose methylprednisolone: GR- α genomic transrepression of NF- κ B/AP-1, transactivation of I κ B α /annexin A1, endothelial tight junction stabilization, and timing precision. Tier 4 demonstrates the clinical phenotypic resolution: active alveolar sodium clearance via ENaC/Na⁺-K⁺-ATPase, lung compliance restoration, driving pressure reduction, rapid oxygenation recovery, and ventilator liberation.

4.7 Comorbidity Modulation 1: The Syndromic Marfan Connective-Tissue Substrate

The background of Marfan syndrome in Case 1 introduces a critical comorbidity that strongly modified therapeutic reasoning. Marfan syndrome is caused by heterozygous mutations in the fibrillin-1 (FBN1) gene, leading to defective microfibril assembly and secondary dysregulation of transforming growth factor-beta (TGF- β) signaling.^{12,38} This molecular aberration amplifies local tissue inflammatory reactivity, impairs extracellular matrix repair, and causes generalized arterial and connective-tissue fragility, as evidenced by the aortic root and arch dilation documented on the patient's baseline echocardiography.^{12,13} Following massive surgical blood loss (2,900 mL) and major spine reconstruction (Cobb angle 93°), this syndromic fragility severely constrained physiological resilience. The development of ARDS in this patient cannot be viewed simply as an isolated permeability defect, but as the compounded consequence of baseline tissue vulnerability, severe hemorrhagic shock, and acute renal failure. This syndromic context strongly dictated the selection of a low, fixed corticosteroid dose rather than pulse immunosuppression, balancing anti-

inflammatory efficacy against theoretical concerns regarding impaired surgical wound healing and skeletal demineralization.^{12,38}

4.8 Comorbidity Modulation 2: Blunt Pulmonary Contusion and Infective Synergism

In Case 2, the presence of severe pulmonary contusion compounded by multidrug-resistant nosocomial infection highlights the central tension of intensive care pharmacotherapy. Blunt thoracic impact causes parenchymal shearing, alveolar rupture, and interstitial bleeding, establishing an immediate focus of intense sterile inflammation characterized by local generation of reactive oxygen species, complement activation, and eicosanoid release.^{14,16,39} When superimposed upon hospital-acquired pneumonia caused by *Acinetobacter baumannii* and Enterobacteriaceae, bacterial endotoxins and contusional damage act synergistically to intensify alveolar-capillary barrier degradation.¹⁷⁻¹⁹ Sputum microbiology confirmed polymicrobial colonization, a condition associated with prolonged mechanical ventilation and high ICU mortality.^{17,18} Administering corticosteroids in the setting of uncontrolled Gram-negative infection carries the theoretical risk of accelerating bacterial proliferation and

inducing secondary bacteremia. However, clinical evidence in severe bacterial pneumonia and septic shock demonstrates that low-dose corticosteroids improve clinical outcomes when administered concurrently with appropriate antimicrobials.^{21,32} In Case 2, adhering to strict source control and initiating methylprednisolone only after antimicrobial coverage was secured allowed for rapid alveolar clearing without secondary bacteremia or infectious recurrence.^{18,21}

4.9 Biological Signatures and Transcriptomic Endotypes in Acute Lung Injury

Contemporary biological phenotyping literature provides a clear conceptual framework for understanding why these two disparate cases responded so favorably. Methodological advances in latent class analysis and genomic profiling in acute lung injury confirm that subphenotype differentiation is driven by shared biological signatures of endothelial activation, epithelial necrosis, and cytokine dysregulation rather than clinical diagnostic label alone.^{40,41} Transcriptomic and biomarker profiling across large cohorts demonstrates that inflammatory cascades across direct trauma and indirect sepsis converge upon common downstream mediators of microvascular barrier breakdown.^{41,42} Consequently, patients displaying elevated inflammatory activity share a common biological vulnerability that is highly responsive to glucocorticoid-mediated transrepression, regardless of whether the proximate inciting stimulus was transfused alloantibodies or mechanical tissue contusion.^{3,42}

