The Opportunity of Surfactant Protein D as a Potential Biomarker for Detecting Acute Lung Injury

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Contents

Abstract

Acute lung injury is a medical problem that causes a high mortality rate if it is not detected early and followed by appropriate treatment. The detection of acute lung injury is generally by clinical, radiological, and arterial blood gas analysis. This is a little late because when clinical symptoms appear, the cure rate will decrease. We need an early diagnosis of acute lung injury so that, as clinicians, we can anticipate further organ damage. One idea to detect acute lung injury is by examining the serum surfactant protein D. Although it still has to be combined with clinical examination and other examinations, at least there is a simple

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technique to increase the sensitivity and specificity of the overall diagnostic method if done holistically before more extensive organ damage occurs.

Keywords

Biomarker · Diagnostic · Surfactant protein D · Acute lung injury · Acute respiratory distress syndrome · Alveolar type II pneumocyte · Clara cells · Collectin family · Collagen-containing C-type lectin · External lung injury

Abbreviations

ALI	Acute lung injury
Ang-2	Angiopoietin-2
ARDS	Acute respiratory distress syndrome
AT2	Alveolar type II pneumocyte
BAL	Bronchoalveolar lavage
BMI	Body mass index
CD4	Cluster of differentiation 4
CD91	Cluster of differentiation 91
CF	Cystic fibrosis
COPD	Chronic obstructive pulmonary disease
CRD	Carbohydrate recognition domain
ELISA	Enzyme-linked immunosorbent assay
IPF	Interstitial pulmonary fibrosis
KGF	Keratinocyte growth factor
KL-6	Krebs von den Lungen 6
LPS	Lipopolysaccharides
MAPK	Mitogen-activated protein kinase
MBL	Mannose-binding lectin
NF-κB	Nuclear factor kappa light chain enhancer of activated B cells
PAMPs	Pathogen-associated molecular pattern molecules
PARS	Pediatric acute respiratory distress syndrome
PTB	Pulmonary tuberculosis
RAGE	Receptor for advanced glycation end products
SARS	Severe acute respiratory syndrome
SNPs	Single-nucleotide polymorphisms
SP-A	Surfactant protein A
SP-B	Surfactant protein B
SP-C	Surfactant protein C
SP-D	Surfactant protein D
sRAGE	Soluble receptor for advanced glycation end products
Th1	T helper 1 cells
VEGF	Vascular endothelial growth factor
VWF	von Willebrand factor

Definitions of Words and Terms

Acute Lung Injury	A diffuse heterogeneous lung injury characterized by widespread capillary leakage, low lung compliance, non-cardiogenic pulmonary edema, and hypoxemia and a milder form of ARDS
Acute Respiratory Distress Syndrome	A severe lung injury that allows fluid to leak into the lungs which is characterized by impaired carbon dioxide excretion, increased permeability pulmonary edema, and severe arterial hypoxemia
Chronic Hypoxemic Respiratory Failure	An ongoing condition of not enough oxygen in the bloodstream, but the levels of carbon dioxide are close to normal
Pulmonary Infiltrates	A substance denser than air that lingers within the lung parenchyma
SP-D, Surfactant Protein D	A collagen-containing C-type lectin which is produced by alveolar type II and Clara cells and known to play a role in surfactant homeostasis and pulmonary immunity

Key Facts

Key Facts for Acute Lung Injury

- Considered as a condition of acute inflammation which causes the endothelial and epithelial barriers in the lungs to be disrupted.
- Biomarkers present on the epithelium and endothelium, as well as those that are involved in the inflammatory and coagulation cascades, are used to predict morbidity and mortality in ALI patients.

Key Facts for Surfactant Protein D

- SP-D is mainly produced by alveolar type II and Clara cells.
- The presence of SP-D in the plasma of ALI/ARDS patients is thought to indicate permeability and damage to the alveolar epithelial barrier.
- The detection of lung damage can be aided by measuring serum SP-D levels.

