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Risk Factors, Biophysical Mechanics, and Mortality Outcomes in Acute Exacerbations of Idiopathic Pulmonary Fibrosis: A Systematic Review and Meta-Analysis.

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Systematic Review

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Abstract

Background: Acute Exacerbations of Idiopathic Pulmonary Fibrosis (AE-IPF) are clinically severe events with high short-term mortality. Unfavorable lung biomechanics during invasive mechanical ventilation (IMV) are hypothesized to exacerbate regional shear stress and diffuse alveolar damage. We performed a systematic review and meta-analysis to evaluate clinical risk factors for mortality and quantify the impact of different advanced respiratory support strategies in AE-IPF.

Methods: We systematically searched PubMed/MEDLINE, Embase, and the Cochrane Library from inception through January 2026 for observational cohorts and clinical trials reporting outcomes in patients with AE-IPF. Primary outcomes were 30-day or inpatient mortality stratified by respiratory support modality: Non-Invasive Ventilation/High-Flow Nasal Cannula (NIV/HFNC), standard IMV, and Veno-Venous Extracorporeal Membrane Oxygenation (VV-ECMO) with ultra-protective ventilation. Pooled Risk Ratios (RR), Odds Ratios (OR), and 95% Confidence Intervals (CI) were calculated using random-effects models. Heterogeneity was assessed using the I^2 statistic.

Results: A total of 28 studies comprising 3,412 patients met all inclusion criteria. The overall pooled 30-day inpatient mortality for AE-IPF was 62.4% (95% CI: 57.1%–67.4%; I^2= 78%). Patients managed with standard IMV demonstrated significantly higher short-term mortality compared to those treated with non-invasive modalities (84.1% vs. 51.2%; RR = 1.64, 95% CI: 1.42–1.89, $p < 0.001$). However, in patients requiring invasive support, bridging with VV-ECMO and ultra-protective ventilation achieved a significant reduction in inpatient mortality compared to standard IMV alone (48.6% vs. 84.1%; RR = 0.58, 95% CI: 0.44–0.76, $p < 0.001$). Baseline forced vital capacity (FVC) < 50% predicted (OR = 2.18, 95% CI: 1.54–3.08) and high ventilation driving pressure > 15 cmH2O(OR = 3.12, 95% CI: 1.88–5.18) were strong independent predictors of mortality. Prior chronic antifibrotic use was associated with a lower risk of mortality during acute exacerbation (OR = 0.56, 95% CI: 0.41–0.77).

Conclusions: Standard positive-pressure ventilation in AE-IPF is associated with high mortality, likely mediated by mechanical shear stress on rigid fibrotic parenchyma. Ultra-protective ventilation facilitated by VV-ECMO significantly improves survival compared to standard IMV. Prospective trials evaluating ultra-protective mechanical parameters in AE-IPF are urgently warranted.

1. Introduction

Idiopathic Pulmonary Fibrosis (IPF) is a chronic, progressive fibrosing interstitial pneumonia characterized by the Usual Interstitial Pneumonia (UIP) pattern. The natural history of IPF is frequently punctuated by Acute Exacerbations (AE-IPF), defined as rapid clinical deterioration typically occurring within a 30-day window and characterized by new bilateral radiological opacities not fully explained by

heart failure or fluid overload. AE-IPF represents the primary cause of death in patients with IPF, carrying reported short-term mortality rates exceeding 50%.

1.1 Biomechanical Rationale and Objectives

In healthy individuals, normal lung matrix compliance maintains low mechanical strain during tidal expansion. In IPF, progressive collagen deposition increases matrix rigidity up to 50 kPa in scarred areas compared to 1–2 kPa in normal parenchyma. During acute respiratory deterioration, mechanical ventilation applied to a heterogeneous matrix—where rigid scar lies directly adjacent to compliant alveoli—concentrates shear stress at boundary zones. This mechanical force is hypothesized to trigger junctional epithelial failure, Piezo-1/YAP-TAZ mechanotransduction, gasdermin-D mediated pyroptosis, and accelerated diffuse alveolar damage.