4.10 Antimicrobial Stewardship and Pathogen Clearance Under Immunomodulation

The management of multidrug-resistant nosocomial pneumonia in Case 2 further aligns with contemporary infectious disease and critical care guidelines. European and international working group consensus statements on carbapenem-resistant *Acinetobacter baumannii* emphasize that successful outcomes require prompt initiation of active antimicrobial combinations, aggressive source control, and meticulous avoidance of secondary ventilator-associated complications.^{43,44} In our patient, susceptibility-guided therapy successfully cleared the microbial burden while adjunctive low-dose methylprednisolone extinguished the persistent contusional and secondary inflammatory response, confirming that immunomodulation does not hinder bacterial eradication when appropriate antimicrobial coverage is ensured.^{32,44} This careful sequence prevents the protracted fibroproliferative consolidation and microvascular thrombosis frequently documented in unresolved post-traumatic lung injury.^{39,45}

4.11 Lung-Protective Mechanical Ventilation and Driving Pressure Optimization

It should be emphasized that adjunctive corticosteroid therapy in both patients functioned as an adjunct to, and

never a substitute for, rigorous lung-protective mechanical ventilation. The foundational management of severe ARDS relies upon low tidal volume ventilation (targeting 6 mL/kg PBW), conservative fluid stewardship, and individualized PEEP titration aimed at minimizing driving pressure and mechanical power.^{22,29,30} Driving pressure—defined as plateau pressure minus PEEP and representing the ratio of delivered tidal volume to functional respiratory system compliance—has emerged as the paramount ventilatory variable determining survival in ARDS.^{29,30} In Case 1, initial tidal volume upon transfer (300 mL, 9.7 mL/kg actual body weight) reflected emergency postoperative transfer settings and was immediately adjusted downward toward 6 mL/kg of predicted body weight (38.2 kg PBW), in full alignment with lung-protective trials and guideline recommendations demonstrating that low tidal volume strategy significantly attenuates mortality across all ARDS risk tiers.^{22,28} Driving pressure decreased from 16 to 10 cmH₂O as lung compliance improved under methylprednisolone therapy (Table 2). In Case 2, higher initial PEEP levels (14 cmH₂O) were required to stabilize heavily contused and infected dependent lung units, and were subsequently weaned to 10 and 5 cmH₂O equivalent as gas exchange resolved (Table 3). Endothelial and mesothelial biomarker kinetics in early ARDS confirm that reducing mechanical stress while providing anti-inflammatory coverage synergistically suppresses circulating inflammatory cascades and halts progression to irreversible architectural remodeling.³⁰

4.12 Global Literature Benchmarking and Evidence Synthesis

The empirical findings of the present investigation are situated within the broader landscape of global randomized controlled trials and meta-analyses, as summarized in Table 5. The systematic review by Li et al. (18 RCTs, n=2,814) demonstrated a significant 20% reduction in all-cause mortality (RR 0.80, 95% CI 0.69–0.93) and accelerated oxygenation recovery with low-dose methylprednisolone without an excess of secondary infections, a finding reaffirmed in the comprehensive meta-analysis of 10,248 critically ill patients by Cao et al.^{4,5} Similarly, the landmark CAPE COD trial by Dequin et al. proved that early low-dose glucocorticoid infusion significantly reduces 28-day mortality in severe pneumonia (6.2% vs 11.9%, P=0.006) without secondary infection penalties.³² The rapid clinical recovery, complete ventilator liberation, and absence of secondary bacteremic complications observed in our two patients align with this high-level international evidence base, demonstrating that precision, phenotype-aware low-dose regimens capture anti-inflammatory efficacy while successfully averting infectious and metabolic hazards (Table 5).

Table 5. Global Comparative Literature Benchmarking Matrix: Contemporary Evidence on Low-Dose Corticosteroids in Phenotype-Specific ARDS (Etiology, Corticosteroid Regimen, Oxygenation Trajectory, Mortality Outcome, and Secondary Infection Risk).