Introduction

ARDS cannot be diagnosed by a single laboratory examination. The risk of establishing a false-positive ARDS diagnosis is high since no specific biomarkers for ARDS have been reported. This is due to the ease with which ARDS can be identified in patients with transient or chronic hypoxemic respiratory failure due to an underlying disease and bilateral pulmonary infiltrate. One of the most significant challenges in diagnosing and effectively treating ARDS is the lack of specific biomarkers. Biomarkers are being developed to better understand the risk and severity of ARDS in patients. The perfect biomarker will be able to distinguish patients who are at risk of developing ARDS as their lung injury progresses. The use of biomarkers to predict or track the progression of ARDS is hoped to make it easier for clinicians to collect data from the therapy that has been administered. This has aided clinical practice as well as the advancement of innovative testing technologies and medications that can improve outcomes (Isabel García-Laorden et al. 2017).

Surfactant protein D (SP-D) is synthesized by type II pneumocytes and belongs to the collectin family, and its primary function is to recognize pathogen-associated molecular patterns allowing microbial elimination. SP-D participates in the neutralization and clearance of influenza viruses, given its molecular affinity to viral hemagglutinin. SP-D levels correlate with pro-inflammatory immune responses, mainly when alveolar macrophages interact with the trimeric form through their CD91 receptor, leading to the activation of the p38 MAPK signaling pathway that elicits Th1 responses. Various lung disorders influence SP-D production, and its role as a biomarker of lung inflammation has been described (Table 1). Based on the central role of SP-D in the pulmonary host defense and the regulation of inflammatory responses and its dysregulation in lung diseases, we hypothesize that circulating levels of SP-D are modified as a result of lung tissue damage in critically ill A/H1N1-infected patients and that SP-D is a valuable biomarker to predict poor outcomes in ARDS patients with A/H1N1 infection. According to recent studies, the analysis of circulating levels of SP-D is helpful as a diagnostic tool in severe sepsis patients with ARDS and to evaluate the progression of lung injury in critically ill patients with mechanical ventilation in whom circulating levels of this protein positively correlate with the lung injury score as a parameter to measure the pathophysiological features of ARDS (Delgado et al. 2015).

Biomarker Combination

Several studies on markers of epithelial and endothelial injury, coagulation, and inflammation have shown that combining multiple biomarkers can predict mortality better than clinical or single biomarkers alone. The use of combined biomarkers is superior to clinical risk factors alone in predicting mortality in ARDS and is helpful for ARDS diagnosis. In severe sepsis, a combination of biomarkers such as RAGE, SP-D, and Club cell protein 16 is more sensitive in diagnosing ARDS (Spadaro et al. 2019; Ware et al. 2013).

Table 1 Serum SP-D levels as a biomarker in acute lung injury/acute respiratory distress syndrome

