J Current Biomed Report
ISSN: 2717-1906
2025, Volume 6, Number 4
Review Paper

Impact of genetic variants on outcomes in ICU patients with acute respiratory failure syndromes

Niloofar Keikhaei[1], Hamed Hekmatnezhad[2], Mohsen Farrokhpour[3]*, Mahnaz Mohammadnezhad[4], Nilufar Bavafa[5]

1. *Department of Internal Medicine, Sayad Shirazi Hospital, School of Medicine, Golestan University of Medical Sciences, Gorgan, Iran*
2. *Department of Basic Sciences, Sari Agricultural Sciences and Natural Resources University, Sari, Iran*
3. *Firouzgar Hospital, Department of Internal Medicine, School of Medicine, Iran University of Medical Sciences, Tehran, Iran*
4. *Department of Midwifery, School of Nursing and Midwifery, Ardabil University of Medical Sciences, Ardabil, Iran*
5. *Department of Food Microbiology, Sanjesh Zagros Mokrian Laboratory, Mahabad, Iran*

Article info:
Received: 07 Nov 2025
Accepted: 15 Dec 2025

Keywords:
Acute respiratory failure
Genetic susceptibility
ARDS
Pharmacogenomics
ICU management

ABSTRACT

Acute respiratory failure (ARF) and acute respiratory distress syndrome (ARDS) represent major causes of morbidity and mortality in the intensive care unit (ICU). Although clinical triggers such as pneumonia, sepsis, trauma, and viral infections are well characterized, substantial inter-individual variability in disease susceptibility, severity, and treatment response suggests an important contribution of genetic factors. Emerging evidence from genome-wide association studies, polygenic analyses, and sequencing of rare variants highlights key pathways including endothelial barrier regulation, innate immunity, and inflammatory signaling that shape host responses during critical illness. Pharmacogenomic studies further indicate that genetic variation influences responses to sedatives, corticosteroids, and other ICU therapies, although clinical translation remains limited. Environmental exposures and critical care interventions interact with inherited variation, emphasizing the multidimensional nature of ARF. This review synthesizes current knowledge on genetic determinants of ARF and ARDS, examines their relationship with clinical outcomes in the ICU, and outlines how gene-environment interactions and pharmacogenomics contribute to treatment heterogeneity. Despite promising discoveries, major gaps persist, including limited ancestry diversity, modest effect sizes, and scarce genotype-informed interventional trials. A deeper integration of genomics with multi-omics profiling and clinical phenotyping is essential to advance precision medicine approaches for critically ill patients.

Corresponding Author(s):
Mohsen Farrokhpour, MD
Address: *Firouzgar Hospital, Department of Internal Medicine, School of Medicine, Iran University of Medical Sciences, Tehran, Iran*
Tel: +98 21 82141000
E-mail: Mohsenfrkh@gmail.com, farrokhpour.m@iums.ac.ir

1. Introduction

Acute respiratory failure (ARF) is a clinical condition characterized by a rapid decline in pulmonary gas exchange, resulting in life-threatening hypoxemia and/or hypercapnia, often emerging in previously stable patients. It arises from a wide spectrum of respiratory, cardiovascular, and systemic disorders that overwhelm the lungs' ability to maintain adequate oxygenation and carbon dioxide removal [1]. ARF is broadly classified into hypoxemic (type 1) and hypercapnic (type 2) forms, with the latter associated with elevated arterial carbon dioxide levels and respiratory acidosis [2].

Acute respiratory distress syndrome (ARDS) represents a severe, non-cardiogenic subtype of ARF marked by diffuse alveolar damage and bilateral infiltrates, most often triggered by pneumonia, sepsis, aspiration, or severe viral infections such as *coronavirus disease (*COVID-19) [3]. ARF remains one of the leading reasons for intensive care unit (ICU) admission worldwide, particularly due to its frequent requirement for invasive mechanical ventilation or advanced non-invasive respiratory support.

Multicenter studies indicate that ARDS-related ARF carries high morbidity and substantial mortality, with ICU fatality rates commonly in the range of 30–40% in moderate-to-severe cases, and even higher in selected subgroups, particularly during the COVID-19 pandemic [4]. Evidence-based practices such as high-flow nasal oxygen, non-invasive ventilation, and lung-protective ventilation strategies have become central pillars of ARF management.

Beyond short-term survival, ARF and its interventions significantly shape long-term functional outcomes, quality of life, and healthcare utilization among ICU survivors, underscoring the need to examine both clinical and biological determinants of disease trajectories [5,6].

Figure 1 provides an overview of ARF and ARDS, illustrating the causes, physiological pathways, clinical manifestations, and the rationale for intensive monitoring and ventilator support in the ICU.

This narrative review aims to synthesize current evidence on the genetic and pharmacogenomic determinants of ARF and ARDS in critically ill patients. It explores how genetic variation shapes susceptibility, disease severity, host responses, and treatment outcomes in the ICU; summarizes emerging insights from genome-wide studies, sequencing approaches, and multi-omics research; and evaluates the role of gene-environment interactions in modulating clinical trajectories.

