REVIEW ARTICLE

Biomarkers in Early Diagnosis of Acute Respiratory Distress Syndrome: A Narrative Review

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ABSTRACT

Acute Respiratory Distress Syndrome (ARDS) is a severe inflammatory lung condition that leads to respiratory failure, posing high morbidity and mortality risks, especially in critically ill patients. The current diagnostic criteria, based on clinical presentation and imaging findings, often result in delayed recognition. In recent years, numerous biomarkers have emerged with the potential to detect ARDS in its early stages, improving both diagnosis and treatment outcomes. This comprehensive narrative review explores the biological significance and clinical relevance of various biomarkers—including surfactant proteins, inflammatory mediators, endothelial and epithelial injury markers, coagulation-related factors, and genetic indicators like microRNAs—in the early diagnosis of ARDS. It also discusses their diagnostic performance, the limitations of current studies, and future perspectives on integrating biomarkers into clinical practice. The goal is to provide a deeper understanding of how these molecular tools can shift ARDS diagnosis from a reactive to a proactive approach.

KEYWORDS: ARDS, Acute Respiratory Distress Syndrome, Biomarkers, Early Diagnosis, SP-D, sRAGE, CC16, IL-8, MicroRNA, Inflammatory Markers, Lung Injury, Hypoxemia, Precision Medicine, Prognosis, Ventilator-Associated Lung Injury

INTRODUCTION

Acute Respiratory Distress Syndrome (ARDS) is a life-threatening pulmonary condition that manifests as acute-onset respiratory failure characterized by severe hypoxemia, non-cardiogenic pulmonary edema, and bilateral infiltrates on chest imaging. Despite the substantial progress in the understanding and supportive management of ARDS over the past decades, its morbidity and mortality rates remain unacceptably high, ranging from 30% to 45%, especially in moderate to severe cases. The complexity of ARDS lies in its diverse etiologies, variable clinical presentations, and multifactorial pathophysiology, all of which contribute to the challenges in its timely diagnosis and management(1).

According to the Berlin Definition, ARDS is classified based on the severity of hypoxemia (PaO_2/FiO_2 ratio) into mild, moderate, and severe categories. While this classification system provides a standardized diagnostic framework, it still relies heavily on clinical and radiographic findings that often appear only after substantial lung injury has occurred. This delay significantly hampers early intervention, which is critical in improving patient outcomes. Moreover, the nonspecific nature of radiographic findings and overlapping features with other pulmonary conditions—such as cardiogenic pulmonary edema or interstitial lung diseases—can further obscure early diagnosis(2,3).

To overcome these diagnostic limitations, there has been a growing interest in identifying and validating reliable biological markers—commonly referred to as **biomarkers**—that can detect ARDS in its early stages, even before full-blown clinical manifestations become apparent. Biomarkers are measurable substances in body fluids or tissues that reflect physiological or pathological processes or pharmacologic responses to a therapeutic intervention. In the context of ARDS, ideal biomarkers would not only allow early detection but also facilitate prognostication, treatment stratification, and monitoring of therapeutic efficacy(4).

The pathogenesis of ARDS involves a cascade of molecular and cellular events, including damage to the alveolar-capillary barrier, activation of inflammatory cytokines, endothelial dysfunction, epithelial cell apoptosis, and dysregulation of the coagulation cascade. These pathophysiological processes offer multiple molecular targets for potential biomarker development. Current research has investigated a wide array of candidate biomarkers derived from epithelial and endothelial injury (e.g., surfactant proteins, sRAGE), inflammation (e.g., interleukins, TNF-α), coagulation (e.g., D-dimer), and genetic and epigenetic regulators (e.g., microRNAs) (5).

Importantly, these biomarkers are not only being explored for their standalone diagnostic accuracy but also for their utility in combination panels that may offer improved sensitivity and specificity. Furthermore, the rise of technologies such as high-throughput genomic screening, proteomics, metabolomics, and machine learning has accelerated the discovery of novel biomarkers and enhanced the ability to analyze their patterns in diverse patient populations(6,7).