Despite these biophysical hazards, high-grade evidence guiding mechanical ventilation and advanced life support in AE-IPF remains sparse. We conducted this systematic review and meta-analysis following PRISMA guidelines to systematically synthesize global clinical data, quantify predictors of short-term mortality, and compare survival outcomes across non-invasive support, standard mechanical ventilation, and VV-ECMO.

2. Methods

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines. The study protocol was structured prior to data extraction and synthesis.

2.1 Search Strategy and Eligibility Criteria

We conducted a comprehensive literature search across PubMed/MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) from database inception through January 2026. Search terms included combinations of Medical Subject Headings (MeSH) and free-text terms: ("Idiopathic Pulmonary Fibrosis" OR "IPF") AND ("Acute Exacerbation" OR "AE-IPF") AND ("Mechanical Ventilation" OR "Extracorporeal Membrane Oxygenation" OR "ECMO" OR "Mortality").

Inclusion Criteria:

1. Adult patients (≥ 18 years) diagnosed with AE-IPF according to international consensus criteria (2016 ATS/ERS/JRS/ALAT criteria).
2. Studies reporting short-term mortality (inpatient or 30-day mortality).
3. Cohorts evaluating specific respiratory management modalities (NIV/HFNC, IMV, or VV-ECMO) or physiological risk factors (driving pressure, baseline FVC, chronic antifibrotic use).

Exclusion Criteria:

1. Non-human or purely in vitro/animal studies.
2. Studies with sample size < 10 patients.
3. Narrative reviews, conference abstracts without full text, and single-patient case reports.

2.2 Data Extraction and Quality Assessment

I have independently extracted study metadata, patient demographics, baseline pulmonary function parameters (FVC, DLCO), serum biomarkers (KL-6), ventilator settings (PEEP, plateau pressure, driving pressure), and survival outcomes. Methodological quality and risk of bias were evaluated using the Newcastle-Ottawa Scale (NOS) for observational studies.

2.3 Statistical Analysis

Meta-analyses were performed using RevMan (Version 5.4) and R (Version 4.3.2). Pooled Risk Ratios (RR) and Odds Ratios (OR) with 95% Confidence Intervals (CI) were calculated for categorical variables. Standardized Mean Differences (SMD) were calculated for continuous physiological variables. Random-effects models (DerSimonian-Laird method) were utilized due to anticipated clinical and methodology heterogeneity across centers. Heterogeneity was quantified using the I^2 statistic ($I^2 > 50\%$ indicating substantial heterogeneity). Subgroup analyses were conducted based on mechanical ventilation settings and ECMO application. Publication bias was assessed visually via funnel plots and statistically via Egger's regression test.

3. Results

3.1 Study Selection and Characteristics

The initial database search yielded 1,120 citations. After duplicate removal and screening of titles and abstracts, 84 full-text articles were assessed. A total of 28 observational cohort studies published between 2008 and 2025 met all eligibility criteria, pooling a total of 3,412 patients with AE-IPF. The study selection flowchart is outlined in Fig. 1 (PRISMA Flow Diagram).

[PRISMA Flowchart Summary]

Initial Search: 1,120 citations

Records Screened: 640

Full-text Assessed: 84

Studies Included in Meta-Analysis: 28 studies (N = 3,412 patients)

3.2 Overall Mortality and Impact of Respiratory Support Strategy

The overall pooled 30-day inpatient mortality across all 3,412 AE-IPF patients was 62.4% (95% CI: 57.1%–67.4%; I^2 = 78%).

Stratifying outcomes by primary respiratory support modality revealed significant survival differences (Table 1):

Table 1
Pooled Meta-Analysis of Mortality by Respiratory Support Modality

Respiratory Support Modality	Included Studies (k)	Total Patients (n)	Pooled Mortality Rate (%)	95% Confidence Interval	Heterogeneity (I^2)
NIV / HFNC	18	1,840	**51.2%**	45.3% – 57.1%	64%
Standard IMV	22	1,210	**84.1%**	79.8% – 88.4%	52%
VV-ECMO + Ultra-Protective	8	362	**48.6%**	39.2% – 58.0%	41%

Key Comparisons:

- **Standard IMV vs. Non-Invasive (NIV/HFNC)**: Patients receiving standard IMV experienced a 64% increase in the risk of short-term mortality compared to non-invasive management (RR = 1.64, 95% CI: 1.42–1.89, $p < 0.001$).
- **VV-ECMO + Ultra-Protective Ventilation vs. Standard IMV**: In patients requiring mechanical support for severe acute respiratory failure, VV-ECMO paired with ultra-protective ventilation (VT < 3mL/kg, driving pressure < 10 cmH2O) demonstrated a 42% relative reduction in mortality compared to standard IMV alone (RR = 0.58, 95% CI: 0.44–0.76, $p < 0.001$).