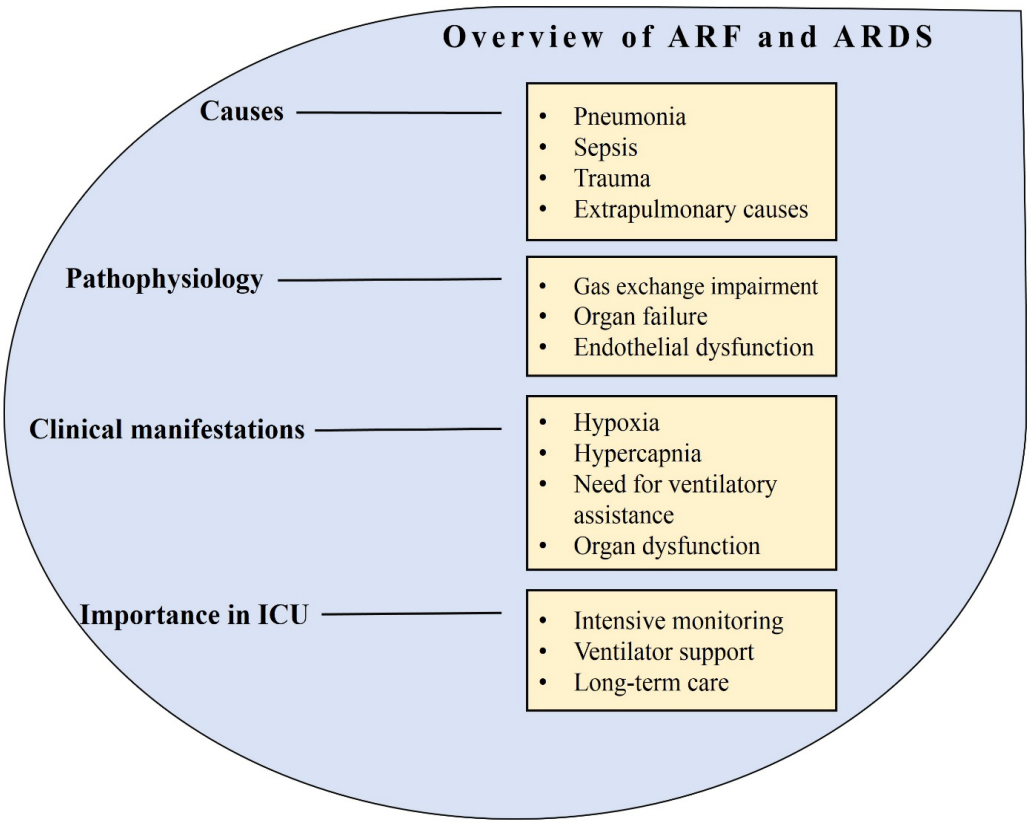

Figure 1. A visual summary of the key aspects of ARF and ARDS in the ICU. It illustrates the causes, physiological processes, clinical manifestations, and importance of ICU management for these critical conditions. This figure simplifies complex clinical information, enabling healthcare professionals to quickly grasp the interrelationships between the various factors involved in ARF and ARDS, supporting more informed decision-making in patient care.

Furthermore, the review outlines key knowledge gaps and future research priorities including the need for large multi-ancestry cohorts, harmonized phenotyping, and genotype-informed interventional trials to advance precision medicine strategies in the management of ARF and ARDS.

2. The Role of Genetic Variability in ARF and ARDS

Despite sharing similar precipitating insults such as pneumonia, sepsis, trauma, or viral infection critically ill patients demonstrate substantial heterogeneity in susceptibility to ARF, inflammatory profiles, organ dysfunction severity, and survival. This variability strongly suggests a key contribution of host genetic factors to the pathophysiology of ARF and ARDS [7,8]. Over the past decade, genetic studies of sepsis and ARDS have identified variants in pathways related to endothelial and epithelial barrier integrity, innate immune activation, and coagulation, all of which influence disease susceptibility and outcomes [9]. Additionally, variants in cytokine signaling, pattern-recognition receptors, and interferon pathways have been associated with severe viral respiratory failure, including COVID-19, highlighting that host genetic architecture can significantly modulate disease progression independent of pathogen characteristics [10]. Research in septic ICU cohorts has further demonstrated that both common and rare genetic variants shape the balance between hyperinflammatory and immunosuppressive responses, thereby affecting organ injury patterns and mortality [11]. Despite this growing body of evidence from genome-wide association studies (GWAS), candidate-gene analyses, and multi-omics profiling, integration of genetic insights into clinical practice remains limited. Current findings are fragmented due to heterogeneity in population structure, inconsistent ARDS definitions, variable clinical management, and inadequate sample sizes across studies [7,12]. These challenges highlight the need for more robust, harmonized, and multi-ancestry genetic investigations to better elucidate the contribution of host genomics to ARF susceptibility and clinical outcomes.