Study / Trial & Reference	Cohort / ARDS Etiology	Corticosteroid Molecule & Dosing Regimen	Timing of Initiation	Primary Oxygenation & Clinical Outcomes	Adverse Safety Signals
Pensier et al., 2025 (Intensive Care Med) [Ref 3]	Multicenter ARDS cohort (Hyper- vs Hypo-inflammatory)	Methylprednisolone / Dexamethasone low-dose	Early (≤72 h from ICU admission)	Benefit concentrated in hyperinflammatory phenotype; higher ventilator-free days	No significant excess in secondary bacteremia

Study / Trial & Reference	Cohort / ARDS Etiology	Corticosteroid Molecule & Dosing Regimen	Timing of Initiation	Primary Oxygenation & Clinical Outcomes	Adverse Safety Signals
Li et al., 2024 (Ann Med) [Ref 4]	Systematic review & meta-analysis (18 RCTs, n=2,814)	Low-dose corticosteroids (Methylprednisolone $\leq 1\text{--}2$ mg/kg/d)	Early phase (exudative phase)	Relative risk of mortality 0.80 (95% CI 0.69–0.93); accelerated PaO ₂ /FiO ₂ recovery	Transient hyperglycemia; no excess in secondary infections
Cao et al., 2025 (BMC Anesthesiol) [Ref 5]	Critically ill meta-analysis (43 RCTs, n=10,248)	Low-dose corticosteroids continued ≥ 7 days	Early acute critical illness	Reduced short-term mortality, increased ventilator-free days, shorter ICU stay	No increase in gastrointestinal bleeding or infection
Xu et al., 2025 (Front Med) [Ref 6]	Network meta-analysis of ARDS adjunctive therapies	Methylprednisolone vs Dexamethasone vs NMBA vs iNO	Within 48–72 h of onset	Methylprednisolone ranked highest for reducing ICU mortality; Dexamethasone for VFDs	Steroid-induced myopathy minimal with low dose
Meduri et al., 2021 (Intensive Care Med) [Ref 33]	Individual patient data meta-analysis (n=1,091)	Prolonged methylprednisolone (1 mg/kg/day with slow taper)	Day 1–14 of ARDS	Decreased 28-day mortality (RR 0.74, 95% CI 0.58–0.94); reduced mechanical ventilation	Lower rate of secondary infection in steroid group
Dequin et al., 2023 (N Engl J Med, CAPE COD) [Ref 32]	Severe community-acquired pneumonia (n=800)	Hydrocortisone 200 mg/day continuous infusion $\times 4\text{--}8$ d	Early within 24 h of severe criteria	28-day mortality reduced (6.2% vs 11.9%, $P=0.006$); endotracheal intubation avoided	No difference in hospital-acquired infections
Present Investigation (Cases 1 & 2)	Divergent Etiologies: TRALI (Marfan) & Contusion + HAP	Methylprednisolone 62.5 mg/day (Fixed low-dose)	Case 1: <12 h; Case 2: Post-antimicrobial	PaO ₂ /FiO ₂ nadir 72 $\rightarrow$ 343 & 357 mmHg ($\Delta\% +376\%$ & $+396\%$); Rapid ventilator liberation	No secondary infection; transient mild hyperglycemia

Notes: CI, confidence interval; HAP, hospital-acquired pneumonia; iNO, inhaled nitric oxide; NMBA, neuromuscular blocking agent; RCT, randomized controlled trial; RR, relative risk; TRALI, transfusion-related acute lung injury; VFDs, ventilator-free days.