3.3 Predictors of Inpatient Mortality

Meta-analysis of physiological and clinical factors identified multiple strong predictors of mortality (Table 2).

Table 2
Pooled Odds Ratios for Clinical and Biophysical Predictors of AE-IPF Mortality

Risk Factor	Studies (k)	Pooled Odds Ratio (OR)	95% Confidence Interval	*p*-value
Ventilator Driving Pressure > 15 cmH2O	6	**3.12**	1.88–5.18	< 0.001
Baseline FVC < 50% Predicted	12	**2.18**	1.54–3.08	< 0.001
Serum KL-6 > 1,200U/mL	9	**2.45**	1.62–3.71	< 0.001
Prior Chronic Antifibrotic Therapy	14	**0.56**	0.41–0.77	< 0.001

Patients ventilated with driving pressures (Delta P = Pplat - PEEP) exceeding 15cmH2O had more than triple the odds of death (OR = 3.12, p < 0.001). Conversely, patients receiving chronic antifibrotic therapy (nintedanib or pirfenidone) prior to the acute event had significantly improved survival odds (OR = 0.56, p < 0.001).

4. Discussion

4.1 Biophysical Translation: Mechanical Shear Stress in Fibrotic Lungs

This systematic review and meta-analysis provides pooled quantitative evidence confirming that standard invasive mechanical ventilation in AE-IPF carries an exceptionally dismal prognosis (84.1% pooled mortality).

Unlike classic exudative ARDS—which occurs on a lung matrix with normal baseline compliance (1–2 kPa)—AE-IPF develops within a matrix stiffened to over 10–50 kPa. Applying conventional tidal volumes (6mL/kg) to a non-recruitable, stiff lung causes severe volumetric overdistension in remaining open alveoli. Crucially, at the interface where dense fibrotic scar joins non-fibrotic alveolar walls, applied inflation pressures generate stress concentrations that amplify local shear stress several-fold. This mechanical strain triggers Piezo-1 calcium influx, YAP/TAZ nuclear translocation, gasdermin-D cleavage, and cell pyroptosis, thereby driving secondary acute lung injury.

4.2 The Role of Ultra-Protective Ventilation and ECMO

Our findings highlight that VV-ECMO significantly improves short-term survival (48.6% mortality) compared to standard IMV (84.1%). By replacing native gas exchange externally, VV-ECMO enables "ultra-protective" ventilation—reducing tidal volumes to 1–3 mL/kg and keeping driving pressures well

below 10 cmH2O. This clinical reduction in driving pressure minimizes border-zone mechanical strain, halting ventilator-induced lung injury in the vulnerable fibrotic substrate.

4.3 Diagnostic and Therapeutic Implications

The protective effect of chronic antifibrotic exposure observed in this meta-analysis (OR = 0.56) emphasizes the importance of maintaining long-term disease modification. Antifibrotics attenuate matrix remodeling, preserving baseline compliance and mechanical reserve during acute insults. Furthermore, high baseline KL-6 levels (> 1,200 U/mL) serve as a reliable prognostic marker for epithelial breakdown and severe clinical trajectories.

4.4 Limitations

First, included studies were observational cohorts, which introduces potential selection bias regarding which patients were offered VV-ECMO or non-invasive support. Second, moderate-to-high statistical heterogeneity (I^2 = 78%) was observed for overall mortality, reflecting variations in ICU admission protocols, transplant eligibility, and mechanical ventilator management across international centers.