References	Main points
Eisner et al. (2003)	ALI/ARDS is a disorder in which the lung reacts severely to various forms of injuries to the lungs ranging from trauma to drug abuse. SP-D level in alive subjects was 73 ng/ml which is ~40% increase to the control serum level. However, increased SP-D levels (101 ng/ml) in postmortem subjects demonstrate the relationship between the substantial increase in lung SP-D and a greater risk of death. A higher level of plasma SP-D early in the course of ALI/ARDS is linked to a worse clinical outcome
Punsawad et al. (2019)	The mean levels of SP-D in the plasma were significantly elevated in the malaria-infected mice with ALI/ARDS (24.79 ± 0.23 ng/mL) compared with those in the malaria-infected mice in the non-ALI/ARDS group (6.24 ± 0.69 ng/mL) and the mice in the control group (5.86 ± 0.64 ng/mL) ($p = 0.009$). An increased level of plasma SP-D was observed in the malaria-infected mice with ALI/ARDS compared with that in the malaria-infected mice in the non-ALI/ARDS group and the mice in the control groups. This finding suggests that serum SP-D could be useful for evaluating and monitoring signs of ALI
Determann et al. (2010)	SP-D levels were not significantly different between ALI/ARDS patients and patients without lung injury. In ALI/ARDS patients, SP-D and KL-6 levels increased over time, which was attenuated by lung-protective mechanical ventilation using lower tidal volumes. Plasma levels of SP-D rise with potentially injurious ventilator settings and thus may serve as biological markers of VALI in patients with ALI/ARDS
Ware et al. (2010)	A combination of biomarkers and clinical predictors is superior to clinical predictors or biomarkers alone for predicting mortality in ALI/ARDS and may be useful for stratifying patients in clinical trials. Across all models tested, the two best performing biomarkers were IL-8 and SP-D, confirming the importance of these pathways in the pathogenesis of clinical ALI/ARDS
Park et al. (2017)	Patients with ARDS had higher SP-D levels (20.8 ng/ml) in plasma than those without ARDS (7.9 ng/ml). The results showed that plasma SP-D has acceptable discriminatory ability for the diagnosis of ARDS. This findings seem to provide sufficient support for further consideration of SP-D as a promising biomarker for diagnosis of ARDS

A biomarker can take many forms, from physiologic parameters (e.g., blood pressure) to radiographic findings (e.g., carotid intima-media thickness), cell-based markers (e.g., CD4 levels), and molecules (e.g., low-density lipoproteins). In recent years, genetic profiles, single-nucleotide polymorphisms (SNPs), and protein expression patterns have increasingly been viewed as potentially valuable biomarkers (Walter et al. 2014).

What Is Surfactant Protein D?

SP-D is a collagen-containing C-type lectin that belongs to the collectin family and is known to play a role in surfactant homeostasis and pulmonary immunity. Alveolar type II and Clara cells are the main producers of SP-D, which is secreted into the lungs' airspace. A cysteine-rich N-terminus, a triple-helical collagen region

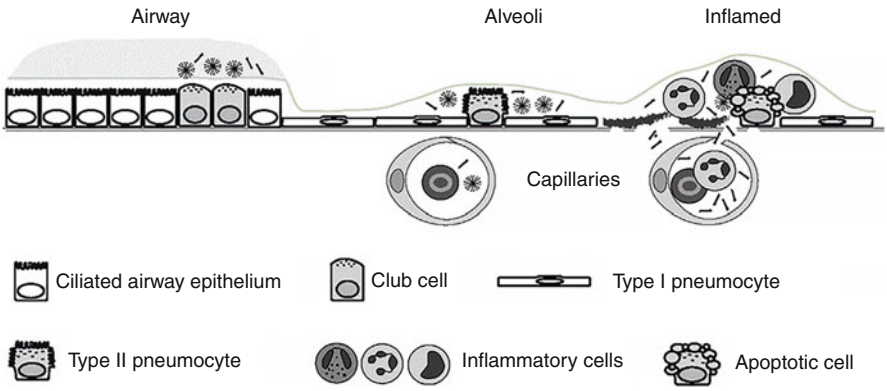

Fig. 1 Circulatory spillover of pulmonary surfactant protein D (SP-D) in inflammatory disease. SP-D is synthesized by Club cells, type II alveolar cells, and endothelial cells, and the levels of SP-D multimers and trimers in the serum are highly genetically determined. In the inflamed lung, the production of trimeric SP-D is increased, due to various chemical modifications and proteolytic breakdown of the protein, and loss of air-blood barrier integrity allows spillover of pulmonary SP-D into the circulation. For simplicity, only alveolar damage is illustrated. Moreover, only fuzziball SP-D multimers are depicted (Sorensen 2018)

consisting of Gly-X-Y triplet repeats, an a-helical coiled neck region, and a C-terminal C-type lectin or carbohydrate recognition domain (CRD) form its primary structure. SP-D can interact with a variety of pathogens (Table 2), activating clearance mechanisms against viruses, bacteria, and fungi, as well as apoptotic cells, as an innate immune molecule (Hsieh et al. 2020).