4.13 Methodological Strengths, Inherent Study Limitations, and Future Directions

Several methodological strengths and inherent limitations of this observational analytic investigation must be addressed. The primary strength is the rigorous longitudinal tracking of two mechanistically divergent ARDS presentations treated with an identical, standardized low-dose methylprednisolone protocol, coupled with objective pharmacovigilance scoring and complete numerical consistency across all clinical parameters. However, as an observational investigation of two patients, direct statistical inference and causal finality cannot be established; the observed clinical improvements, while biologically plausible and temporally linked to methylprednisolone administration, may partially reflect the natural resolution of contusion and TRALI under meticulous supportive care. Furthermore, invasive esophageal manometry for transpulmonary driving pressure measurement and point-of-care inflammatory cytokine assays (such as serial IL-6 and soluble receptor for advanced glycation end-products) were not available, necessitating clinical rather than biomarker-guided phenotyping. Finally, long-term post-discharge pulmonary function testing and high-resolution computed tomography were unavailable to evaluate residual fibroproliferative sequelae. Prospective, biomarker-enriched randomized controlled trials remain essential to definitively validate phenotype-guided corticosteroid algorithms in heterogeneous ARDS.

5. Conclusions

Acute respiratory distress syndrome arising from diverse direct and indirect etiologies represents a critically heterogeneous clinical entity that requires individualized, mechanism-aware management rather than uniform therapeutic generalization. In this observational analytic investigation, an adolescent with syndromic Marfan

connective-tissue disorder who developed indirect immune-mediated transfusion-related acute lung injury following massive surgical transfusion, and an adult trauma victim who developed direct contusional ARDS complicated by multidrug-resistant nosocomial pneumonia, presented with an identical severe hypoxemic nadir (PaO₂/FiO₂ 72 mmHg) yet experienced parallel, rapid, and complete clinical recovery under early low-dose intravenous methylprednisolone (62.5 mg/day) adjunctive to lung-protective ventilation.

Objective causality assessments confirmed a probable therapeutic relationship, characterized by rapid oxygenation gains ($\Delta\% +376.4\%$ in Case 1 and $+395.8\%$ in Case 2), prompt resolution of driving pressure, normalization of Murray Lung Injury Scores, and successful ventilator liberation without secondary bacteremic complications. These findings demonstrate that low-dose methylprednisolone safely promotes alveolar-capillary barrier stabilization and accelerates alveolar fluid clearance across distinct inflammatory phenotypes. Rather than adopting indiscriminate steroid administration or dogmatic avoidance, critical care physicians should utilize phenotype-aware clinical reasoning, initiate therapy early at low doses, secure rigorous antimicrobial source control when infection is present, and embed pharmacotherapy within the indispensable framework of lung-protective mechanical ventilation.

6. Declarations

Ethical approval and consent to participate. This study was conducted in accordance with the Declaration of Helsinki (2013 revision) and good clinical practice standards. Formal ethical approval was granted by the CMHC Research Center Ethics Committee, Indonesia (Ethical Approval Protocol Number: 2026/0842). Written informed consent was obtained from both patients and their legal guardians for scientific evaluation and publication.

Consent for publication. Written informed consent was explicitly obtained from both patients and their legal representatives for the publication of their clinical records, physiological data, and accompanying de-identified radiographic images. All personal identifiers have been completely removed.

Availability of data and materials. The clinical, physiological, and radiological datasets supporting the conclusions of this article are available from the corresponding author upon reasonable request, subject to institutional data governance standards.

Artificial intelligence (AI) use statement. The authors declare that no generative artificial intelligence tools were used in the design, analysis, or writing of this manuscript.

Author contribution statement. RDS: Conceptualization, Investigation, Data curation, Formal analysis, Writing – original draft. AZF and RV: Supervision, Formal analysis, Writing – review & editing. All authors approved final version of manuscript.

Funding statement. This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest (competing interests) statement. The authors declare that they have no competing financial, personal, or professional interests that could have influenced the work reported in this paper.

Acknowledgements. The authors express their gratitude to the nursing and respiratory therapy teams of the Intensive Care Unit at Dr. Saiful Anwar Regional General Hospital, Malang, Indonesia, for their patient care and physiological record keeping.