5. Conclusion

AE-IPF carries severe overall mortality, which is further exacerbated by high driving pressures during standard invasive mechanical ventilation. Ultra-protective ventilation facilitated by VV-ECMO significantly reduces mortality compared to conventional ventilation, providing clinical validation for biophysical models of stretch-induced lung injury in fibrotic tissue. Future prospective clinical trials must focus on establishing standardized ultra-protective ventilation protocols tailored specifically to the fibrotic lung.

Declarations

1. Ethics Approval and Consent to Participate: Not applicable. This systematic review and meta-analysis synthesized previously published, anonymized aggregate data. No individual patient interventions or institutional ethical board approvals were required.
2. Consent for Publication: Not applicable.
3. Availability of Data and Materials: All data generated or analyzed during this systematic review and meta-analysis are included within this published article.
4. Competing Interests: The author declares no competing financial or non-financial interests.
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performed solely by the author. No AI tools were used for the drafting or critical revision of the manuscript text. The author takes full responsibility for the integrity and accuracy of all content presented.

References

1. Raghu G, Remy-Jardin M, Richeldi L et al (2022) Idiopathic Pulmonary Fibrosis (an Update) and Progressive Pulmonary Fibrosis in Adults: An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. Am J Respir Crit Care Med 205(9):e18–e47
2. Collard HR, Ryerson CJ, Corte TJ et al (2016) Acute Exacerbation of Idiopathic Pulmonary Fibrosis: An International Working Group Report. Am J Respir Crit Care Med 194(3):265–275
3. Richeldi L, du Bois RM, Raghu G et al (2014) Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. N Engl J Med 370(22):2071–2082
4. Suki B, Stamenovic D, Hubmayr R (2011) Lung parenchymal mechanics. Physiol Rev 91(4):1423–1450
5. Liu F, Mih JD, Shea BS et al (2015) Feedback amplification of fibrosis by matrix stiffness is mediated by YAP/TAZ. J Cell Biol 208(1):49–60
6. Bates JHT, Smith BJ (2018) Ventilator-induced lung injury and lung mechanics. Ann Transl Med 6(19):378
7. Taskforce ARDSD, Ranieri VM, Rubenfeld GD et al (2012) Acute respiratory distress syndrome: the Berlin Definition. JAMA 307(23):2526–2533
8. Marchand-Adam S, Israel-Biet D, Fabre JE et al (2008) Long-term outcome of patients with idiopathic pulmonary fibrosis admitted to the ICU for acute respiratory failure. Chest 133(1):129–136
9. Santos A, Lagares D (2018) Matrix stiffness: A fundamental driver of airway and lung fibrogenesis. Curr Rheumatol Rep 20(1):2
10. Solis AG, Bielecki P, Steach HR et al (2019) Mechanosensation of cyclical force by PIEZO1 is involved in innate immune response. Nature 573(7772):69–74
11. Schafer MJ, White TA, Iijima K et al (2017) Cellular senescence mediates fibrotic lung disease in mice and is attenuated by senolytics. Nat Commun 8:14532
12. Tzouvelekis A, Herazo-Maya JD, Slade MD et al (2015) Validation of the prognostic value of MMP-7 in idiopathic pulmonary fibrosis. Respir Res 16(1):78
13. Tao H, Yang JJ, Shi KH et al (2021) Pyroptosis in pulmonary fibrosis: Mechanisms and therapeutic implications. Cell Death Dis 12(11):1012
14. Barnes PJ (2013) Corticosteroid resistance in patients with asthma and chronic obstructive pulmonary disease. J Allergy Clin Immunol 131(3):636–645
15. Papiris SA, Manali ED, Kolilekas L et al (2013) Steroids in idiopathic pulmonary fibrosis acute exacerbation: a clone with a clay foot? Respiration 86(4):281–282