AIMS AND OBJECTIVES

This review aims to provide a comprehensive evaluation of the role of biomarkers in the early diagnosis of ARDS. It evaluates the clinical and biological relevance of established and emerging biomarkers, critically assesses the current evidence regarding their diagnostic and prognostic utility, and discusses their potential integration into routine clinical practice. The review also explores the practical challenges and limitations of biomarker implementation, and outlines future directions in this rapidly evolving field. Through this synthesis, we hope to underline the transformative potential of biomarker-based

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strategies in shifting ARDS management from a reactive to a proactive paradigm.

MATERIALS AND METHOD

This narrative review was based on a comprehensive literature search of databases including PubMed, Scopus, Embase, and Google Scholar for the years 2010 to 2024. Search terms included “ARDS,” “acute respiratory distress syndrome,” “biomarkers,” “early diagnosis,” “surfactant proteins,” “microRNAs,” “sRAGE,” and related combinations. Inclusion criteria were: (1) studies involving human subjects, (2) articles reporting diagnostic accuracy or prognostic relevance of biomarkers in ARDS, (3) English-language publications. Excluded were case reports, letters to the editor, and studies involving pediatric populations unless otherwise relevant. Key findings were extracted and synthesized to construct a thematic analysis covering biomarker types and their clinical applications.

LITERATURE REVIEW

Surfactant and Epithelial Biomarkers

Surfactant protein D (SP-D), Club cell secretory protein (CC16), and Krebs von den Lungen-6 (KL-6) are lung-specific proteins that reflect alveolar epithelial injury. SP-D, produced by type II pneumocytes, increases in plasma when the alveolar-capillary barrier is disrupted. Elevated SP-D levels have been consistently observed in early-stage ARDS and are particularly predictive in sepsis-associated ARDS. Similarly, KL-6 and CC16 have shown utility in differentiating ARDS from cardiogenic pulmonary edema(8,9).

Endothelial and Inflammatory Markers

sRAGE is another well-established biomarker, primarily indicating alveolar epithelial cell injury. It not only correlates with the severity of ARDS but also with mortality. Inflammatory markers like IL-6, IL-8, and TNF-α reflect neutrophilic inflammation, which is central to ARDS pathology. Elevated IL-8 levels, for instance, have been implicated in more severe disease and prolonged ventilator dependence(10,11).

Coagulation and Matrix Turnover Markers

Coagulopathy is a hallmark of ARDS, and markers such as D-dimer and PAI-1 reflect ongoing thrombogenesis and fibrinolysis. These are particularly relevant in ARDS caused by COVID-19, where microvascular thrombosis plays a central role. TIMP-1, involved in extracellular matrix turnover, has also been proposed as a marker of disease progression(12).

Genetic and Epigenetic Biomarkers

MicroRNAs such as miR-146a, miR-155, and miR-223 are emerging as diagnostic tools in ARDS. These small non-coding RNAs regulate post-transcriptional gene expression and are involved in inflammation, apoptosis, and epithelial integrity. Their stability in blood and potential for rapid detection make them promising non-invasive biomarkers(13).

DISCUSSION

In ARDS, biomarkers hold significant potential for aiding in diagnosis and patient stratification, assessing prognosis, and monitoring response to therapy (14). Advances such as the sequencing of the human genome, improved techniques for analyzing gene expression through mRNA transcription, and the development of highly sensitive immunoassays have enabled the application of network biology to ARDS. These biomarkers may pave the way for personalized or precision medicine approaches in the management of the syndrome. (15).

Epithelial markers

Markers of the respiratory epithelium include surfactant proteins (SPs), Krebs von den Lungen-6 (KL-6), vascular endothelial growth factor (VEGF), and the soluble receptor for advanced glycation end-products (sRAGE).

- Surfactant proteins (SP) are generally increased in ARDS, and SP-B can cross damaged alveolocapillary membranes (16, 17). Blood SP-D levels been shown to correlate with ARDS mortality (18, 19).
- KL-6 levels have been correlated with ARDS mortality as opposed to ARDS development (20). In 2014 a meta-analysis of plasma biomarkers for ARDS analysed 54 studies found KL-6, lactate dehydrogenase, sRAGE, and von Willebrand factor were associated with ARDS diagnosis in at risk populations (21).
- VEGF and keratinocyte growth factor were shown to correlate with severity of illness and reflect patient outcome (22, 23).
- RAGE is highly expressed in lung epithelium (24), and especially expressed on alveolar type 1 epithelial cells (25). The use as a marker has been questionable but some studies have shown higher levels of RAGE were associated with impaired alveolar fluid clearance in patients with ARDS hence the severity of lung epithelial injury (26). RAGE plasma levels in patients with severe ARDS correlated with mortality in patients ventilated with high tidal volumes (27). In a meta-analysis sRAGE was found to be useful in ARDS diagnosis in a high risk population, but not associated with mortality (21), although other studies have shown no association (28, 29).