3. Genetic susceptibility to acute respiratory failure

Genetic variation is increasingly recognized as a significant factor contributing to the development of ARF and its progression to acute ARDS. Recent studies have demonstrated that susceptibility to ARF reflects the combined influence of common and rare inherited variants that act across multiple biological pathways. GWAS have identified several key loci, particularly within the vascular endothelial growth factor (VEGF) signaling pathway, including the Fms-Like Tyrosine Kinase 1 (FLT1) gene, which modulates endothelial permeability and influences the severity of acute lung injury. These genetic variants are strongly associated with the risk of ARDS and sepsis-related ARF, highlighting the importance of endothelial integrity in determining ARF susceptibility [8,9]. Additionally, polygenic risk scores (PRS) have provided further insight into how multiple small-effect genetic variants collectively contribute to ARF susceptibility. These scores have revealed overlapping genetic risk factors between ARF, sepsis, and severe pneumonia, indicating that a genetic predisposition to one condition may predispose patients to others, further complicating the clinical presentation of ARF [13]. Sequencing-based studies have also uncovered rare, high-impact variants, particularly in genes related to interferon signaling and innate immunity. These variants, which may represent inborn errors of immunity, contribute to severe viral respiratory failure, especially in critical illness settings like COVID-19 [10]. These findings suggest that genetic predispositions to immune dysregulation may become clinically apparent during critical illness, highlighting a new avenue for exploring genetic contributions to ARF and ARDS. The large-scale COVID-19 GWAS consortia have further reinforced the role of genetics in ARF by identifying significant associations in loci involved in antiviral defense, inflammation, and epithelial barrier response. These associations are biologically plausible across both viral and non-viral forms of ARF, underscoring the relevance of genetic factors beyond the pathogen alone in shaping disease outcomes [14]. Despite these advances, much of the genetic evidence remains fragmented, and current findings are limited by small sample sizes, heterogeneous patient populations, and variable ARDS definitions. Nevertheless, these genetic studies provide a coherent framework for understanding the role of inherited variation in determining susceptibility to ARF. Moving forward, comprehensive, multi-ancestry studies with larger sample sizes and more consistent phenotyping will be essential to validate these findings and better translate genetic insights into clinical practice.

4. Genetic variants and clinical outcomes in the ICU

Genetic variants play a crucial role in shaping the clinical course and outcomes of critically ill patients with ARF and ARDS. While susceptibility to ARF and ARDS is influenced by a variety of factors, including environmental and clinical exposures, emerging evidence suggests that genetic variations contribute significantly to both the development of these conditions and their progression in the ICU. Recent studies have linked specific genetic polymorphisms to important clinical outcomes, including ICU mortality, the severity of organ failure, and the need for mechanical ventilation or vasopressor support. For example, polymorphisms in genes involved in

endothelial function, such as those in the VEGF pathway, have been associated with more severe ARDS and poorer short-term survival rates in ICU patients. Similarly, variations in stress-response genes like Silent Information Regulator 2-Related Enzyme 1 (SIRT1: a gene involved in cellular stress tolerance) are linked to differences in patient outcomes, including organ failure progression [15]. Furthermore, recent research has emphasized the role of inherited immune-related variants in determining the clinical trajectory of ARDS. In particular, polymorphisms in genes related to immune regulation, such as cytokine receptors and pattern-recognition receptors, appear to influence how patients respond to infections, contributing to variations in ARF severity and survival rates. For instance, specific genetic markers are associated with a hyperinflammatory endotype of ARDS, which typically leads to worse outcomes, including higher ICU mortality, prolonged ventilation, and extended organ dysfunction [8]. In addition to single genetic variants, the concept of host-response subphenotypes is gaining traction in ARF research. These subphenotypes, such as hyperinflammatory versus hypoinflammatory profiles, are shaped by genetic predispositions and are crucial in determining patient prognosis. Studies show that patients with a hyperinflammatory response to ARDS tend to experience worse outcomes, including higher mortality rates and fewer ventilator-free days, compared to those with a hypoinflammatory response [16]. Pharmacogenomic data have also added a layer of complexity to understanding ICU outcomes. Variants in drug-metabolizing enzymes, such as cytochrome P450 (CYP450) and catechol-O-methyltransferase (COMT), influence how patients process sedatives, analgesics, and other critical medications. For example, genetic differences in CYP3A4/5 can alter how patients respond to sedatives like midazolam and dexmedetomidine, leading to differences in the effectiveness of sedation and the risk of oversedation or undersedation. However, current pharmacogenomic panels only account for a small portion of the variability in achieving optimal sedation and do not yet result in significant improvements in clinical outcomes such as ICU length of stay or survival [17].

Overall, the influence of genetic variants on clinical outcomes in the ICU is multifaceted. While certain genetic markers have shown clear associations with ARDS severity, organ failure progression, and patient survival, the effect sizes are often modest, and findings remain context-dependent. The complexity of linking genetic data to clinical outcomes highlights the need for large, well-phenotyped cohorts that integrate genetic information with biomarkers, clinical interventions, and environmental factors.

