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GENE POLYMORPHISM ASSOCIATED WITH ACUTE RESPIRATORY DISTRESS SYNDROME (ARDS): A LITERATURE REVIEW

Ari Wahyuni [1] , Zen Hafy[2], Debby Handayati Harahap[3], Syazili Mustofa[4]
[1]Doctoral Program, Department of Biomedical Science, Medical Faculty, Sriwijaya University, Palembang, Indonesia
[1]Department of Anesthesiology and Intensive Care, Medical Faculty, Lampung University, Lampung, Indonesia
[2]Department of Biomedical Sciences, Department of Histology, Faculty of Medicine, Sriwijaya University, Palembang, Indonesia
[3]Department of Biomedical Sciences, Department of Pharmacology, Faculty of Medicine, Sriwijaya University, Palembang, Indonesia
[4]Department of Biochemistry, Molecular Biology and Physiology, Medical Faculty, Lampung University, Lampung, Indonesia
ariwahyuni1099@gmail.com

Abstract

Gene polymorphisms can influence susceptibility, severity, and prognosis of ARDS. Genetic studies in ARDS have evolved from studies focused on candidate genes to studies that rely on a hypothesis-free approach to identify novel loci associated with ARDS risk or severity. In this review we outline the role of gene polymorphisms in ARDS susceptibility, severity, and prognosis. Several academic search engines were used in the literature search, including EMBASE/Elsevier. Science Direct, PubMed Central, Google Scholar, and Cochrane Review. Two subtopics were searched using Boolean Operators with keywords (ARDS OR acute respiratory distress syndrome) and (polymorphism) AND (ARDS) OR (genetic polymorphism) AND (ARDS) OR (polymorphism in ARDS). The studies retrieved discussed the impact of gene polymorphisms associated with ARDS including genes encoding interleukin 6 (IL-6), interleukin 10 (IL-10), vascular endothelial growth factor A (VEGF), angiotensin converting enzyme (ACE), interleukin 1 receptor antagonist (IL1RN), Fms Related Receptor Tyrosine Kinase 1 (FLT1) and Inducible Factor-1α (HIF-lα). These genes support significant associations and are involved in the regulation of gene expression associated with ARDS risk. Polymorphisms of IL-6, IL-10, VEGF, ACE, IL1RN, FLT1, HIF-lα play a role in susceptibility, severity, and prognosis of ARDS.

Keywords : *ARDS, Genetic, Polymorphism, Sepsis*.

* Corresponding author :
Address : Department of Anesthesiology and Intensive Care, Medical Faculty, Lampung University, Lampung, Indonesia
Email : ariwahyuni1099@gmail.com
Phone : +6281913082967

INTRODUCTION

Acute respiratory distress syndrome (ARDS) is characterized by increased pulmonary vascular permeability and reduced lung tissue that occurs from various causes, including sepsis, pneumonia, trauma, and severe COVID-19 (Fan et al., 2018; Suarez-Pajes et al., 2023). ARDS is not a genetic disease, however, gene polymorphisms can affect the susceptibility, severity, and prognosis of ARDS (Liu & Li, 2014).

Genetic polymorphism is the occurrence of two or more discontinuous genotypes or alleles simultaneously in a population. These alleles do not cause disease, but under certain conditions can affect the susceptibility, clinical manifestations, and response of the carrier to treatment of a disease (Liu & Li, 2014).

Identifying ARDS predisposing genes has the potential to offer new perspectives on disease pathogenesis and identify additional risk factors; improve risk stratification models and patient care and determine individual disease patterns, leading to the development of new therapies and better individualized care (Hernández-Beeftink et al., 2019). Distinguishing ARDS subphenotypes is critical for personalized patient management promising predictive and prognostic enrichment for future clinical trials (Zheng et al., 2022).

This literature review will discuss the role of gene polymorphisms and some genes involved in ARDS susceptibility, severity and prognosis.