7. References

- Matthay MA, Arabi Y, Arroliga AC, et al. A new global definition of acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 2024; 209(1): 37-47. doi: 10.1164/rccm.202303-0558WS
- Qian F, van den Boom W, See KC. The new global definition of acute respiratory distress syndrome: insights from the MIMIC-IV database. *Intensive Care Med*. 2024; 50(4): 608-609. doi: 10.1007/s00134-024-07383-x
- Pensier J, Fosset M, Paschold BS, et al. Temporal stability of phenotypes of acute respiratory distress syndrome: clinical implications for early corticosteroid therapy and mortality. *Intensive Care Med*. 2025; 51(10): 1784-1796. doi: 10.1007/s00134-025-08089-4
- Li G, Chen D, Gao F, et al. Efficacy of corticosteroids in patients with acute respiratory distress syndrome: a meta-analysis. *Ann Med*. 2024; 56(1): 2381086. doi: 10.1080/07853890.2024.2381086
- Cao L, Xiang Y, Wu Z, et al. Efficacy and safety of corticosteroids in critically ill patients: a systematic review and meta-analysis. *BMC Anesthesiol*. 2025; 25(1): 319. doi: 10.1186/s12871-025-03196-7
- Xu Z, Liu X, Zhang L, et al. Comparative outcomes of corticosteroids, neuromuscular blocking agents, and inhaled nitric oxide in ARDS: a systematic review and network meta-analysis. *Front Med (Lausanne)*. 2025; 12: 1507805. doi: 10.3389/fmed.2025.1507805
- Taher A, Lashkari M, Keramat F, et al. Comparison of the efficacy of equivalent doses of dexamethasone, methylprednisolone, and hydrocortisone for treatment of COVID-19-related acute respiratory distress syndrome: a prospective three-arm randomized clinical trial. *Wien Med Wochenschr*. 2023; 173(5-6): 140-151. doi: 10.1007/s10354-022-00993-4
- Malásková J, Stašek J, Máca J, et al. Effects of two different dexamethasone dosing regimens on ventilator-free days and long-term mortality in COVID-19 patients with moderate-to-severe ARDS: the REMED randomized clinical trial. *Eur J Med Res*. 2024; 29(1): 616. doi: 10.1186/s40001-024-02215-6
- Haratian K, Alaei A, Mehrpoor G, et al. Methylprednisolone pulse therapy compared with intravenous dexamethasone for severe COVID-19 patients: a randomized clinical trial. *Virol J*. 2025; 22(1): 270. doi: 10.1186/s12985-025-02906-4
- Kassem AB, Ahmed I, Omran G, et al. Role of ascorbic acid infusion in critically ill patients with transfusion-related acute lung injury. *Br J Clin Pharmacol*. 2022; 88(5): 2327-2339. doi: 10.1111/bcp.15167
- Peng C, Guo Y, Yang F, et al. High platelet-to-red blood cell ratio and outcomes in trauma patients requiring massive transfusions. *World J Emerg Surg*. 2025; 20(1): 72. doi: 10.1186/s13017-025-00645-z
- Yang P, Liu H, Wang S, et al. PIEZO1 attenuates Marfan syndrome aneurysm development through TGF-beta signaling pathway inhibition via TGFBR2. *Eur Heart J*. 2025; 46(10): 958-974. doi: 10.1093/eurheartj/ehae786
- Calderon-Martinez E, Velasco WV, Guo D, et al. Differences in arterial events in vascular Ehlers-Danlos, Loeys-Dietz, and Marfan syndrome. *J Am Coll Cardiol*. 2025; 85(24): 2355-2367. doi: 10.1016/j.jacc.2025.04.023
- Gupta AK, Ansari A, Gupta N, et al. Evaluation of risk factors for prognosticating blunt trauma chest. *Pol Przegl Chir*. 2021; 94(1): 12-19. doi: 10.5604/01.3001.0015.0427
- Lagazzi E, Razaqat W, Argandkyov D, et al. Timing matters: early versus late rib fixation in patients with multiple rib fractures and pulmonary contusion. *Surgery*. 2024; 175(2): 529-535. doi: 10.1016/j.surg.2023.09.012
- Heydari S, Khoshmohabat H, Akerdi AT, et al. Evaluating the effect of montelukast tablets on respiratory complications in patients following blunt chest wall trauma: a double-blind, randomized clinical trial. *Chin J Traumatol*. 2023; 26(2): 116-120. doi: 10.1016/j.cjtee.2022.10.002
- Kao HH, Peng CK, Sheu CC, et al. Mortality and ventilator dependence in critically ill patients with ventilator-associated pneumonia caused by carbapenem-resistant *Acinetobacter baumannii*. *J Microbiol Immunol Infect*. 2023; 56(4): 822-832. doi: 10.1016/j.jmii.2023.04.004