5. Pharmacogenomics and response to treatment

Pharmacogenomics plays a critical role in understanding the variability in treatment responses among critically ill patients with ARF. In the ICU, pharmacological interventions such as sedatives, analgesics, neuromuscular blockers, corticosteroids, and vasopressors are commonly used to manage ARF and its underlying causes. However, the response to these therapies can vary significantly between patients due to genetic differences in drug metabolism, receptor sensitivity, and other pharmacokinetic and pharmacodynamic factors [18]. Figure 2 provides a visual representation of the treatment flow for patients with ARF and ARDS in the ICU. The process is organized into four stages: Initial assessment, initiating treatment, monitoring and assessment, and discharge or continued care. The initial assessment involves evaluating clinical symptoms, vital signs, and determining the need for mechanical ventilation. Treatment initiation includes administering antimicrobial medications, sedatives, and ventilatory support. Continuous monitoring of respiratory and hemodynamic status follows, with necessary adjustments in medication and ventilator settings. The final stage prepares the patient for discharge or continued ICU care, focusing on long-term monitoring and complications. This structured approach ensures a comprehensive management of ARF and ARDS, optimizing patient outcomes through timely interventions and ongoing assessment [6,19-21].

Genetic polymorphisms in drug-metabolizing enzymes, transporters, and receptors are key determinants of drug efficacy and toxicity in the ICU. For example, variations in CYP450 enzymes (such as CYP2B6 and CYP3A4/5) can affect the metabolism of commonly used sedatives like midazolam and dexmedetomidine. These genetic differences may lead to altered drug clearance, which can influence the appropriate dosing required for achieving the desired level of sedation and analgesia. Additionally, polymorphisms in the COMT gene and opioid receptor genes have been linked to differences in pain management and sedation, affecting both the efficiency and safety of treatment protocols [17].

Pharmacogenomic studies have also highlighted the role of genetic variation in modulating responses to corticosteroids and other immunomodulatory therapies used in ARF management. Variants in the glucocorticoid receptor gene and genes involved in inflammatory signaling pathways influence how patients respond to corticosteroids in conditions like ARDS and severe pneumonia.

This genetic variation may explain why corticosteroid treatments do not always produce consistent outcomes across different patient populations and contribute to the variability in treatment response observed in clinical trials [22]. Moreover, genetic differences in vasopressor receptors and other targets involved in hemodynamic regulation can also alter the effectiveness of vasopressors, which are crucial for managing shock in ARF patients.

