

Trauma Related ARDS Biomarkers: Rapid Review

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ABSTRACT

Introduction: The major reasons behind death after severe traumas are multiple organ dysfunction syndrome (MODS) and systemic inflammatory response syndrome (SIRS). Acute respiratory distress syndrome (ARDS) is one complication of MODS. Biomarkers are important in the prediction of ARDS, including early detection, risk of adverse outcomes and prognosis.

Objective: The aim of this review is to collect ARDS biomarkers among traumatic patients.

Methodology: A web based search was used and online data bases from PUBMED and MEDLINE were searched. Studies from 1999 to 2018 were included. A total of 50 studies fulfilled the review parameters and were included.

Results: When trauma occurs, the level of biomarkers rises within first 24 to 48 hours before it returns to normal. For the diagnosis of ARDS in traumatic patients, multiple biomarkers are used. Examples are von Willebrand factor (vWF), angiotensin-2 (Ang- 2), Krebs von den Lungen-6 (KL-6), soluble receptor for advanced glycation end products (RAGE), tumor necrosis factor-alpha (TNF- α), interleukin-1 beta (IL-1 β), interleukin-4 (IL-4), interleukin-6 (IL-6), interleukin-8 (IL-8), Procollagen III peptide (PCPIII) and macrophage migration

inhibitory factor (MMIF). Presence of IL-1 β , IL-4, KL-6 and angiotensin-2 increases the probability of mortality.

Conclusion: Initial increase in the level of biomarkers is predictive of the disease severity as they are the early diagnostic biomarkers for ARDS. Therefore, early measurement of these biochemical markers could be incorporated into trauma management protocols along with Injury Severity Score and Revised Trauma Score.

Keywords: Acute Respiratory Distress Syndrome, Trauma Complication, ARDS Biomarkers.

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INTRODUCTION

Trauma remains the main cause of death in all age groups, leaving behind the summation of the years of life lost as a result of cancers, heart attacks and strokes altogether.¹ The major reasons behind death in severe traumas are multiple organ dysfunction syndrome (MODS) and systemic inflammatory response syndrome (SIRS).^{2,3}

In the last few decades, multiple studies have been done to understand the underlying pathophysiology after trauma and its subsequent complications. Soon after trauma, an immunological hyperactivity takes place followed by a decompensation phase with immunological anergy. These immunological reactions and the severe inflammatory response that takes place in multiple organs lead to infections and eventually the development of MODS.³

Multiple studies reveal association between inflammatory cytokines and Injury Severity Score (ISS), Glasgow Coma Score (GCS), Revised Trauma Score (RTS) as well as the Acute Physiology and Chronic Health Evaluation II (APACHE-II).⁴

Acute respiratory distress syndrome (ARDS) is one of the major

complications of MODS among traumatic patients^{5,6} with incidence of about 12% to 25%.^{7,8} Moreover, it is the most common cause of mortality after trauma with a mortality rate of about 41%.⁹ ARDS is characterized by tachypnea, hypoxemia, loss of compliance and damage of lung tissue.¹⁰ In fact, it is a lethal cause of hypoxemic respiratory failure.¹¹

According to diagnostic criteria of 1994, ARDS is confirmed when a chest radiograph shows bilateral infiltration or pulmonary-artery wedge pressure ≤ 18 mmHg or a ratio of pulmonary artery pressure to fraction of inspired oxygen (PaO₂:FiO₂) that is ≤ 200 .¹²⁻¹⁴

Multiple insults such as pancreatitis, aspiration, sepsis, abdominal trauma, pulmonary contusion, pelvic fractures, and multiple long bone fractures are risk factors for the development of ARDS. One of the studies mentioned that abdominal trauma in which the Abdominal Trauma Index is ≥ 15 has an incidence of about 18%. Incidence of ARDS with hyper-transfusion is about 21%, in pulmonary contusion is about 25%, and in multiple fractures is around 48%.¹⁵ These numbers indicate the multidimensional

complexity in identifying biomarkers to early predict the risk of either the development of ARDS or its adverse outcome and prognosis.¹⁶

Some reviews have been done before; however, few did specify trauma as the focus. Thus, the current review aims to collect biomarkers that are used for the diagnostic purpose among traumatic patients.