METHOD

In the literature search, several academic search sites were used, including EMBASE/Elsevier. Science Direct, PubMed Central, Google Scholar, and Cochrane Review. Two subtopics of the research question were searched on the five search sites using Boolean Operators. For references regarding the ARDS subtopic, they were searched using the keywords: (ARDS OR acute respiratory distress syndrome) while references regarding the gene polymorphism subtopic in ARDS were searched using the keywords: (polymorphism) AND (ARDS) OR (genetic polymorphism) AND (ARDS) OR (polymorphism in ARDS). After a number of references were obtained from the search results with the specified keywords, the references were then filtered first before being assessed for their relevance to the review to be compiled. The references were then collected and summarized.

RESULT AND DISCUSSION

Genetic studies in ARDS have evolved from studies focused on candidate genes to studies that rely on a hypothesis-free approach to identify novel loci associated with ARDS risk or severity (Hernández-Beeftink et al., 2019). This is due to several technical, statistical, and bioinformatic improvements over the past 15 years that have facilitated the use of commercial microarrays for efficient and inexpensive single-nucleotide polymorphism (SNP) genotyping and variant imputation to conduct genome-wide association studies/GWAS (Abdellaoui et al., 2023).

A total of 81 genes were differentially identified in ARDS in 68 independent studies (Acosta-Herrera et al., 2014). Most studies reported that genes encoding cytokines encoding IL-6), interleukin 10 (IL-10), vascular endothelial growth factor A (VEGFA; also known as VEGF), angiotensin-converting enzyme (ACE), mannose-binding lectin (protein C) 2, soluble (MBL2), interleukin 1 receptor antagonist (IL1RN) and NAMPT were significantly associated with ARDS. Variants in the Fms Related Receptor Tyrosine Kinase 1 (FLT1) gene are also involved in the regulation of gene expression associated with ARDS risk.4 In addition, polymorphisms in the Hypoxia Inducible Factor-1α (HIF-lα), HIF-2α and prolyl hydroxylase domain 2 (PHD2) genes were also found in ARDS patients (Dötsch et al., 2017; Guillen-Guio et al., 2020; Sipahioglu et al., 2024).

Interleukin-6 (IL6) Gene Polymorphism and ARDS

The IL-6 gene, located at 7p15.3, is responsible for regulating transcriptional activity during inflammatory reactions. The gene encoding IL-6, a cytokine involved in inflammation and B cell maturation, is an excellent candidate because cross-species comparisons of gene expression patterns in experimental models of ARDS have shown that IL6 is highly regulated. Furthermore, high circulating IL-6 concentrations in ARDS patients have been reported by some clinical studies (Zheng et al., 2022).

A possible association between the −174 G/C polymorphism (rs1800795) in the promoter region of the IL-6 gene and sepsis risk and mortality has been widely investigated. The IL-6 −174 C allele is believed to reduce the binding affinity of norepinephrine-inducible transcription factors to the IL-6 promoter region, leading to decreased IL-6 expression. This reduced expression is considered advantageous because it may attenuate excessive inflammatory responses, which are central to the pathogenesis and severity of inflammatory diseases (Gragossian & Siuba, 2022). The CC genotype is a favorable genotype in sepsis patients showing lower sepsis-related organ failure assessment (SOFA) scores, lower serum IL-6 levels and a lower risk of 30-day mortality (Ranieri et al., 2012).

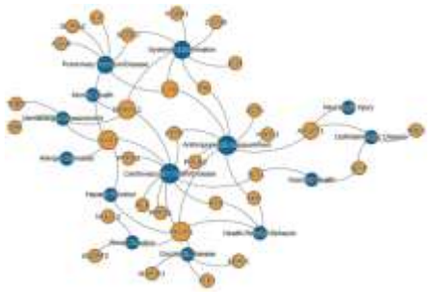

Figure 1. Association Between ARDS Candidate Genes and Phenotypes Reported by GWAS (Whitney et al., 2022).

Notes (circles) represent genes or phenotypes and associated genotype–phenotype pairs are connected by curved lines.The size of the node corresponds to the number of reported genotype–phenotype associations.