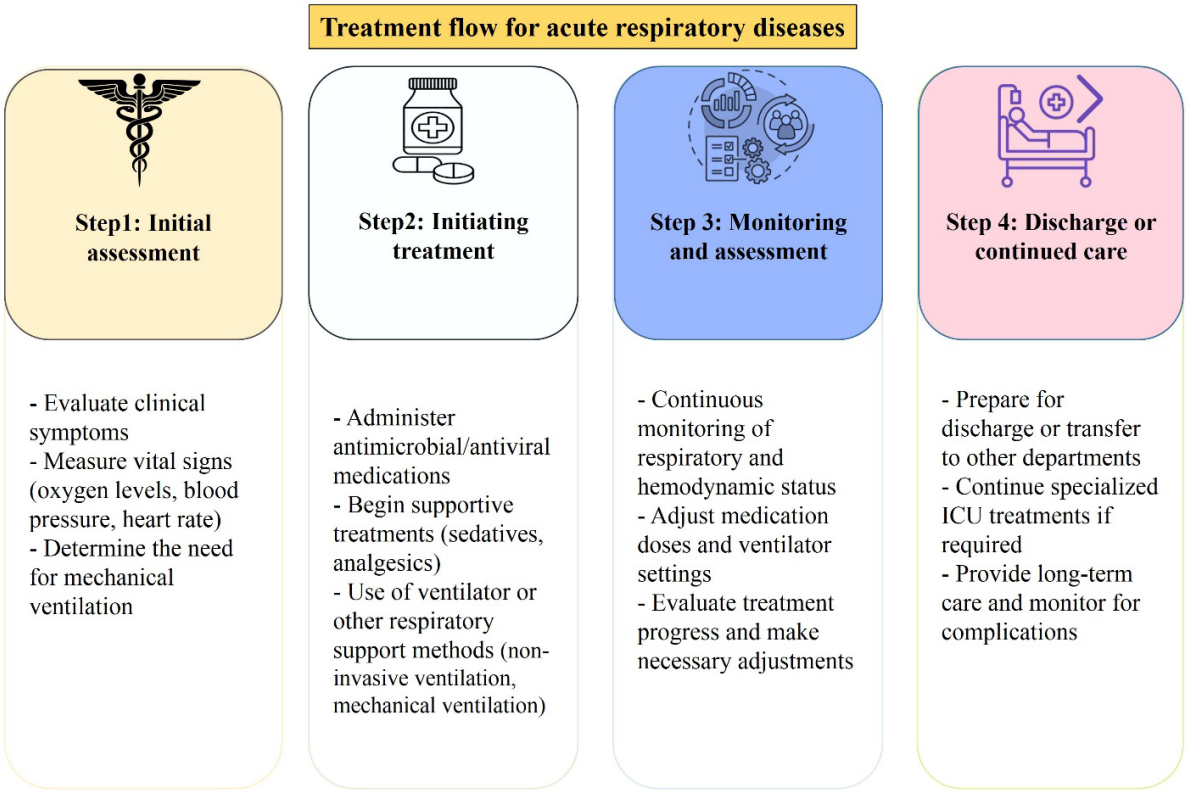

Figure 2. This flowchart illustrates the step-by-step process of managing ARF and ARDS in the ICU. It highlights the key stages of care, including initial assessment, initiating treatment, monitoring and assessment, and discharge or continued care. Each stage is color-coded for clarity, guiding healthcare professionals through the critical decision-making process for optimal patient management.

Variants in these pathways may impact the patient's hemodynamic stability, influencing both the required dose and the overall therapeutic outcome. Despite these advances, the clinical utility of pharmacogenomics in ARF remains limited. Most findings are based on small, single-center studies, and the effect sizes for many genetic variants are modest, making it challenging to translate pharmacogenomic data into routine clinical practice.

Furthermore, pharmacogenomic panels currently used in the ICU provide only a partial explanation for the variability in drug response, and their application in everyday clinical decision-making remains underdeveloped.

Nonetheless, accumulating evidence supports the integration of pharmacogenomic information with other clinical and physiological data to improve the precision of treatment. When combined with biomarkers, physiologic monitoring, and individualized treatment plans, pharmacogenomics has the potential to optimize drug dosing, reduce adverse drug reactions, and improve patient outcomes in the ICU [23].

To fully realize the clinical benefits of pharmacogenomics in ARF, larger, multicenter studies and interventional trials are needed to validate genetic markers, refine drug treatment protocols, and demonstrate their impact on long-term patient recovery and survival.

6. Gene-environment interaction

The development of ARF and its outcomes in critically ill patients is influenced not only by genetic predisposition but also by a complex interplay between genetic factors and environmental exposures. Gene-environment (G×E) interactions refer to the ways in which the effect of genetic variants on disease risk is modified by environmental factors such as infections, trauma, medical interventions, or lifestyle factors like smoking and air pollution. This concept is crucial in understanding the heterogeneous response to ARF, as it helps explain why some patients with similar environmental exposures may experience more severe disease or better recovery outcomes than others [24,25].

In the context of ARF, G×E interactions align with the "multi-hit" hypothesis, which suggests that multiple insults or stressors such as chronic comorbidities combined with pneumonia, sepsis, or mechanical ventilation can push a genetically predisposed individual past a critical threshold, resulting in overt lung injury and ARF. Genetic variants affecting endothelial function, immune responses, and inflammation may amplify or mitigate the effects of these environmental exposures, contributing to variations in disease severity, organ failure progression, and overall survival [26].

Recent studies have highlighted how genetic variants

in key pathways, such as inflammation and immune modulation, influence the host's response to environmental factors like infection and mechanical ventilation. For instance, patients with specific genetic variants in inflammatory signaling pathways may develop hyperinflammatory or hypoinflammatory responses to infections, which can affect both the severity of ARF and the response to interventions like corticosteroids or other immunomodulatory treatments [27,28].

This variability in response underscores the importance of considering not just the genetic background of a patient, but also the environmental context in which these genetic predispositions manifest. Moreover, multi-omics studies have provided additional insights into how gene-environment interactions shape ARF outcomes. These studies have identified distinct subphenotypes of sepsis and ARDS, such as hyperinflammatory versus hypoinflammatory endotypes, that not only differ in their biomarker profiles but also in their response to specific environmental triggers, including infection load, ventilator settings, and adjunctive therapies. These subphenotypes are thought to emerge from the interaction of genetic factors with environmental exposures, highlighting the systems-level complexity of ARF pathogenesis.

The growing recognition of G×E interactions in ARF emphasizes the need for future research to adopt a more integrated approach. Large-scale, multi-ancestry cohorts that capture both genetic data and detailed environmental exposures, along with repeated biomarker sampling and multi-omics profiling, will be crucial for identifying how specific genetic variants influence treatment outcomes in different clinical settings. This comprehensive approach will be necessary to move beyond simplistic genetic models and to develop more personalized, precision-medicine strategies for managing ARF in the ICU [29].

7. Challenges and research priorities

Despite significant advances in understanding the genetic architecture of ARF and ARDS, several limitations still hinder the translation of these findings into routine clinical practice. Most GWAS and sequencing efforts have been conducted in relatively small cohorts with limited statistical power, which often focus on populations of European ancestry. This restriction limits the discovery of genetic variants with modest effects and impedes the generalizability of findings to diverse, multi-ethnic populations [7,30]. Furthermore, the heterogeneity of ARF and ARDS resulting from varying underlying causes such as pneumonia, sepsis, and trauma poses challenges in identifying consistent genetic markers across different clinical subgroups. Differences in ARDS definitions, patient enrollment criteria, and variations in clinical management also complicate the interpretation of genetic data [8,31,32].