METHODOLOGY

A web based search was used and online data bases from PUBMED and MEDLINE were searched for ARDS. The key words used for the search were "trauma and ARDS", "biomarkers in trauma patients", "biomarkers of ARDS", "association of ARDS with inflammatory mediators", "gene association with ARDS". Studies from 1999 to 2018 were included. Out of 80 studies, 50 were included in the review which fulfilled the study parameters.

The current review included articles that show trauma related biomarkers leading to ARDS and were available in English.

Trauma Induced Biomarkers Associated with ARDS

Several inflammatory mediators and cytokines are involved in the process of acute lung injury and ARDS. Cytokines are produced either by the locally released inflammatory mediators, by lung epithelial cells or by fibroblasts. In ARDS, both endothelial as well as alveolar epithelial injuries occur. The alveolar epithelial injury leads to alveolar flooding which increases the susceptibility to bacterial pneumonia and eventually sepsis. Fibrosis on the other hand, occurs as a consequence of the impaired alveolar epithelial repair mechanisms and decreased surfactant production which results in an alveolar collapse.¹⁷⁻¹⁹ (Fig.1) Endothelial injury however results in an increased permeability, which is the reason behind subsequent pulmonary edema.¹⁹

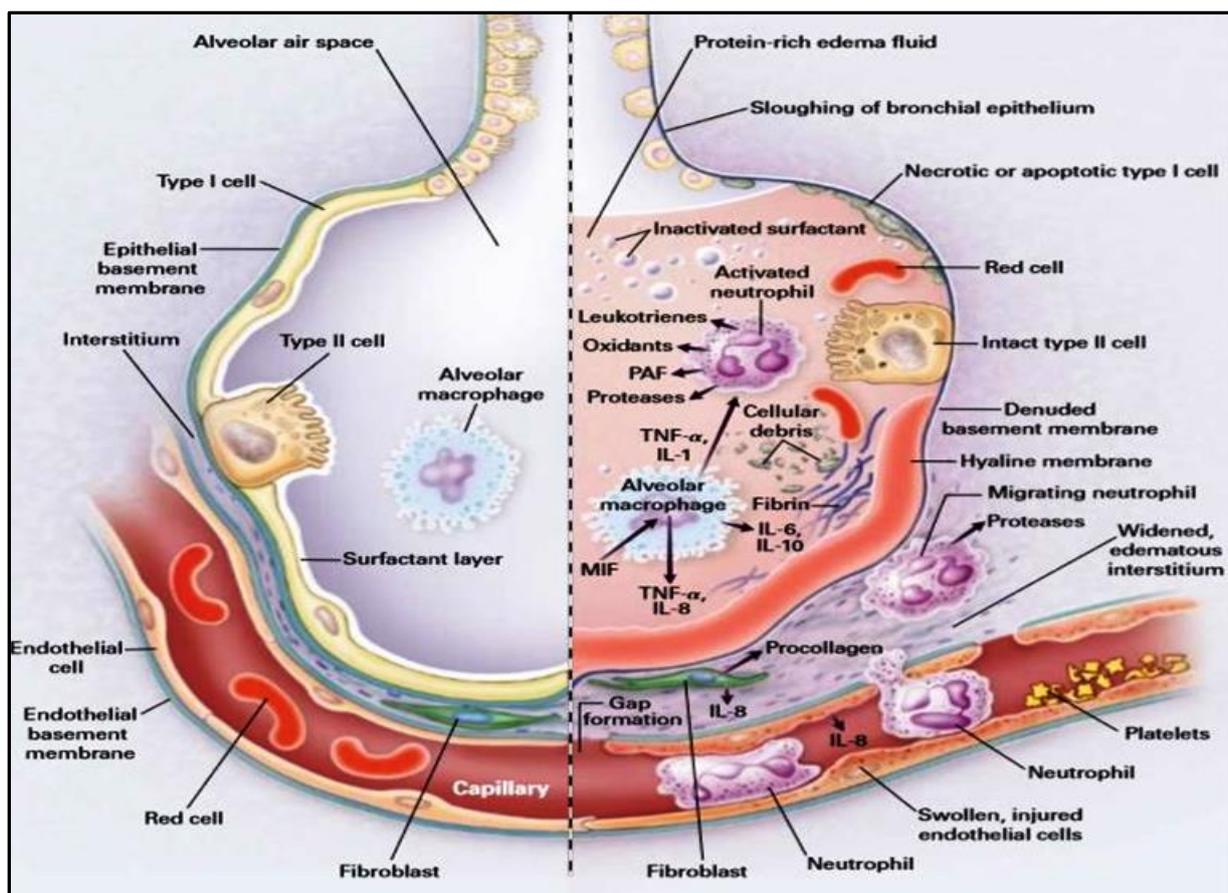


Fig 1: Comparison of normal alveolus (Left-Hand Side) with the injured alveolus of ARDS (Right-Hand Side)¹⁹

The presence of confounders or effect modifiers adds to the complexity of isolating biomarkers for ARDS in traumatic patients. Intrinsic characteristics among traumatic patients such as age or comorbidities like diabetes and hypertension as well as lifestyle characteristics such as smoking or alcoholism are examples. The severity or the pattern of injury or treatment modalities such as the use of protective ventilation all play role.^{20,21} Advanced age is one of the most important confounders in traumatic patients and is linked to a higher mortality. One study compared non-traumatic surgical patients with traumatic patients and shows a strong positive correlation of ARDS with age.¹⁵ The second most important confounder is the severity or pattern of injury. Studies reported that injuries by blunt trauma leading to pulmonary or