SP-D belongs to the C-type lectin family, which has four structural domains: a cysteine-rich domain at the N-terminus, a collagenous domain at the center, a neck region, and a carbohydrate recognition domain (CRD) at the C-terminus (Seaton et al. 2010). SP-D is involved in innate host defense and inflammatory response control in a variety of infectious diseases. SP-D knockout (KO) mice have demonstrated an increased resistance to Gram-negative and Gram-positive bacteria, viruses, and fungi-induced lung infection. Endotoxemia caused increased inflammation and lung damage in SP-D KO mice (King and Kingma 2011). SP-D facilitates the uptake and clearance of pathogens by phagocytes and epithelial cells, the clearance of apoptotic cells, and the modulation of inflammatory processes through the NF-κB pathway by binding to pathogen-associated molecular patterns (PAMPs) (Waters et al. 2009; Du et al. 2018).

SP-D is a 43-kDa collectin superfamily member that is found in lung surfactant and has been shown to play an important role in the innate immune system as a pattern recognition molecule (Korfhagen et al. 1998; Crouch and Wright 2001). Surfactant protein D (SP-D) is known to bind to various bacterial, fungal, and viral surfaces and immune cells, playing an important role in host defense and regulation of immune responses and lung phospholipid levels (Korfhagen et al. 1998). SP-D also affects the role of lymphocytes and neutrophils by promoting chemotaxis of antigen-presenting cells. SP-D is a protein formed almost exclusively by type II cells

of the alveolar epithelial system. The presence of SP-D in the plasma of patients with ALI/ARDS is thought to reflect on damage to the alveolar epithelial barrier and increased permeability (Eisner et al. 2003; Fig. 1). The composition of pulmonary surfactant is 90% lipid and 10% protein. Surfactant-associated proteins include two collagenous carbohydrate-binding glycoproteins (SP-A and SP-D), as well as two tiny hydrophobic proteins (SP-B and SP-C).

The extreme acute respiratory syndrome (i.e., SARS virus infection) has also been shown to bind to SP-D. SARS is an enveloped virus that belongs to the *Coronaviridae* family of viruses that infect both humans and animals. In 2002 and 2004, there were two self-limiting SARS outbreaks that resulted in a highly infectious and potentially life-threatening form of pneumonia. The spike protein, also known as S-protein, is a trimerized virus fusion protein found in the SARS virus. SP-D was discovered to bind to recombinant trimeric proteins, with the binding being calcium dependent and inhibited by maltose, exhibiting the characteristics of a classic C-type lectin-carbohydrate relationship. Purified MBL did not interact with the S-protein, indicating that the interaction was unique to SP-D and highlighting that the collectins have different ligands (Watson et al. 2018).

A complex interaction of inflammation, injury to alveolar cells types I and II, injury to bronchiolar and endothelial cells, and activation of coagulation causes acute lung injury in the initial (or exudative) process of ALI/ARDS (Fig. 2) (Mokra and Kosutova 2015). The measurement of serum SP-D levels is a useful tool for detecting lung damage, and it can be used in both toxicological and pharmacological studies (Murata et al. 2016).

Respiratory Epithelium Markers

Respiratory epithelium markers include surfactant proteins (SP), Krebs von den Lungen 6 (KL-6) protein, vascular endothelial growth factor (VEGF), and soluble receptor for advanced glycation end products (sRAGE) (Spadaro et al. 2019).