In addition, while numerous genetic loci have been identified as potential contributors to ARF susceptibility and ARDS outcomes, the effect sizes for these variants are often small, and functional validation of these loci remains limited. Despite the statistical significance of many identified variants, the causal genes and the cellular and molecular mechanisms by which they influence ARF pathogenesis are still poorly understood. There is a critical need for functional studies that go beyond statistical discovery to explore the biological relevance of these genetic variants and to identify the key cell types and signaling pathways involved [7]. Another limitation is the fragmented nature of current research, with many studies focusing on individual omics layers (e.g., genomics, transcriptomics) in isolation. To overcome this, future research should adopt a multi-omics approach that integrates genomics with other layers of biological information such as transcriptomics, proteomics, metabolomics, and epigenomics.

This integrated approach will provide a more comprehensive understanding of the complex molecular mechanisms underlying ARF and ARDS, enabling the identification of treatable molecular traits and biomarkers that can predict clinical outcomes [33]. Looking ahead, large, multi-ancestry consortia are essential to increase the statistical power of genetic studies and to ensure that genetic findings are applicable to diverse patient populations. These consortia should focus on harmonizing ARDS/ARF definitions, standardizing biospecimen collection, and sharing data and analytic pipelines to minimize bias and improve the robustness of findings. Collaboration across multiple research institutions and integration of global datasets will be key in identifying novel genetic loci and refining the understanding of genetic susceptibility to ARF [30,32].

Finally, prospective, genotype-informed interventional trials are urgently needed to assess the clinical utility of genetic and multi-omics data in guiding patient management in the ICU. For instance, studies could explore whether personalized ventilatory strategies or immunomodulatory treatments based on genetic profiles can improve patient outcomes. Such trials would bridge the gap between genetic discovery and clinical application, ultimately enabling more individualized prevention and treatment strategies for ARF in the ICU [33,34].

8. Conclusion

Over the past decade, genomic and multi-omics research has transformed our understanding of why only a fraction of patients exposed to similar clinical insults progress to ARF or ARDS. Evidence from GWAS, rare-variant sequencing, and pharmacogenomic analyses consistently demonstrates that inherited genetic variation contributes to susceptibility, inflammatory and

immune trajectories, treatment responsiveness, and clinical outcomes. Yet genetics alone cannot account for the marked heterogeneity observed in ARF. Instead, disease expression emerges from the interplay between genetic predisposition, environmental exposures, host immune state, and ICU-level therapeutic interventions. Key biological pathways including endothelial barrier regulation, innate immune activation, and cytokine signaling have been repeatedly implicated, supporting the idea that specific genetic profiles shape both vulnerability and clinical course. Pharmacogenomic findings further highlight how genetic variation may influence responses to sedatives, corticosteroids, and immunomodulatory therapies, underscoring the potential for individualized treatment strategies even though their current predictive value remains modest. The evolving landscape of respiratory failures research reinforces the need for integrative models that combine genetic, molecular, environmental, and clinical data. Such approaches will be essential for identifying meaningful endotypes, refining risk stratification, and improving prognostication. As the field moves forward, genotype-informed interventions and precision-based treatment strategies represent the next major step toward translating biological insights into improved patient outcomes. Although genetic research has not yet reshaped routine respiratory failure management, it provides a critical foundation for a more personalized and biologically informed approach to critical care.

Acknowledgement

During the preparation of this manuscript, AI-assisted tools were used solely for language refinement and improving the clarity of the text. All generated or edited content was carefully reviewed, verified, and approved by the authors to ensure accuracy and integrity.

Authors' contributions

NK, HH, MF: conceptualized the study and defined the scope of the review. HH, MM, NB: performed the literature search and organized the data. NK, MM, NB: drafted the initial version of the manuscript. HH, MF: provided critical revisions and intellectual contributions to refine the manuscript. All authors read and approved the final version of the article.

Conflict of interest

No potential conflict of interest was reported by the authors.

Ethical declarations

Not applicable.

Financial support

Self-funded.