myocardial contusion or by penetrating trauma leading to bowel perforation and secondary abdominal infections have a strong positive correlation with risks of developing ARDS and mortality.^{15,22} Comorbidities such as diabetes and hypertension lead to vascular endothelial dysfunction. When combined with trauma, these factors lead to the early development of ARDS. Likewise, smoking and alcohol abuse cause pulmonary immune dysfunction as well as a vascular endothelial injury, which also occur in trauma. Thus, enhancing the potential towards ARDS development.²³ Initial treatment modalities like the use of protective ventilation, that is mechanical ventilation with high positive end-expiratory pressure (PEEP), in severe trauma have protective effects.²⁴

Whenever there is trauma, the level of biomarker rises within the first 24 to 48 hours before it returns to normal. This temporary surge in the level of biomarkers is alarming.²⁵ For the diagnosis of ARDS in traumatic patients, multiple biomarkers are used. Examples are von Willebrand factor (vWF), angiotensin-2 (Ang-2), Krebs von den Lungen-6 (KL-6), soluble receptor for advanced

glycation end products (RAGE), tumor necrosis factor-alpha (TNF- α), interleukin-1 beta (IL-1 β), interleukin-4 (IL-4), interleukin-6 (IL-6), interleukin-8 (IL-8), Procollagen III peptide (PCPIII) and macrophage migration inhibitory factor (MMIF). Presence of IL-1 β , IL-4, KL-6 and angiotensin-2 increases the probability of mortality.^{3,26,27} These biomarkers are summarized in Table 1.

Table 1: Biomarkers associated with ARDS after trauma

Pathology	Biomarkers	Risk of ARDS	MODS free-days	Mortality
Vascular endothelium	vWF	Increased ⁽²⁸⁾	Decreased ⁽²⁸⁾	Predictive ⁽²⁹⁾
	Ang-2	Increased ⁽³⁰⁾	Decreased ⁽³⁰⁾	Predictive ⁽³¹⁾
Alveolar epithelium	KL-6	Increased ^(32,33)	Decreased ^(32,33)	Predictive ⁽³³⁾
	RAGE	Increased ⁽³⁴⁾	Decreased ⁽³⁴⁾	Predictive ⁽³⁵⁾
Inflammatory mediators	TNF- α	Increased ⁽³⁾	Decreased ⁽³⁶⁾	Predictive ⁽³⁾
	IL-1 β	Increased ⁽³⁷⁾	Decreased ⁽³⁾	Predictive ⁽³⁸⁾
	IL-4	Decreased ⁽³⁹⁾	Increased ⁽³⁹⁾	Low-risk ⁽⁴⁰⁾
	IL-6	Increased ⁽³⁾	Decreased ⁽³⁾	Predictive ⁽³⁸⁾
	IL-8	Increased ^(41,42)	Decreased ^(41,42)	Predictive ⁽⁴³⁾
Others	PCPIII	Increased ⁽¹⁶⁾	Decreased ⁽¹⁶⁾	Predictive ⁽⁴⁴⁾
	MMIF	Increased ⁽⁴⁵⁾	Decreased ⁽⁴⁵⁾	Predictive ⁽⁴⁵⁾
Genomics	ANGPT2	Increased ⁽⁴⁶⁾	Decreased ⁽⁴⁶⁾	Predictive ⁽⁴⁶⁾
	IL1RN	Decreased ⁽⁴⁷⁾	Increased ⁽⁴⁷⁾	Low-risk ⁽⁴⁷⁾