(a) Surfactant proteins (SP) are generally increased in ARDS, and SP-B can cross the damaged alveolar-capillary membranes (Greene et al. 1999). SP-D blood levels have been shown to correlate with ARDS mortality (Ware et al. 2010; Spadaro et al. 2019).
(b) KL-6 levels have been associated with ARDS mortality (Sato et al. 2004). KL-6, lactate dehydrogenase, sRAGE, and von Willebrand factor were found to be correlated with a diagnosis of ARDS in a high-risk population in a meta-analysis of plasma biomarkers for ARDS that analyzed 54 studies in 2014 (Terpstra et al. 2014).
(c) The levels of vascular endothelial growth factor (VEGF) and keratinocyte growth factor (KGF) are linked to the seriousness of the disease and the patient's outcome (Koh et al. 2008).
(d) RAGE utility as a biomarker is still questionable. Higher RAGE levels have been linked to impaired alveolar fluid clearance in ARDS patients and thus

Table 2 Surfactant protein D interacts with various pathogens (Nayak et al. 2012)

Pathogen	Target	Implication	References
Virus			
SARS coronavirus	S-protein	nd	Leth-Larsen et al. (2007)
Human immunodeficiency virus	Glycoprotein 120 (gp120)	Neutralization	Meschi et al. (2005)
Respiratory syncytial virus	G protein	Neutralization	Hickling et al. (1999)
Rotavirus (bovine)	VP7 glycoprotein	Agglutination, neutralization	Reading et al. (2004)
Fungi			
Candida albicans	Mannose, maltose	Agglutination, growth inhibition, and inhibition of phagocytosis	Van Rozendaal et al. (2000)
Aspergillus fumigatus	Mannose, maltose, 45 and 55 kDa	Binds to conidia forms, agglutination, attachment to phagocytes, and enhanced uptake	Madan et al. (1997)
Blastomyces dermatitidis	1,3-β-Glucan	Binds to yeast form	Lekkala et al. (2006)
Saccharomyces cerevisiae	1,6-β-Glucan	Agglutination	Allen et al. (2001)
Gram-negative bacteria			
Escherichia coli	LPS	Agglutination, enhanced uptake, and growth inhibition[b]	Kuan et al. (1992), Wu et al. (2003), Hartshorn et al. (1998)
Enterobacter aerogenes	LPS	Inhibits growth[a]	Wu et al. (2003)
Legionella pneumophila	LPS	Inhibits growth	Sawada et al. (2010)
Gram-positive bacteria			
Bacillus subtilis	Lipoteichoic acid	nd	Van de Wetering et al. (2001)
Staphylococcus aureus	Peptidoglycan	Enhanced uptake	Hartshorn et al. (1998), Van de Wetering et al. (2001)
Mycobacterium tuberculosis	Lipoarabinomannan	Reduces uptake by macrophages	Ferguson et al. (1999)
Streptococcus pneumoniae	nd	Agglutination[b] and enhanced uptake[b]	Hartshorn et al. (1998), Jounblat et al. (2004)

(continued)

Table 2 (continued)

Pathogen	Target	Implication	References
Protozoa			
Schistosoma mansoni	nd	nd	Van De Wetering et al. (2004)

nd not determined
[a]Strain dependent
[b]rough/smooth LPS – Strain dependent

represent the seriousness of the pulmonary epithelial injury, according to several reports. Soluble RAGE (sRAGE) helped diagnose ARDS in a high-risk population in a meta-analysis review, but it was not linked to mortality (Isabel García-Laorden et al. 2017).

(e) Angiopoietin-2 (Ang-2) and endothelial dysfunction markers are examples of endothelial markers. Ang-2 levels that are elevated in ARDS patients and at-risk patients are predictors of mortality. Furthermore, the von Willebrand factor (VWF) tends to be linked to mortality in ARDS patients (Spadaro et al. 2019).

The Advantage and Disadvantage of Using Circulating SP-D

SP-D levels in the blood have been studied to see whether they could be used as a biomarker for dermatitis, acute lung injury (ALI)/acute respiratory distress syndrome (ARDS), periodontitis, interstitial pulmonary fibrosis (IPF), chronic obstructive pulmonary disease (COPD) (Sin et al. 2007), emphysema, cystic fibrosis (CF), coronary disease, sclerosis, cancer, and sarcoidosis. There have also been research looking at SP-D levels in people with Turner syndrome and paraquat toxicity and swimming in always treated lakes, lung transplant patients, patients undergoing neurosurgical procedures, drowning victims, and people with polymyositis/dermatomyositis, dementia, lupus, and sleep apnea (Bratcher and Gaggar 2014).