References

1. Fujishima S. Guideline-based management of acute respiratory failure and acute respiratory distress syndrome. J Intensive Care. 2023;11(1):10. DOI: 10.1186/s40560-023-00658-3 PMID: 36895001
2. Pintaudi G, Cutuli SL, Rosà T, Michi T, Cardu A, Bongiovanni F, et al. High-Flow Nasal Oxygen in Patients with Acute Hypercapnic Respiratory Failure: A Narrative Review of the Physiological Rationale and Clinical Evidence. J Clin Med. 2024;13(21):6350. DOI: 10.3390/jcm13216350 PMID: 39518490
3. Matthay MA, Zemans RL, Zimmerman GA, Arabi YM, Beitler JR, Mercat A, et al. Acute respiratory distress syndrome. Nat Rev Dis Primers. 2019;5(1):18. DOI: 10.1038/s41572-019-0069-0 PMID: 30872586
4. Perez J, Brandan L, Telias I. Monitoring patients with acute respiratory failure during non-invasive respiratory support to minimize harm and identify treatment failure. Crit Care. 2025;29(1):147. DOI: 10.1186/s13054-025-05369-9 PMID: 40205493
5. Frat JP, Coudroy R, Marjanovic N, Thille AW. High-flow nasal oxygen therapy and noninvasive ventilation in the management of acute hypoxemic respiratory failure. Ann Transl Med. 2017;5(14):297. DOI: 10.21037/atm.2017.06.52 PMID: 28828372
6. Oczkowski S, Ergan B, Bos L, Chatwin M, Ferrer M, Gregoretti C, et al. ERS clinical practice guidelines: high-flow nasal cannula in acute respiratory failure. Eur Respir J. 2022;59(4):2101574. DOI: 10.1183/13993003.01574-2021 PMID: 34649974
7. Hernández-Beeftink T, Guillen-Guio B, Villar J, Flores C. Genomics and the Acute Respiratory Distress Syndrome: Current and Future Directions. Int J Mol Sci. 2019;20(16):4004. DOI: 10.3390/ijms20164004 PMID: 31426444
8. Suarez-Pajes E, Tosco-Herrera E, Ramirez-Falcon M, Gonzalez-Barbuzano S, Hernandez-Beeftink T, Guillen-Guio B, et al. Genetic Determinants of the Acute Respiratory Distress Syndrome. J Clin Med. 2023;12(11):3713. DOI: 10.3390/jcm12113713 PMID: 37297908
9. Guillen-Guio B, Lorenzo-Salazar JM, Ma SF, Hou PC, Hernandez-Beeftink T, Corrales A, et al. Sepsis-associated acute respiratory distress syndrome in individuals of European ancestry: a genome-wide association study. Lancet Respir Med. 2020;8(3):258-266. DOI: 10.1016/S2213-2600(19)30368-6 PMID: 31982041
10. Velavan TP, Pallerla SR, Rüter J, Augustin Y, Kremsner PG, Krishna S, et al. Host genetic factors determining COVID-19 susceptibility and severity. EBioMedicine. 2021;72:103629. DOI: 10.1016/j.ebiom.2021.103629 PMID: 34655949
11. Gao Q, Teng Y, Zhu L, Zhang W, Li Z. The immunosuppressive mechanisms induced by sepsis and the corresponding treatment strategies. Front Immunol. 2025;16:1643194. DOI: 10.3389/fimmu.2025.1643194 PMID: 41209006
12. Zhang W, Nguyen-Hoang N, Rivrud SCS, Zandbergen AF, Yan Y, Cox EGM, et al. Genetic association studies in critically ill patients: a systematic review. EBioMedicine. 2025;114:105678. DOI: 10.1016/j.ebiom.2025.105678 PMID: 40168842
13. Cox EGM, Zhang W, van der Voort PHJ, Lunter G, Keus F, Snieder H. Genetic association studies in critically ill patients: protocol for a systematic review. Syst Rev. 2023;12(1):233. DOI: 10.1186/s13643-023-02401-3 PMID: 38093336
14. Loktionov AV, Kobzeva KA, Karpenko AR, Sergeeva VA, Orlov YL, Bushueva OY. GWAS-significant loci and severe COVID-19: analysis of associations, link with thromboinflammation syndrome, gene-gene, and gene-environmental interactions. Front Genet. 2024;15:1434681. DOI: 10.3389/fgene.2024.1434681 PMID: 39175753