Interleukin-10 (IL10) Gene Polymorphisms and ARDS

Lower IL-10 levels were found in patients with ARDS compared to critically ill non-ARDS patients and high plasma IL-10 but low bronchoalveolar lavage IL-10 concentrations were correlated with increased mortality (Gong et al., 2006). Considering IL-10 gene polymorphisms, patient stratification based on IL-10 genotype, and the presence of sepsis, it was concluded that septic patients with the Å1082G/G genotype had a higher risk of developing sepsis compared to patients with the Å1082A/* genotype (Accardo Palumbo et al., 2012; Guillen-Guio et al., 2020; Meyer et al., 2013). The IL-10 −592C/A polymorphism was associated with sepsis susceptibility in Caucasian populations while the IL-10 −1082A/G polymorphism was associated with sepsis susceptibility in Asian populations (Pan et al., 2015).

A functional IL10 promoter gene variant that results in higher circulating IL10 levels appears to be associated with increased susceptibility to sepsis-associated ARDS. The GG genotype of the interleukin (IL)-10 promoter polymorphism at position -1082 (-1082GG) has been associated with increased IL-10 production and with the development of ARDS, but only when there was a significant interaction between the -1082GG genotype and age.[16] These results differ from previous research conducted by Gong et al, who reported that among patients with ARDS, the -1082GG genotype was associated with decreased disease severity on admission, lower daily organ dysfunction scores, and lower 60-day mortality (Gong et al., 2006).

Angiotensin-converting enzyme (ACE) Gene Polymorphism and ARDS

The human ACE gene, located on chromosome 17q23, has an RFLP, consisting of an insertion/deletion of a 287 bp *Alu* repeat in the 16th intron of the ACE gene (Liu & Li, 2014). Comparison of the ACE genotypes of ARDS patients, patients with respiratory failure without ARDS, patients undergoing coronary artery bypass surgery and healthy individuals, showed that the frequency of the DD (deletion/deletion) genotype in ARDS patients was significantly higher than in the other three groups and that the mortality rate of ARDS patients with the DD genotype was much higher (Marshall et al., 2002).

The ACE I/D (insertion/deletion) polymorphism was significantly associated with an increased risk of ARDS. Based on race, Caucasians with the ACE I/D polymorphism showed an increased risk of ARDS. However, Asians with this polymorphism did not show a significantly increased risk of ARDS. Based on age group, adults showed an increased risk of ARDS, while pediatric patients did not experience an increased risk of ARDS (Deng et al., 2015).

Studies in mouse and human models have shown that I/D polymorphisms in the angiotensin-converting enzyme (ACE) gene located on chromosome 17q23 play a significant role in ARDS. DD homozygous carriers were found to have the highest serum ACE activity compared to II homozygous and ID heterozygous carriers, who showed low and intermediate ACE activity, respectively. Because the ACE I/D polymorphism accounts for 20% of the variance in ACE levels and 50% of the variance in ACE activity, the impact of this single polymorphism on endpoints such as sepsis and ARDS is substantial. In adults, the DD genotype was found to be associated with significantly higher mortality and worse severity of ARDS and sepsis (Pabalan et al., 2021). In children, the I/D variant failed to show an association with paediatric acute respiratory distress syndrome (PARDS) status but increased frequency of the D allele was associated with PARDS severity (Cruces et al., 2012).

Vascular Endothelial Growth Factor A (VEGFA/VEGF) Gene Polymorphisms and ARDS

VEGF facilitates vascular endothelial cell proliferation, formation of vascular support structures, increased vascular permeability, and inhibition of apoptosis in tumor cells (Yabo et al., 2025). Alterations in these VEGF functions are believed to have substantial effects on the trajectory and prognosis of lung injury, particularly in response to endogenous or exogenous stimuli that increase or decrease VEGF levels. Consequently, VEGF is widely recognized for its important role in the pathophysiology of ARDS (Zhai et al., 2007). In the human lung, low VEGF levels are associated with ARDS severity while increased VEGF levels are associated with recovery from ARDS, suggesting a role for VEGF in the repair process of lung injury (Medford et al., 2009; Zhai et al., 2007).