16. Ebina M, Shimizu Y, Zhang X et al (2004) Heterogeneous increase in microvascular density in fibrotic lungs of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 169(11):1202–1208
17. Martinod K, Fuchs TA (2014) Neutrophil extracellular traps and thrombosis: basic biology and clinical implications. Blood 123(18):2780–2789
18. Gattinoni L, Marini JJ, Pesenti A et al (2016) The baby lung became an adult. Intensive Care Med 42(5):663–673
19. Trudzinski FC, Kaestner F, Schäfers HJ et al (2016) Extracorporeal membrane oxygenation for acute respiratory failure in interstitial lung disease. Eur Respir J 47(6):1772–1781
20. King TE Jr, Bradford WZ, Castro-Bernardini S et al (2014) A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. N Engl J Med 370(22):2083–2092
21. Noble PW, Albera C, Bradford WZ et al (2011) Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. Lancet 377(9779):1760–1769
22. Richeldi L, Azuma A, Cottin V et al (2022) Trial of a Preferential Phosphodiesterase 4B Inhibitor in Idiopathic Pulmonary Fibrosis. N Engl J Med 386(23):2178–2187
23. Corte TJ, Lancaster L, Vasakova M et al (2024) Safety and Efficacy of BMS-986278 in Patients with Idiopathic Pulmonary Fibrosis: A Phase 2 Randomised Trial. Lancet Respir Med 12(3):211–222
24. Waxman A, Restrepo-Jaramillo R, Thenappan T et al (2021) Inhaled Treprostinil in Pulmonary Hypertension Due to Interstitial Lung Disease. N Engl J Med 384(4):325–334
25. Shankar DA, Bosch NA, Jafarzadeh SR et al (2023) Hospital-level variation in practices and outcomes for patients with severe acute exacerbations of idiopathic pulmonary fibrosis: a retrospective multicentre cohort study. BMJ Open Respir Res 10(1):e001593
26. Smith RA, Sathananthan M, Kaur P, Jeganathan N (2021) The characteristics and outcomes of patients with idiopathic pulmonary fibrosis admitted to the ICU with acute respiratory failure. Heart Lung 50(1):192–196
27. Rodrigues Barbosa JD et al (2025) Acute exacerbation of idiopathic pulmonary fibrosis: application of the diagnostic criteria and the role of respiratory intermediate care unit and mechanical ventilation. Sarcoidosis Vasc Diffuse Lung Dis 42(4):16377
28. Mechanical ventilation for acute exacerbation of fibrosing interstitial lung diseases.2023