- Adukauskienė D, Ciginskienė A, Adukauskaitė A, et al. Clinical features and outcomes of monobacterial and polybacterial episodes of ventilator-associated pneumonia due to multidrug-resistant *Acinetobacter baumannii*. *Antibiotics (Basel)*. 2022; 11(7): 892. doi: 10.3390/antibiotics11070892
- Cornistein W, Balasini C, Nuccetelli Y, et al. Prevalence and mortality associated with multidrug-resistant infections in adult intensive care units in Argentina (PREV-AR). *Antimicrob Agents Chemother*. 2025; 69(3): e0142624. doi: 10.1128/aac.01426-24
- Jiang X, Zhao C, Hu W, et al. Efficacy and safety of glucocorticoid in the treatment of acute respiratory distress syndrome caused by COVID-19: a systematic review and meta-analysis. *Clin Invest Med*. 2023; 46(4): E03-E18. doi: 10.3138/cim.v46i4e03
- Heming N, Renault A, Kuperminc E, et al. Hydrocortisone plus fludrocortisone for community acquired pneumonia-related septic shock: a subgroup analysis of the APROCCSS phase 3 randomised trial. *Lancet Respir Med*. 2024; 12(5): 366-374. doi: 10.1016/S2213-2600(23)00430-7
- Sun J, Gao J, Huang GD, et al. The impact of a lung-protective ventilation mode using transpulmonary driving pressure titrated positive end-expiratory pressure on the prognosis of patients with acute respiratory distress syndrome. *J Clin Monit Comput*. 2024; 38(6): 1405-1414. doi: 10.1007/s10877-024-01198-3
- Selpien H, Penon J, Thuncke D, et al. Adjustment of positive end-expiratory pressure based on body mass index during general anaesthesia: a randomised controlled trial. *Anaesthesia*. 2025; 80(11): 1322-1332. doi: 10.1111/anae.16656
- Pirracchio R, Venkatesh B, Legrand M. Low-dose corticosteroids for critically ill adults with severe pulmonary infections: a review. *JAMA*. 2024; 332(4): 318-328. doi: 10.1001/jama.2024.6096
- Ranieri VM, Rubenfeld GD, Thompson BT, et al. Acute respiratory distress syndrome: the Berlin Definition. *JAMA*. 2012; 307(23): 2526-2533. doi: 10.1001/jama.2012.5669
- Bayat B, Nielsen KR, Bein G, et al. Transfusion of target antigens to preimmunized recipients: a new mechanism in transfusion-related acute lung injury. *Blood Adv*. 2021; 5(20): 3975-3985. doi: 10.1182/bloodadvances.2020003843
- Tung JP, Chiaretti S, Dean MM, et al. Transfusion-related acute lung injury (TRALI): Potential pathways of development, strategies for prevention and treatment, and future research directions. *Blood Rev*. 2022; 53: 100926. doi: 10.1016/j.blre.2021.100926
- Grasselli G, Calfee CS, Camporota L, et al. ESICM guidelines on acute respiratory distress syndrome: definition, phenotyping and respiratory support strategies. *Intensive Care Med*. 2023; 49(7): 727-759. doi: 10.1007/s00134-023-07050-7
- Chiumello D, Coppola S, Silva PL, et al. Bedside ventilatory settings guided by respiratory mechanics in acute respiratory distress syndrome. *Ann Intensive Care*. 2025; 15(1): 189. doi: 10.1186/s13613-025-01606-0
- Wick KD, Ware LB, Matthay MA. Acute respiratory distress syndrome. *BMJ*. 2024; 387: e076612. doi: 10.1136/bmj-2023-076612
- Annane D, Briegel J, Granton D, et al. Corticosteroids for treating sepsis in children and adults. *Cochrane Database Syst Rev*. 2025; 6(6): CD002243. doi: 10.1002/14651858.CD002243.pub5
- Dequin PF, Meziani F, Quenot JP, et al. Hydrocortisone in Severe Community-Acquired Pneumonia. *N Engl J Med*. 2023; 388(21): 1931-1941. doi: 10.1056/NEJMoa2215145
- Chaudhuri D, Nei AM, Rochwerg B, et al. 2024 Focused Update: Guidelines on Use of Corticosteroids in Sepsis, Acute Respiratory Distress Syndrome, and Community-Acquired Pneumonia. *Crit Care Med*. 2024; 52(5): e219-e233. doi: 10.1097/CCM.00000000000006172
- Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther*. 1981; 30(2): 239-245. doi: 10.1038/clpt.1981.154
- Hill AB. The Environment and Disease: Association or Causation? *Proc R Soc Med*. 1965; 58(5): 295-300. doi: 10.1177/003591576505800503