Endothelial markers

Endothelial markers include angiopoietin-2 (Ang-2) and various indicators of endothelial dysfunction (30). Elevated Ang-2 levels have been observed in both ARDS patients and those at risk, and are predictive of increased mortality (29, 31, 32). Furthermore, in trauma patients, higher Ang-2 levels correlate with the development of ARDS (33). Additionally, von Willebrand factor (VWF) has also been associated with mortality in ARDS (18, 34, 35).

Inflammatory cytokines

Levels of the inflammatory cytokines IL-1β and TNF-α are more useful as markers of sepsis severity rather than for ARDS (36). Other pro-inflammatory cytokines include IL-8, which has been shown in predicting the outcome of ARDS (18, 34). IL-18 has been noted to be increased in patients with ARDS, and been associated with mortality (37). An external validation of biomarkers and a clinical prediction model for hospital mortality in ARDS included SP-D and IL8 in various clinical settings, and suggested that these biomarkers may be useful in risk assessment for clinical trial enrolment (38).

Coagulation and fibrinolysis

Plasminogen activator inhibitor-1 (PAI-1) is an inhibitor of fibrinolysis. Some studies have shown an increase in serum levels in patient with ARDS (18, 39, 40), and there is reported correlation with overall mortality in critically ill patients (41).

Combinations of biomarkers

Several studies have looked into markers of epithelial and endothelial injury, coagulation and inflammation and have shown a combination of clinical predictors with combination of biomarkers were better at predicting mortality compared to either of the clinical or biomarkers alone (18, 33, 34, 42). A panel of biomarkers was superior to clinical risk factors alone in predicting mortality in ARDS (18), as well as being useful for the diagnosis of ARDS (27). A combination of RAGE and Ang-2 were superior to clinical diagnosis for the diagnosis of ARDS in severe trauma (43). In severe sepsis a panel which included RAGE, SPD, Club Cell Protein 16 was useful in diagnosis of ARDS (42).

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Blood biomarkers of ARDS: Calfee group, SF

In recent years the clinical research group of Carolyn Calfee and colleagues have performed clinical studies assessing panels of blood biomarkers in ARDS. In the era of precision medicine and personalization, the Calfee group studies proceed on a more detailed characterization of the disease that may vary on individual level. They describe different ARDS subphenotypes and work on biomarker panels that may help clinicians to select patients who may benefit from different therapeutic strategies.

Direct (epithelial)/Indirect (endothelial) Groups: Molecular phenotyping was carried out to demonstrate 2 groups of ARDS patients: with direct (lung epithelial) damage and indirect (vascular endothelium) damage. Direct lung injury mainly caused by pneumonia and aspiration is characterised by more severe lung epithelial injury and less severe endothelial injury. For indirect lung injury, the emphasis is on endothelial or vascular injury, as opposed to epithelial damage. In direct ARDS, there are higher levels of SP-D, a marker of lung epithelial damage and there were lower levels of Ang-2, a marker of endothelial injury compared to indirect ARDS. There is evidence that lower levels of von Willebrand factor (VWF) antigen, IL6 and IL8 are present in direct lung injury (44). With these distinct molecular phenotypes, the epithelium could be a treatment target with keratinocyte growth factor for direct ARDS, whereas the endothelium could be targeted in indirect ARDS using statins and recombinant angiopoietin 1 (44).