The following are some of the advantages of the circulating SP-D test for detecting acute lung injury:

1. Collection of specimens is quick and easy.
2. The enzyme-linked immunosorbent assay (ELISA) method makes inspection relatively simple.
3. The effects of circulating SP-D levels, which serve as a warning that "something" is wrong with the body's organs, especially the lungs (Kuroki et al. 1998).

The following are some of the SP-D examination disadvantages for detecting acute lung injury:

1. Levels of SP-D have also been linked to genetic factors (Heidinger et al. 2005), body mass index (BMI) (Sorensen et al. 2006) (Zhao et al. 2007), age (Engström

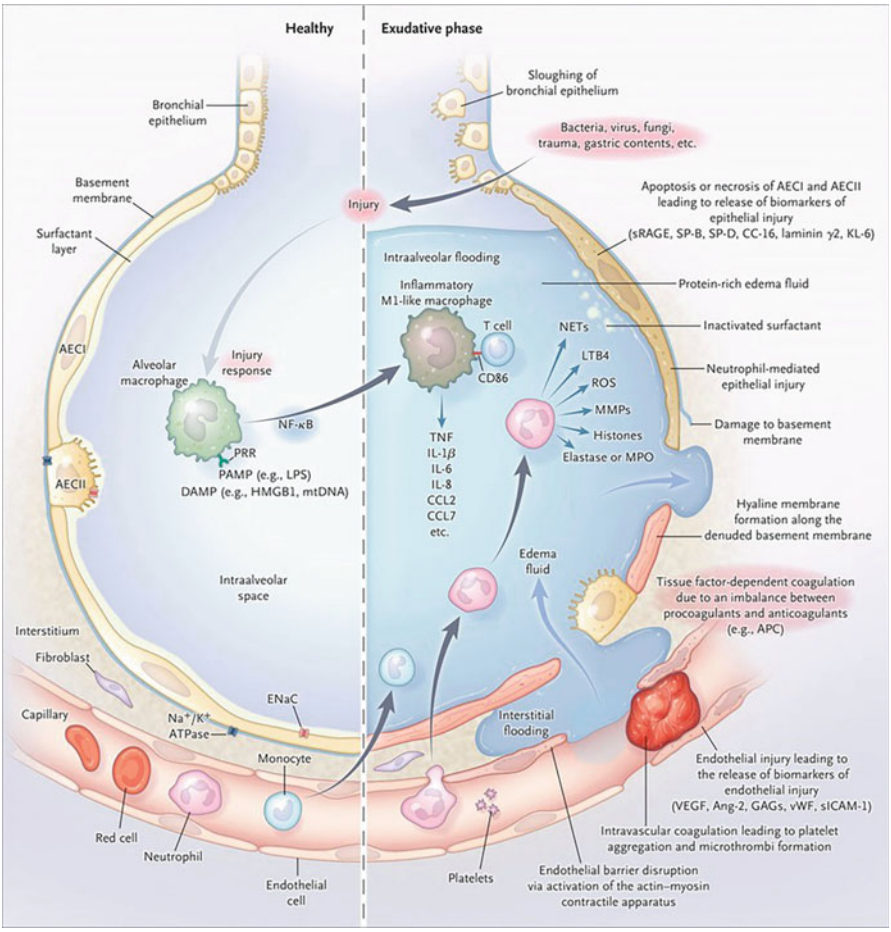

Fig. 2 The healthy lung is shown on the left, and the exudative phase of ARDS is shown on the right. Injury is initiated by either direct or indirect insults to the delicate alveolar structure of the distal lung and associated microvasculature. In the exudative phase, resident alveolar macrophages are activated, leading to the release of potent pro-inflammatory mediators and chemokines that promote the accumulation of neutrophils and monocytes. Activated neutrophils further contribute to injury by releasing toxic mediators. The resultant injury leads to loss of barrier function, as well as interstitial and intra-alveolar flooding. Tumor necrosis factor (TNF)-mediated expression of tissue factor promotes platelet aggregation and microthrombus formation, as well as intra-alveolar coagulation and hyaline membrane formation (Thompson et al. 2017)