15. He J, Yang M, Lin Y, Qin W, Yang R, Qin Y, et al. Clinical significance and prognostic value of SIRT1 genetic variants in sepsis: a multicenter hospital-based case-control study. Clin Epigenetics. 2025;17(1):135. DOI: 10.1186/s13148-025-01944-7 PMID: 40739268
16. Kitsios GD, Yang L, Manatakis DV, Nouraie M, Evankovich J, Bain W, et al. Host-Response Subphenotypes Offer Prognostic Enrichment in Patients With or at Risk for Acute Respiratory Distress Syndrome. Crit Care Med. 2019;47(12):1724-1734. DOI: 10.1097/CCM.0000000000004018 PMID: 31634231
17. Mohamed ME, Nguyen TT, Larson J, Schwake B, Rivers Z, Beilman G, et al. Pharmacogenomic variation and sedation outcomes during early intensive care unit admission: A pragmatic study. Clin Transl Sci. 2024;17(12):e70107. DOI: 10.1111/cts.70107 PMID: 39673727
18. Dzierba AL, Stollings JL, Devlin JW. A pharmacogenetic precision medicine approach to analgesia and sedation optimization in critically ill adults. Pharmacotherapy. 2023;43(11):1154-1165. DOI: 10.1002/phar.2768 PMID: 36680385
19. Dinglas VD, Faraone LN, Needham DM. Understanding patient-important outcomes after critical illness: a synthesis of recent qualitative, empirical, and consensus-related studies. Curr Opin Crit Care. 2018;24(5):401-409. DOI: 10.1097/MCC.0000000000000533 PMID: 30063492
20. Ogbonnaya CN, Alsaedi BSO, Alhussaini AJ, Hislop R, Pratt N, Nabi G. Radiogenomics Reveals Correlation between Quantitative Texture Radiomic Features of Biparametric MRI and Hypoxia-Related Gene Expression in Men with Localised Prostate Cancer. J Clin Med. 2023;12(7):2605. DOI: 10.3390/jcm12072605 PMID: 37048688
21. Rochwerg B, Einav S, Chaudhuri D, Mancebo J, Mauri T, Helviz Y, et al. The role for high flow nasal cannula as a respiratory support strategy in adults: a clinical practice guideline. Intensive Care Med. 2020;46(12):2226-2237. DOI: 10.1007/s00134-020-06312-y PMID: 33201321
22. Cazzola M, Rogliani P, Calzetta L, Matera MG. Pharmacogenomic Response of Inhaled Corticosteroids for the Treatment of Asthma: Considerations for Therapy. Pharmgenomics Pers Med. 2020;13:261-271. DOI: 10.2147/PGPM.S231471 PMID: 32801837
23. Scott MJ. Perioperative Patients With Hemodynamic Instability: Consensus Recommendations of the Anesthesia Patient Safety Foundation. Anesth Analg. 2025;140(2):e18. DOI: 10.1213/ANE.0000000000007300 PMID: 38153876
24. Gong MN. Genetic epidemiology of acute respiratory distress syndrome: implications for future prevention and treatment. Clin Chest Med. 2006;27(4):705-24; abstract x. DOI: 10.1016/j.ccm.2006.07.001 PMID: 17085257
25. Kleeberger SR, Cho HY. Gene-environment interactions in environmental lung diseases. Novartis Found Symp. 2008;293:168-78; discussion 178-83. DOI: 10.1002/9780470696781.ch13 PMID: 18972752
26. Wu M, Yan Y, Xie X, Bai J, Ma C, Du X. Effect of endothelial responses on sepsis-associated organ dysfunction. Chin Med J (Engl). 2024;137(23):2782-2792. DOI: 10.1097/CM9.0000000000003342 PMID: 39501810
27. Neyton LPA, Sinha P, Sarma A, Mick E, Kalantar K, Chen S, et al. Host and Microbe Blood Metagenomics Reveals Key Pathways Characterizing Critical Illness Phenotypes. Am J Respir Crit Care Med. 2024;209(7):805-815. DOI: 10.1164/rccm.202308-1328OC PMID: 38190719
28. Slim MA, van Amstel RBE, Bos LDJ, Cremer OL, Wiersinga WJ, van der Poll T, et al. Inflammatory subphenotypes previously identified in ARDS are associated with mortality at intensive care unit discharge: a secondary analysis of a prospective observational study. Crit Care. 2024;28(1):151. DOI: 10.1186/s13054-024-04929-9 PMID: 38715131
29. Petrick PL, Mirus M, Heubner L, Harb H, Menk M, Spieth PM. Clinical Phenotyping in Acute Respiratory Distress Syndrome: Steps Towards Personalized Medicine. J Clin Med. 2025;14(20):7204. DOI: 10.3390/jcm14207204 PMID: 41156075
30. Guillen-Guio B, Suarez-Pajes E, Tosco-Herrera E, Hernandez-Beeftink T, Lorenzo-Salazar JM, Chang D, et al. Genome-wide association study of susceptibility to acute respiratory distress syndrome. EBioMedicine. 2025;120:105951. DOI: 10.1016/j.ebiom.2025.105951 PMID: 41033104
31. Clohisey S, Sinha P. Genome-wide association studies in ARDS: SNPing the tangled web of heterogeneity. Intensive Care Med. 2021;47(7):782-785. DOI: 10.1007/s00134-021-06462-7 PMID: 34173858
32. Matthay MA, Arabi YM, Siegel ER, Ware LB, Bos LDJ, Sinha P, et al. Phenotypes and personalized medicine in the acute respiratory distress syndrome. Intensive Care Med. 2020;46(12):2136-2152. DOI: 10.1007/s00134-020-06296-9 PMID: 33206201
33. Al-Husinat L, Araydah M, Al Sharie S, Azzam S, Battaglini D, Alrababah A, et al. Advancing omics technologies in acute respiratory distress syndrome: paving the way for personalized medicine. Intensive Care Med Exp. 2025;13(1):61. DOI: 10.1186/s40635-025-00766-4 PMID: 40512301
34. Baillie JK, Angus D, Burnham K, Calandra T, Calfee C, Gutteridge A, et al. Causal inference can lead us to modifiable mechanisms and informative archetypes in sepsis. Intensive Care Med. 2024;50(12):2031-2042. DOI: 10.1007/s00134-024-07665-4 PMID: 39432104