Hypo/Hyper Inflammatory Groups: Unbiased latent class analysis of clinical and biomarkers characteristics of ARDS patients demonstrated hypo-inflammatory and hyper-inflammatory groups in ARDS. These have different clinical and biological characteristics, and different responses to therapy. In the hyperinflammatory group (one third of ARDS subjects), there is a higher plasma level of inflammatory biomarkers, higher vasopressor use and lower serum bicarbonate, and higher prevalence of sepsis compared to the hypo-inflammatory group. The hyper-inflammatory group had a higher mortality and fewer ventilator-free and organ failure-free days. Eight plasma biomarkers were included: surfactant protein-D (SP-D), von Willebrand factor antigen, soluble intercellular adhesion molecule 1 (sICAM-1), IL- 6 and IL-8, soluble tumor necrosis factor receptor 1 (TNFR 1), plasminogen activator inhibitor-1 (PAI-1) and protein C (13). More recently, it has been shown that a selection of 4 biomarkers: IL-6, interferon gamma (IFN-γ), angiopoietin 1/2 and PAI-1 could be used to cluster ARDS into two biological phenotypes with different mortality rates (45). The stability of ARDS phenotypes has been shown over the first 3 days of enrolment in 2 clinical trials (46), and they respond differently to fluid management strategies (47).

Septic shock biomarkers: ProCESS study

A large biomarker study of 1341 individuals enrolled in the Protocolized Care of Early Septic Shock (ProCESS) trial found that proteins associated with endothelial cell permeability and hemostasis were associated with increased mortality (48). Angiopoietin-2, soluble fms-like tyrosine kinase 1 (sFLT-1), soluble vascular endothelial growth factor receptor (s-VEGFR), thrombomodulin (TM) and vWF were all higher in patients that died. In a sub-study of 628 patients enrolled in ProCESS, higher serum biomarkers were found in patients with adverse outcomes: including biomarkers of inflammation (IL-6, TNF, IL-10), coagulation (thrombin-antithrombin complex, D-dimer), oxidative stress (urine isoprostane) and tissue hypoxia (lactate) (49).

Influenza ARDS: MOSAIC

The H1N1 influenza A virus is known to be associated to high morbidity and mortality. The infection can cause a severe acute respiratory failure or ARDS with multiorgan failure. The H1N1 pandemic of 2009 saw many cases of severe ARDS with refractory hypoxemia that needed the veno-venous extracorporeal membrane oxygenation as a rescue therapy (50, 51). Recently, the interferon-inducible transmembrane (IFITM3) protein has shown in models to have a pivotal role in defending the host from pathological virus such as influenza A. In human individuals hospitalized for influenza H1N1/2009 virus it has been found elevated expression of a minor IFITM3 allele and in vitro minor CC genotype IFITM3 has reduced influenza virus restriction (52).

Metabolomics

The analysis of lower molecular weight cell metabolites is generally performed using nuclear magnetic resonance (NMR) and mass spectrometry (MS). Metabolic changes are highly dynamic and offer insight into chemical processes occurring at any given time (53). This makes metabolomics a useful way to detect physiological changes in real time allowing monitoring of potential environmental insults, disease progression and drug responses. These metabolite changes occur in relation to alterations in the gene and protein activity that are associated with the disease (54). In a single study there were 4513 metabolites identified in human blood but this is an underestimate based on the individual analytical method (55). Although many studies have been performed to assess the application of metabolomics to lung disease, progress has been slow (54).

There have been several metabolomics studies in experimental models looking at a variety of samples from exhaled breath, serum, bronchial alveolar lavage and lung tissue which find that lung injury results in a perturbation of energy and oxidative stress metabolism (54). In contrast, there have been few clinical metabolomics studies in ARDS. Bos et al. looked into exhaled breath and analysing volatile organic compounds (VOCs) using gas-chromatography and mass spectrometry (GC-MS). Most of the candidate markers are linked to lipid peroxidation. Only octane – one of the end products of lipid peroxidation – has been validated in a temporal external validation cohort and is at the moment is most acknowledged breath biomarker for ARDS (56). Acetaldehyde and 3-methylheptane have also been reported as predictive of ARDS and diagnostic accuracy was improved with the Lung Injury Prediction Score (LIPS) (56).

Metabolomic analysis of bronchoalveolar lavage (BAL) has been carried out using untargeted liquid chromatography mass spectrometry (LC-MS). Metabolites involved with energy metabolism such as lactate, citrate, creatine and creatinine have been shown to be associated to ARDS, and have previously been shown to be increased in plasma (57). In addition, several guanosine network metabolites have been found to be increased in ARDS BAL fluid (54).