et al. 2012), circadian rhythm (Bratcher and Gaggar 2014), and particle exposure and cigarette smoking habits (Mutti et al. 2006; Vinod et al. 2019).

2. If AT2 cells are damaged (e.g., as a result of the SARS COV-2 virus), an increase in circulating SP-D levels cannot be used as a marker for tissue damage. A decrease in circulating SP-D levels is most likely a sign of lung organ injury (Shtepa 2018).

3. While SP-D has been reported to be able to predict external lung injury, further research is needed to determine how responsive and specific it is for extra-pulmonary detection.

The Rationalization of Using Circulating SP-D as Biomarker Diagnostic for Acute Lung Injury Based on Literature Study

1. In children with acute respiratory failure, elevated circulating SP-D levels are linked to extreme pediatric acute respiratory distress syndrome (PARS) and poor outcomes (Dahmer et al. 2020).
2. Diagnosing and differentiating pulmonary pathology can be difficult. Lower concentrations of surfactant proteins A and D in bronchoalveolar fluid and higher concentrations in plasma have been linked to more severe lung damage and poor clinical outcomes in patients intubated for acute lung injury. Pulmonary pathology is sometimes challenging to diagnose and differentiate. Lower concentrations of surfactant proteins A and D in bronchoalveolar fluid and higher concentrations in plasma have been linked to more serious lung damage and poor clinical outcomes in patients intubated for acute lung injury (Czechowski et al. 2008).
3. Increased permeability of lung vessels in inflammatory conditions, such as ARDS, may result in an alveolar-to-vascular leakage of SP-D; the integrity of alveolar concentrations of surfactant proteins A and D in bronchoalveolar fluid and higher concentrations in plasma have been linked to more serious lung damage and poor clinical outcomes in patients intubated for acute lung injury. Epithelial secretory cells may be compromised in pulmonary inflammation, resulting in an efflux of SP-D from epithelial cells into the alveoli and alveolar vessels, and since SP-D is less tightly associated with surfactant lipids than the other surfactants, it may be effluxed. High levels of SP-D in the blood may be due to a slower clearance rate of SP-D from the bloodstream in inflammatory states; epithelial surfaces of many nonpulmonary organs secrete SP-D and are possible sources of SP-D in the blood (Heinrich et al. 2006).
4. The outward intravascular leakage of secreted lung proteins and inward edematous flooding in the interstitium and airspaces were caused by a loss of air-blood barrier integrity. Thus, in acute and chronic lung injury, a concentration gradient of SP-D causes SP-D to be synthesized in the respiratory tract and leak into the bloodstream (Sorensen 2018).
5. In patients infected with SARS-CoV, a related coronavirus that causes severe acute respiratory syndrome (SARS), studies have shown that SP-D levels increase with disease severity and IgG levels (Dahmer et al. 2020; Park et al. 2017; Kerget et al. 2020).
6. SP-A and SP-D have also been found in serum and could be used as biomarkers for lung disease, especially when alveolar epithelial integrity is compromised (Park et al. 2017).