a) Biomarkers from Vascular Endothelium

1. Von Willebrand Factor

Endothelial injury is one of the major causes of MODS while lung injury and ARDS are the primary manifestations in MODS. The von Willebrand factor (vWF) antigen is stored and secreted mainly by the endothelium and a small amount comes from platelets. After injury to the endothelium, it is released into the circulation.²⁸ Therefore, studies considered vWF as an indicator of endothelial injury in traumatic patients with high risk of developing ARDS.^{28,29} Nevertheless, one study reported no association between vWF and ARDS.⁴⁸ High level of vWF shows association with poor outcomes or with mortality after trauma. One study reported 83% increased risk of mortality if the level of vWF is equal or higher than 450%.²⁹ The limitation to this finding is that the vWF is not a good prognostic factor.²⁸

2. Angiotensin-2

Angiotensin is a mediator in signaling pathways, working along with vascular endothelial growth factor (VEGF). Angiotensin-1 (Ang-1) is an endothelial stabilizing factor during the process of inflammation. It maintains the endothelial integrity and prevents the endothelial permeability, tissue factor activation as well as adhesion of leukocytes.⁴⁹ In contrast, angiotensin-2 (Ang-2), which is also released by the endothelium during inflammation, is an antagonist to Ang-1. Ang-2 disrupts the endothelial integrity and enhances the vasculature inflammatory response to trauma.¹⁶ Some studies compared the ratio of Ang-2 to Ang-1 in ARDS and reported a strong correlation with ARDS development.³⁰ Also, with poor prognosis.³¹ According to Gajic et.al, Ang-2 is a good predicting biomarker for the development of ARDS, so it could be added into the Lung Injury Prediction Score.⁵⁰

b) Biomarkers from Alveolar Epithelium

1. Krebs von den Lungen-6

Krebs von den Lungen-6 (KL-6) is expressed mainly on type-2 alveolar epithelial cells. Increased levels of KL-6 indicate alveolar type-2 cell injury, so it is considered as an important biomarker for ARDS.⁵¹ Multiple studies reported a strong association of KL-6 with the development of ARDS and poor outcomes.^{32,33,52} The strength of this biomarker is that it is a good prognostic indicator.¹⁰

2. Receptor For Advanced Glycation End Products

The transmembrane receptor for advanced glycation end products (RAGE) is expressed on multiple cells including type-1 alveolar epithelial cells. It plays an important role in apoptosis, microtubular stabilization and proliferation of vascular smooth muscles. Considering ARDS, the pro-inflammatory ligands express the RAGE, which enhances the inflammatory process. It is not only expressed in alveolar epithelial injury but in the endothelial injury as well.⁵³ Studies report that the RAGE biomarker is less informative when the disease is not severe.³⁴ Another limitation of the RAGE as a biomarker is its specificity as it increases in other severe conditions as well.³⁵

c) Inflammatory Mediators

1. Tumor Necrosis Factor-Alpha

Tumor necrosis factor alpha (TNF- α) affects the endothelium by inducing clotting mechanisms, leukocytes adhesion and altering endothelial permeability. Endothelial activation is considered as the reason behind the involvement of multiple organs.³⁶ Endothelial injury as well as increased vascular permeability are a well-established factors for the development of pulmonary edema in ARDS.⁵⁴