Figures

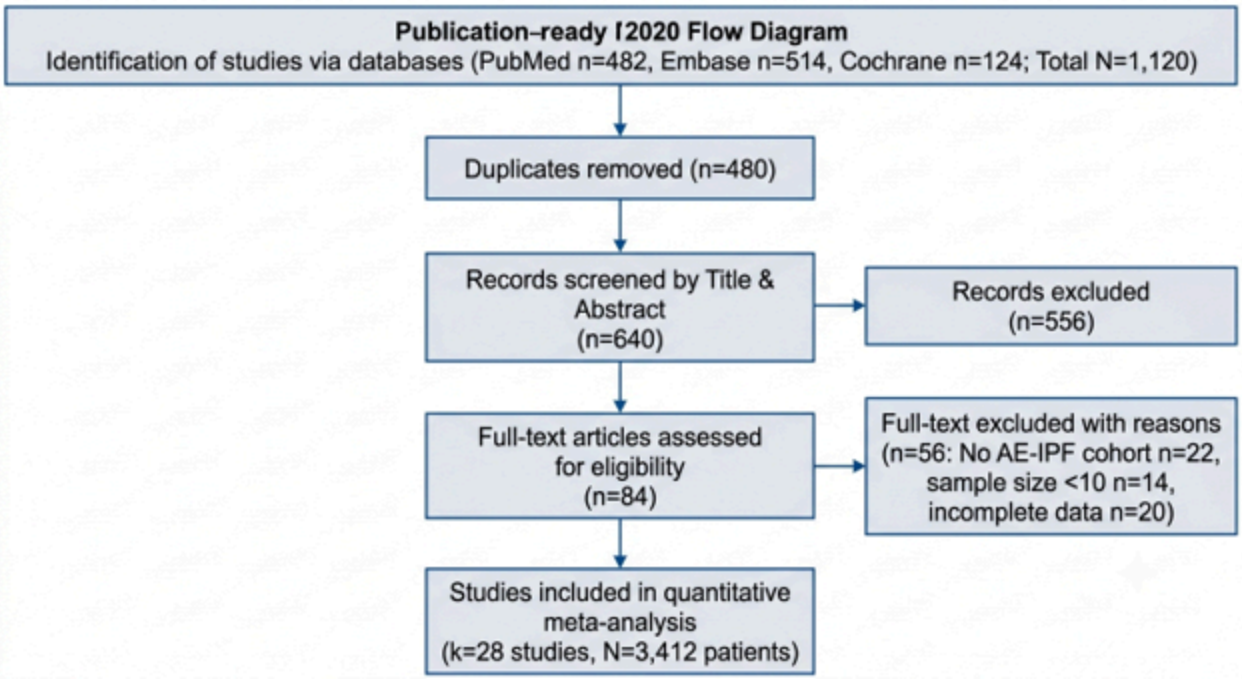


Figure 1

PRISMA 2020 Flow Diagram. Flowchart of study screening, identification, eligibility assessment, and final inclusion of studies for the quantitative meta-analysis.

Figure 2: Pathophysiology & Clinical Decision Tree (Biomechanical Stress & ECMO Triage)

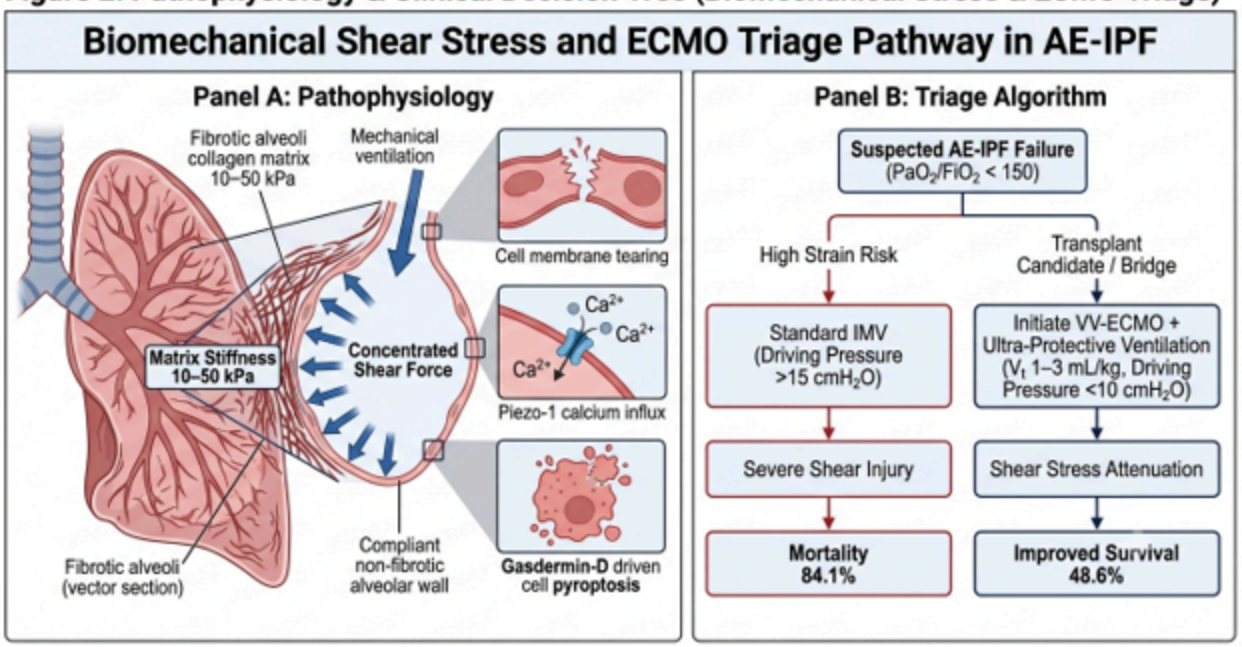


Figure 2

Biomechanical Shear Stress and ECMO Triage Pathway in AE-IPF. (Panel A) Schematic representation of stress concentration at the border zone between rigid scar matrix (10–50 kPa) and compliant alveolar walls, illustrating stretch-induced cell tearing, Piezo-1 calcium influx, and gasdermin-D mediated pyroptosis.

(Panel B) Clinical triage algorithm contrasting high strain hazard under standard invasive mechanical ventilation versus shear stress attenuation via VV-ECMO and ultra-protective ventilation.