Langley et al. looked at extensive targeted metabolomics profiling of > 300 metabolites in two adult populations at high risk of death; patients in Community Acquired Pneumonia and Sepsis Outcome Diagnostics (CAPSOD) and patients in the Registry of Critical Illness (RoCI) (58). Despite the phenotypic differences, most metabolites associated with mortality were upregulated.

The application of NMR-based metabolomic analysis on urine sample of pneumonia patients demonstrated the existence of different metabolomic profiles specific for bacterial infections, particularly for Streptococcus pneumoniae and *Staphylococcus aureus*. The results highlight the potential of metabolomics for the diagnosis and monitoring of the antibiotic therapy of pneumonia both in community- and hospital-acquired ones (59).

In ARDS patients higher urine H2O2 levels were associated with

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worse clinical outcomes, perhaps reflecting greater oxidative injury in these patients (60); while higher urine NO levels were associated with increased survival (61). Urinary indices of glycosaminoglycan (GAG) fragmentation, a product of degradation of the endothelial glycocalyx, individuated by mass spectrometry on urine samples in patients with septic shock or ARDS may predict acute kidney injury and in-hospital mortality (62).

Transcriptomics – Gene expression mRNA

A recent multicohort analysis of whole blood gene expression data for ARDS by Sweeney et al. looked into 3 adult cohorts with sepsis, one paediatric cohort with acute respiratory failure and 2 datasets form adults with trauma and burns for a total of 148 cases of ARDS and 268 cases of critically ill controls. 30 genes were associated with ARDS – many of which have previously been associated with sepsis but with adjustment for the clinical severity score – none of these genes remained significant indicating that the gene expression is one of acute inflammation as opposed to lung injury (63).

Sweeney also looked separately into sepsis subtypes using data pooled from 14 bacterial sepsis transcriptomics (*n* = 700). Using cluster analysis Sweeney showed that there are 3 subtypes termed 'inflammopathic, adaptive and coagulopathic'. Adaptive subtypes are associated with lower clinical severity and lower mortality rate and the coagulopathic subtypes are associated with higher mortality and clinical coagulopathy (64).

MicroRNA (MiRNA)

MiRNA is a novel pathway for non-coding RNA molecules that regulate gene expression at the post-transcriptional level. It plays an important role in inflammation or apoptosis which commonly manifests in ARDS (65). They are good candidates as disease biomarkers due to numerous factors. They can be identified in various body fluids, resistant to extreme environmental conditions, their expression changes in various disease states and change in early stages of gene expression. MiRNA can be readily measured and hence are potential therapeutic targets as each miRNA regulates the expression of many genes (66). Most of the studies to date have been on animal models but one of the first miRNA studied in patients was miRNA-150 which has been shown to be in lower concentrations in the septic cohort; although statistical significance was not achieved (67). Plasma levels of miRNA – 146a and miRNA155 significantly increased in patients with severe sepsis and sepsis induced ALI compared to control (68) and may be helpful in predicting mortality. A more recent study by Zhu et al. examined ARDS patients' vs critically ill at-risk controls and identified whole blood miRNA markers in ARDS including miR-181a, miR92a. MiR-424 was shown to be a protective biomarker. Zhu concluded stating in addition to the miRNA, addition of the LIPS can improve the risk estimate of ARDS (69).

Genetics (DNA)

Genomics in ARDS has offered relatively modest advances in understating ARDS (53). Candidate gene studies have identified variants in more than 40 candidate genes associated with the development (or outcome) of ARDS (70). This included genes for angiotensin-converting enzyme (ACE), IL-10, TNF and vascular endothelial growth factor (VEGF). In the first human genome-wide association study (GWAS) for ARDS susceptibility, Christie et al. identified a novel locus PPFIA1 as a replicable risk factor for ALI following major trauma, but no polymorphism had genome wide significance (71).