Some studies reported increased mortality in traumatic patients with high level of TNF- α .³ It is well-documented that soon after trauma, the TNF- α level rises immediately likewise in patients at risk of developing ARDS. High levels of TNF- α have been reported in bronchoalveolar lavage fluids.²

2. Interleukin-1 beta (IL-1 β)

Laboratory findings of ARDS patients after trauma show increased levels of IL-1 β with adverse outcome.^{3,38} It is a highly sensitive and specific marker for the early stage of ARDS. Therefore, its utilization regarding ARDS prediction in traumatic patients is indispensable.³⁷

3. Interleukin-4

Low levels of the anti-inflammatory mediator Interleukin-4 (IL-4) predict the risk for ARDS.³⁹ In traumatic patients, low levels of IL-4 have been observed which show immediate reaction in response to injury.^{40,55}

4. Interleukin-6

Interleukin-6 (IL-6) is produced by macrophages and T-lymphocytes. It is a pro-inflammatory cytokine but also has some anti-inflammatory effects. In the event of excessive inflammation, IL-6 induces the secretion of anti-inflammatory cytokines including IL-4 to overcome the inflammatory reaction.³⁹ Nevertheless, few studies reported high mortality rates in traumatic patients with ARDS amongst whom high levels of IL-6 were detected.^{3,38}

5. Interleukin-8

Interleukin-8 (IL-8) is considered as one of the important chemotactic factors for neutrophils in blood or in bronchoalveolar lavage fluids in patients at risk of ARDS.^{42,43,56} Neutrophils isolated from trauma patients show high migration activities which are stimulated by IL-8.⁵⁶ Initially, IL-8 accumulates at the site of injury before it migrates to lung tissues and build up there. Thus, high level of IL-8 in bronchoalveolar lavage fluids is a predictor for the risk of developing ARDS.⁴¹

d) Others

1. Procollagen III Peptide

In patients with trauma, repair processes by fibrogenic pathways are stimulated. Damaged alveolar epithelium causes pulmonary edema. The accumulation of extracellular matrix protein in edematous fluids leads to fibrosing alveolitis.^{54,57} Procollagen III peptide (PCPIII) is a procollagen that shows significant association with ARDS. High concentration of PCPIII in edema fluids or in bronchoalveolar lavage fluids is an indicator of mortality.^{16,44}

2. Macrophage Migration Inhibitory Factor

Literature reported the presence of macrophage migration inhibitory factor (MMIF) in the lavage of bronchoalveolar fluids among patients with ARDS. This factor is released by the anterior pituitary gland and is responsible for the production of TNF- α and IL-8.^{45,58}

e) Genomics

Recently, genetic analysis has gained an attention in evaluating risks for ARDS. Multiple attempts have been made to identify the single nucleotide polymorphisms (SNPs) that are related to risks for ARDS or its adverse outcome.⁵⁹ Christie et.al reported association between SNPs in the myosin light chain kinase gene and ARDS development after trauma among African American individuals.⁶⁰ Moreover, two SNPs within the ANGPT2 gene were

reported to be significantly associated with risks for developing ARDS.⁴⁶ On the other hand, IL-1 receptor antagonist gene (IL1RN) was not associated with increased but rather with decreased risks.⁴⁷

CONCLUSION

In summary, the identification of ARDS biomarkers is a wide spread and challenging topic. Consistency in findings over several biomarkers is promising but many others are still to be validated. Narrowing down the focus to only include trauma related ARDS biomarkers could simplify the topic and makes it more translatable into clinical practice. The current review attempts to compile biomarkers in traumatic patients that aid in predicting risks of ARDS development, adverse outcomes as well as prognosis.

To conclude, the level of biomarkers particularly IL-1, IL-4, IL-6, IL-8, TNF- α , KL-6, RAGE, vWF, PCPIII as well as angiopoietin-2 in traumatic patients predicts the severity and outcomes as they are the early diagnostic biomarkers for ARDS. Thus, early measurement of these biochemical markers could be incorporated into trauma management protocols along with Injury Severity Score, Revised Trauma Score and the Acute Physiology and Chronic Health Evaluation II scoring system. The clinical application of genetic markers to identify risks for ARDS remains unclear.

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