Genetic polymorphisms in the vascular endothelial growth factor (VEGF) gene are important contributors to susceptibility to ARDS. The most widely studied polymorphisms include +936C/T (rs3025039), −460C/T (rs833061), and +405C/G (rs2010963). The +936C/T polymorphism, particularly the T allele, is associated with reduced plasma VEGF levels, whereas the −460C/T and +405C/G polymorphisms have been shown to significantly increase VEGF production (Yabo et al., 2025).

In postoperative cardiac surgery patients who develop ARDS, the prevalence of these VEGF gene polymorphisms is higher compared with the general population. Genotype analysis further demonstrates that the CT and TT genotypes of the +936C/T polymorphism occur more frequently in ARDS patients than in healthy individuals and are associated with higher APACHE III scores and increased mortality.[25] Additionally, ARDS patients carrying VEGF polymorphisms exhibit lower VEGF levels in bronchoalveolar lavage fluid, which correlates with greater severity of lung injury (Zhai et al., 2007).

Figure 2. The role of VEGF in ARDS (Yabo et al., 2025).

Fms Related Receptor Tyrosine Kinase 1 (FLT1) Gene Polymorphisms and ARDS

Vascular endothelial growth factor receptor 1 (VEGFR1) is a protein encoded by the FLT1 gene in humans. FLT1 is a member of the VEGF receptor gene family. It encodes a receptor tyrosine kinase that is activated by VEGF-A, VEGF-B, and placental growth factor (Medford, 2007; Shibuya, 2006). Soluble variants of FLT-1, or sFLT-1, are prominent in normal physiology and may exacerbate or alleviate certain pathologies. Many studies have used sFLT-1 levels, either alone or in combination with VEGF or PIGF, as a prognostic or diagnostic marker of disease (Wazan et al., 2024). sFLT-1 levels increase with a variety of factors including severity of injury, shock, tissue damage, and inflammation in trauma and sepsis patients. The lack of angiogenic stimulation due to anti-VEGF sFLT-1 inhibition results in reduced blood flow to major organs to reduce blood loss and inflammation (Ostrowski et al., 2012).

Single nucleotide polymorphisms (SNPs) in VEGFR1/FLT1 and downstream mediators of the VEGF signaling pathway (e.g. RAF1 and NRAS) have been consistently associated with the risk of pulmonary complications, one of which is ARDS (Barratt et al., 2014; Guillen-Guio et al., 2020). FLT1 as a novel ARDS susceptibility gene and shows functional evidence of the FLT1 gene being mechanistically involved in ARDS, through its important role in the endothelium, with the pathophysiology of ARDS. Vascular endothelial activation occurs as a result of systemic inflammation, especially inflammation that occurs in response to infection. FLT1 encodes an Fms-like tyrosine kinase that competitively inhibits VEGF. A SNP in FLT1 (rs9513106) is associated with decreased susceptibility to ARDS in people with sepsis (Whitney et al., 2022). A novel significant genomic association with sepsis-related ARDS susceptibility (rs9508032) is located in the Fms-related tyrosine kinase 1 (FLT1) gene. The region containing the sentinel variant and its best proxy acts as a silencer for the FLT1 promoter, and alleles with protective effects on ARDS further reduce promoter activity (p=0.0047) (Guillen-Guio et al., 2020).