7. Surfactant protein D (SP-D) and the receptor for advanced glycation end products (RAGE) are validated alveolar epithelial biomarkers for lung epithelial injury (Johnson and Matthay 2010).
8. Three of the top 5 biomarkers in the current study were lung epithelial injury biomarkers (Ware et al. 2013). SP-D is a natural component of surfactant that is almost entirely formed by alveolar epithelial type II cells. Compared to patients with hydrostatic pulmonary edema, patients with ARDS have higher levels of SP-D in their blood (Cheng et al. 2003).
9. SP-D levels in both BAL and serum rose in response to pro-inflammatory stimuli and during acute inflammation. During the 3 hours of LPS exposure, SP-D nearly instantly translocated from the lungs to the bloodstream. The immediate intravascular leakage is most likely caused by increased endothelial permeability, in which the disruption of SP-D multimeric structure may exacerbate into relatively low-molecular-weight single subunits. Extrapulmonary synthesis of SP-D is unlikely to be the source because it needs extrapulmonary synthesis to react to inflammatory stimuli faster than pulmonary cells, which are known to be the primary source of SP-D synthesis and are located at the site of inflammation (Gaunsbaek et al. 2013).
10. In patients with acute respiratory distress syndrome (ARDS), idiopathic interstitial lung diseases, and alveolar proteinosis, serum levels of SP-A and SP-D are elevated (Honda et al. 1995). In diffuse lung disease, serum levels of both proteins may be used as biomarkers. SP-D tends to be more sensitive and precise than other tests (Fujita et al. 2005). When rats are given acid or bleomycin, their serum SP-D levels increase (Pan et al. 2002). A lack of SP-A harms the host protection against viruses and certain bacteria, but the surfactant system is unaffected. Chronic inflammation, macrophage activation, and alveolar damage are all symptoms of a lack of SP-D. SP-D deficiency is also linked to a decreased ability to clear viruses and bacteria, as well as apoptotic cells (LeVine et al. 2001).
11. Surfactant proteins A, B, and D, as well as interleukin-8, all showed substantial increases in plasma during acute lung injury. Changes in the phosphatidylcholine profile, surfactant proteins, and inflammatory markers of bronchoalveolar lavage fluid and plasma in children with acute lung injury are consistent with alveolar/blood leakage and inflammatory cell membrane degradation. Damage to the alveolar-capillary membrane and cellular infiltration are the causes of these changes (Todd et al. 2010).
12. SP-D is a potential biomarker useful to distinguish severe pandemic influenza A (H1N1) from COVID-19 and other chronic infectious or inflammatory lung conditions such as PTB and COPD. The serum SP-D levels of COVID-19, PTB, and COPD patients were reported as significantly lower than severe pandemic influenza patients. Despite the severity of COVID-19, it was also indicated that the alveolar-capillary membrane of lungs infected with SARS-CoV-2 maintains its selective permeability for SP-D and other proteins (Choreño-Parra et al. 2021).

13. Serum SP-A and SP-D level might be useful as biomarkers of COVID-19 pneumonia severity as it was reported that lung-specific serum SP-A and SP-D levels, which can be detected from relatively early pneumonia, increased with the aggravation of symptoms and disease severity indicated by radiological findings (Saito et al. 2020).
14. SP-D might play a key role in the lung's defense against Gram-negative bacteria. Rat and human BAL caused Ca++ – dependent agglutination of *E. coli* which was dose dependent and inhibited by competing saccharides or anti-SP-D. SP-D was efficiently and selectively adsorbed from rat BAL by incubating it with *E. coli*, and it was revealed that SP-D is the primary *E. coli*-binding protein secreted by freshly isolated cells in culture after incubation of *E. coli* with radiolabeled rat type II cell medium (Kuan et al. 1992).

Summary

- Surfactant protein D has a chance as a marker in cases of acute lung injury even though it cannot stand alone.
- Circulating surfactant protein D levels can strengthen clinical symptoms that appear to play a role in acute respiratory distress syndrome therapy management.
- Surfactant protein D as a biomarker of acute lung injury makes it easier for clinicians to establish the presence of lung epithelial damage.
- The results of circulating surfactant protein D level's measurement may be used as a further rationale for surfactant therapy.
- It is necessary to further investigate the cells that produce SP-D other than AT2, since if AT2 is damaged, the circulating SP-D levels can describe ALI.

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