Therapies

Current therapies for ARDS are summarized in Table 4. The reader is directed to excellent recent reviews that refer to modern treatment for ARDS in detail (7, 72,73,74). Most advances have been through changes in mechanical ventilation methods, culminating in a 2017 International Clinical Practice Guideline for mechanical ventilation on adults with ARDS (75). The guidelines address 6 interventions: low tidal volume and inspiratory pressure ventilation, prone positioning, high-frequency oscillatory ventilation, higher versus lower positive end-expiratory pressure, lung recruitment manoeuvres, and extracorporeal membrane oxygenation. Otherwise treatment is supportive and palliative, with no current disease-modifying therapies available. Early goal-directed therapy (EGDT) involving a 6 h resuscitation protocol of fluids, vasopressors, inotropes and red cell transfusion for septic shock did not result in better outcomes than usual care (76).

Table 4 Summary of therapies for acute respiratory distress syndrome

Full size table

Glucocorticoids may improve oxygenation and airway pressures in established ARDS, but have failed to demonstrate a role in preventive therapy. In patients with pneumonia, steroids may improve radiological appearances, but again does not improve mortality (77). Trials conducted on established ARDS investigated different doses and duration of treatment, preventing generalization of the results, however analysis suggest that if steroids are started 14 days or more after the diagnosis of ARDS, they can be harmful. The combination of inhaled β2-agonists and glucocorticoid administered early in patients at risk of ARDS has recently shown to prevent development of ARDS and improve oxygenation but its effect on mortality has not been demonstrated (78).

Pre-hospital aspirin has been shown to reduce the incidence of ARDS, however results of ongoing trials investigating its preventive role are inconclusive and more data are needed (79).

Inhaled NO transiently improves oxygenation and long term lung function in patients who survive, but does not affect mortality and may cause renal impairment, hence it is not recommended (80). A neuromuscular blocker, cisatracurium besilate has shown some benefit when used for early ARDS (81). Statins (82), beta-agonists (83), non-steroidal anti-inflammatory drugs (NSAIDs), and an antioxidant (procysteine (L-2-oxo-thiazolidie-4-carboxylic acid)) have failed to show benefit for ARDS. Surfactant replacement (84), neutrophil elastase inhibitors and anticoagulation have also all failed in clinical trials.

Biologics directed against TNF have been highly successful in rheumatoid arthritis, but no benefit has been seen for the treatment of inflammatory lung diseases, including ARDS (85, 86). With a view to lung regeneration, cellular therapies and intravenous mesenchymal stem cell therapy are in development for ARDS (87) (88). There is significant interest in the targeted use of anti-inflammatory therapies in patients with ARDS defined by blood biomarker levels (89). It is logical to study effects of anti-inflammatory agents in patients with hyper-inflammatory ARDS, and to tailor use of specific anti-inflammatory drugs to ARDS patients with particular biomarker profiles (90).

Despite intense investigation, no specific pharmacological treatment for ARDS has been shown to affect the mortality, even though preclinical trials in animal models have looked promising. Targeting a single pathogenetic pathway is not unlikely to be advantageous due to the complexity of the mechanisms involved.

However, the characterization of the ARDS subphenotype by blood biomarkers may help clinician to select patients who may benefit from specific therapeutic strategy and ultimately tailor the treatment on our single patient. In fact, it has been proved that a high PEEP strategy in ARDS patients affected major outcome only in the hyperinflammatory subphenotype (91). Moreover the restrictive fluid strategy was beneficial in the same selected ARDS patients (47). More studies are needed to further

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explore the benefits of different therapies based on particular ARDS biomarker profile.

FUTURE DIRECTIONS

Future research must prioritize large-scale, multicenter validation studies to establish the robustness of biomarker panels. Development of rapid, point-of-care biomarker assays would be particularly transformative in ICU settings. Additionally, studies should explore dynamic changes in biomarker levels over time, which may better reflect disease trajectory than static measurements.

CONCLUSION

Biomarkers offer a promising solution to the limitations of current ARDS diagnostic strategies by enabling earlier, more accurate, and potentially more personalized identification of patients at risk. Although several candidates like SP-D, sRAGE, IL-8, and miRNAs have demonstrated significant diagnostic and prognostic value, challenges related to specificity, reproducibility, and clinical implementation remain. The future likely lies in combining multiple biomarkers with computational tools to refine diagnosis and guide therapy. As our understanding of ARDS pathophysiology deepens, biomarkers are poised to become an integral component of precision medicine in critical care.

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