Hypoxia Inducible Factor-1α (HIF-lα) Gene Polymorphisms and ARDS

HIF-controlled genes cause a wide range of biological outcomes. Responses at the cellular level include differentiation, migration, cytoprotection, apoptosis, and changes in organelle function such as mitochondria (Palazon et al., 2014). Responses at the organ or organism level include changes in the inflammatory system, immune regulatory system, and energy metabolism.34 Overexpression of secreted phosphoprotein 1 (SPP1) in blood CD4+ T cells isolated from ARDS patients decreases the expression of von Hippel–Lindau (VHL), a major driver of HIF-1α ubiquitylation, resulting in increased HIF-1α protein expression and thus worsening ARDS (Chen et al., 2023). There is a progressive increase in serum HIF-1α levels, according to the severity of ARDS in COVID-19 patients (Addai Ali & Naser, 2023). HIF-1α polymorphisms in pediatric ARDS patients showed that the presence of SNP rs11549467 (G1790A) is closely associated with the extent of lung infiltration in ARDS patients (Yilmaz et al., 2019).

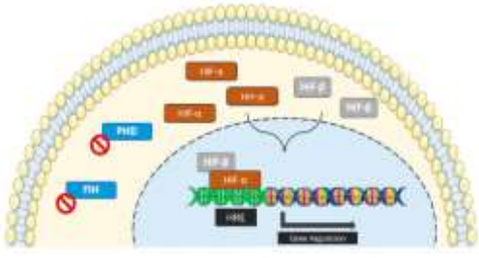

Figure 3. HIF Regulatory Pathway in Hypoxia/Inflammation (Lotsios et al., 2025).

FIH, factor inhibiting HIF; HIF, hypoxia-inducible factor; HREs, hypoxia response elements; PHD, prolyl hydroxylase domain-containing proteins; ROS, reactive oxygen species

Effects of Nucleotide Polymorphisms single rs 11549465 seen in the HIF-1α gene in ARDS clinic showed that patients with polymorphic forms (CT/TT) had better survival compared to the "wild" type (CC). The HIF-lα polymorphism rate was 26.4% for the heterozygous CT genotype and 2.36% for the homozygous TT genotype and was associated with mortality in ARDS patients. The 30-day mortality rate was lower in the homozygous TT and heterozygous CT genotypes compared to the "wild" type CC genotype. In addition, mechanical ventilator support and the use of vasopressor drugs were also less in ARDS patients with variants containing the T allel (Sipahioglu et al., 2024).

Interleukin 1 Receptor Antagonist Gene Polymorphism (IL1RN) and ARDS

IL1RN belongs to the interleukin 1 (IL1) family. Its gene variants are involved in several degenerative conditions due to either overexpression or decreased expression of IL-1β. IL-1RN is well known for its potent immune modulatory properties (Dinarello, 2018). The inflammatory cascade during ARDS is driven by a complex cytokine network, and some of the earliest genetic studies to identify individual risk factors for ARDS have implicated pro-inflammatory and anti-inflammatory mediators, one of which is IL1RN (Zheng et al., 2022). Variants in IL1RN, which encodes a protein that inhibits IL-1 activity, have been associated with decreased susceptibility to ARDS and IL1RN levels are higher in plasma among patients with severe trauma or septic shock (Hernández-Beeftink et al., 2019).

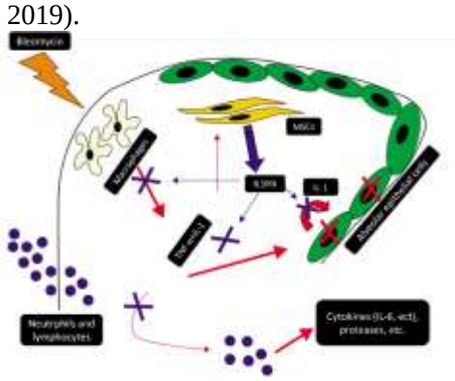

Figure 4. IL1RN Expression by MSCs in Ameliorating the Inflammatory Response (Phinney, 2009).
Red arrows: Bleomycin-induced lung injury induces macrophages residing in the lung
tissue to secrete IL-1α and TNF-α, thereby inducing a pro-inflammatory response.
Red crosses: Cytokines produced by activated macrophages recruit other immune cells into the lung tissue, which also secrete inflammatory cytokines and proteases that alter the lung cytoarchitecture and induce apoptosis or resident epithelial cells.
Blue arrows: Bleomycin-induced pro-inflammatory responses are counterbalanced by the anti-inflammatory effects of IL1RN produced by transplanted MSCs.