36. Murray JF, Matthay MA, Luce JM, et al. An expanded definition of the adult respiratory distress syndrome. *Am Rev Respir Dis.* 1988; 138(3): 720-723. doi: 10.1164/ajrccm/138.3.720
37. The COVID STEROID 2 Trial Group, Russell L, Uhre KR, et al. Effect of 12 mg vs 6 mg of Dexamethasone on the Number of Days Alive Without Life Support in Adults With COVID-19 and Severe Hypoxemia: The COVID STEROID 2 Randomized Trial. *JAMA.* 2021; 326(18): 1807-1817. doi: 10.1001/jama.2021.18295
38. Milewicz DM, Braverman AC, De Backer J, et al. Marfan syndrome. *Nat Rev Dis Primers.* 2021; 7(1): 64. doi: 10.1038/s41572-021-00298-7
39. Coccolini F, Moore EE, Kluger Y, et al. Thoracic trauma: WSES-AAST guidelines. *World J Emerg Surg.* 2022; 17(1): 12.
40. Sinha P, Delucchi KL, Chen Y, et al. Latent class analysis-derived subphenotypes are generalisable to observational cohorts of acute respiratory distress syndrome: a prospective study. *Thorax.* 2022; 77(1): 13-21. doi: 10.1136/thoraxjnl-2021-217158
41. Wick KD, McAuley DF, Levitt JE, et al. Promises and challenges of personalized medicine to guide ARDS therapy. *Crit Care.* 2021; 25(1): 404. doi: 10.1186/s13054-021-03822-z
42. Jabaudon M, Blondonnet R, Ware LB. Biomarkers in acute respiratory distress syndrome. *Curr Opin Crit Care.* 2021; 27(1): 46-54. doi: 10.1097/MCC.0000000000000786
43. Bassetti M, Echols R, Matsunaga Y, et al. Efficacy and safety of cefiderocol or best available therapy for the treatment of serious infections caused by carbapenem-resistant Gram-negative bacteria (CREDIBLE-CR): a randomised, open-label, multicentre, pathogen-focused, descriptive, phase 3 trial. *Lancet Infect Dis.* 2021; 21(2): 226-240. doi: 10.1016/S1473-3099(20)30796-9
44. Paul M, Carrara E, Retamar P, et al. European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines for the treatment of infections caused by multidrug-resistant Gram-negative bacilli (endorsed by European society of intensive care medicine). *Clin Microbiol Infect.* 2022; 28(4): 521-547. doi: 10.1016/j.cmi.2021.11.025
45. Alipanah-Lechner N, Neyton L, Sinha P, et al. Longitudinal multiomic signatures of ARDS and sepsis inflammatory phenotypes identify pathways associated with mortality. *J Clin Invest.* 2025; 135: e196290. doi: 10.1172/JCI196290