In a large-scale genetic study, genetic variants in the IL1RA gene (IL1RN) have been associated with decreased risk of ARDS in several critically ill populations, as well as increased plasma IL1RA in sepsis and trauma. These findings suggest that coding variants in IL1RN provide protection from ARDS by increasing plasma IL1RA (Reilly et al., 2019),(Meyer et al., 2018). Synonymous coding SNPs in the IL1RN gene encode an interleukin-1 receptor antagonist (IL1RA) that have been associated with reduced risk of ARDS in trauma and sepsis populations, associated with reduced sepsis mortality in the VASST septic shock trial (Rogers & Meyer, 2020). The SNP rs315952C of IL1RN may increase plasma IL1RA levels and reduce the risk of ARDS (Pan et al., 2015). More efficient generation of plasma IL1RN may be protective in sepsis (Balzanelli et al., 2022). In contrast, another study reported that individuals carrying the CT genotype (59 percent in ARDS patients compared with 53 percent in controls) and the TT genotype (39 percent compared with 33 percent) of he IL1RN C/T polymorphism showed reduced IL1RN gene expression and a higher susceptibility to ARDS, with the T allele acting as the major contributor to risk (95 percent CI, $p < 0.05$) (Balzanelli et al., 2022).

Table 1 Gene Polymorphisms Associated with Susceptibility to ARDS

Gene	Polymorphism / SNP Position	rs Number (Reference SNP ID)	Association with ARDS / Functional Effect
IL-6	−174 G/C (promoter region)	**rs1800795**	C allele reduces IL-6 transcription → may decrease hyperinflammation and reduce ARDS risk or severity.
IL-10	−1082 A/G	**rs1800896**	G allele linked to higher IL-10 levels; associated with ARDS in interaction with age or sepsis.
	−592 C/A	**rs1800872**	Associated with sepsis susceptibility; may influence ARDS development depending on ethnicity.
VEGFA (VEGF)	+936 C/T	**rs3025039**	T allele lowers plasma VEGF levels; CT/TT genotypes linked to higher ARDS mortality and severity.

Gene	Polymorphism / SNP Position	rs Number (Reference SNP ID)	Association with ARDS / Functional Effect
	−460 C/T	**rs833061**	T allele increases VEGF production; may enhance vascular permeability.
	+405 C/G	**rs2010963**	G allele associated with increased VEGF expression.
ACE	Insertion/Deletion (I/D) in intron 16	**rs4340**	D allele increases ACE activity; DD genotype associated with higher ARDS risk and mortality (adult).
FLT1 (VEGFR1)	Intronic SNP	**rs9513106**	Associated with decreased susceptibility to sepsis-related ARDS.
	Intronic SNP	**rs9508032**	Protective allele reduces FLT1 promoter activity → lowers ARDS risk.
HIF-1α	C1772T (Pro582Ser)	**rs11549465**	T allele increases HIF-1α stability; CT/TT genotypes associated with better survival in ARDS.
	G1790A (Ala588Thr)	**rs11549467**	Associated with lung infiltration severity in pediatric ARDS.
IL1RN (IL-1 receptor antagonist)	Synonymous SNP	**rs315952**	C allele increases IL-1RA levels and decreases ARDS susceptibility.
	IL1RN C/T variant	(rs sometimes not reported)	T allele associated with higher ARDS susceptibility due to lower IL-1RA expression.

CONCLUTION

Several genes are involved in response to external stimuli, cell signal transduction, cell proliferation, immune response, and chemotaxis. Genes encoding interleukin 6 (IL-6), interleukin 10 (IL-10), vascular endothelial growth factor A (VEGF), angiotensin-converting enzyme (ACE), interleukin 1 receptor antagonist (IL1RN), Fms Related Receptor Tyrosine Kinase 1 (FLT1) and Inducible Factor-1α (HIF-lα) support significant association and are involved in the regulation of gene expression associated with ARDS risk.

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