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BIOMARKERS ASSOCIATED WITH ACUTE RENAL INJURY IN SEPTIC SHOCK: AN INTEGRATIVE LITERATURE REVIEW

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Abstract: Introduction: Septic shock is a critical clinical condition that often culminates in significant kidney damage, increasing the risk of mortality. ARF is the result of a complex immune response that causes ATL and compromises renal function. **Objectives:** To highlight the main biomarkers of stress, damage and function in ARF associated with septic shock. **Methodology:** The following descriptors "*Acute Kidney Injury*", "*Biomarkers*", "*Shock Septic*" and "*Sepsis*" were applied to the PubMed, Science Direct, BVS and SciELO databases, selecting original articles published between 2019 and 2024 in the English language. **Results:** The 12 articles analyzed in this review portrayed various biomarkers, with emphasis on NGAL, useful for early detection of ATL. Analyses involving TIMP 1, TIMP 2, adhesion molecules, MR-proADM were postulated as promising prognostic indicators in the context of ARI. As well as HBP, which proved to be significantly effective in predicting the severity of kidney damage. **Conclusion:** The application of these biomarkers represents a significant advance in the clinical management of ARF associated with septic shock, improving early diagnosis and enabling more targeted treatments.
Keywords: Acute kidney injury; Septic shock; Biomarkers.

INTRODUCTION

Sepsis is defined as life-threatening organ dysfunction caused by a generalized inflammatory response that damages the body's tissues and organs. Septic shock is an evolution of the sepsis patient's clinical condition and is characterized by persistent hypotension and, as it progresses, often leads to complications such as significant kidney damage. The progression of septic shock compromises renal blood flow, leading to direct damage to kidney cells. This toxic reaction contributes to the onset of organ dysfunction, thus increasing the risk of mortality[1].

The differential diagnosis of *sepsis* and septic shock has recently been redefined according to the SEPSIS-3 consensus (*The Third International Consensus Definitions for Sepsis and Septic Shock*). SEPSIS-3 highlights the SOFA (*Sequential Organ Failure Assessment*) for assessing the severity of organ dysfunction, with the aim of improving the identification and effective treatment of sepsis, including its critical stage, septic shock[2].

The inflammatory factors associated with sepsis trigger a cascade of events through intrinsic positive *feedback*, resulting in a disproportionate inflammatory response. Simultaneously, there is a compensatory increase in the release of anti-inflammatory factors. Pro-inflammatory and anti-inflammatory responses coexist, thus creating a complex dynamic imbalance of hyperinflammation and inducing an immunosuppressive state[3-4].

Kidney damage is common in critically ill patients with shock with or without sepsis. The risk factors associated with septic Acute Kidney Injury (AKI) include septic shock, increased values of disease severity markers, comorbidities and positive infection in the blood culture. ARF, which arises from a severe infectious condition, is the result of a complex immune response, culminating in Acute Tubular Injury (ATI) with a reduction in glomerular filtration rate and, consequently, compromised renal function[5].

In addition, patients with sepsis may be subjected to nephrotoxic drugs, such as aminoglycosides, vancomycin and non-steroidal anti-inflammatory drugs (NSAIDs), which potentiate the risk of ARF, due to the inherent toxicity of these drugs, as well as their distribution, metabolism and renal excretion. As with sepsis, ATL underlies a large part of drug-induced ARF, due to nephrotoxicity, as well as the metabolism and renal excretion of these drugs resulting in increased tissue stress in the renal tubules[6-7].

Given this problem, the aim of this integrative review is to highlight the main functional and damage biomarkers associated with ARF in patients with septic shock, thus enabling a comprehensive and up-to-date understanding of the biological processes and molecular pathways involved in this phenomenon.

METHODOLOGY

This article is an integrative, exploratory and qualitative review. To prepare this literature review, an eight-step protocol was followed: 1) formulation of the clinical question, 2) search strategy, 3) definition of inclusion and exclusion criteria, 4) selection of studies, 5) assessment of the quality of studies, 6) data extraction, 7) synthesis and assessment of the quality of evidence and 8) writing of the review.

The PICOS method (Population, Intervention, Comparison, Outcome, Type of Study) was applied (Chart 1) to define the question: "What biomarkers are associated with acute kidney injury in patients with septic shock?".

Description	Abbreviation	Question components
Population	P	Patients with septic shock.
Intervention	I	Biomarker predictors of renal damage and function in septic shock.
Comparison	C	Not applicable.
Outcome	O	Acute Kidney Injury
Type of study	S	Experimental and observational.

Table 1. Components of the leading question, followed by the anagram PICOS

Source: Authors (2025).

As a search strategy for scientific literature, the Descriptors in Health Sciences (DeCS) and *Medical Subject Headings* (MeSH) platforms were used to determine the following descriptors: "*Acute Kidney Injury*", "*Biomarkers*", "*Shock Septic*" and "*Sepsis*", combined with the Boolean terms AND and OR in the ScienceDirect, PubMed (*National Library of Medicine*), BVS (Virtual Health Library) and SciELO (*Scientific Electronic Library Online*) databases.

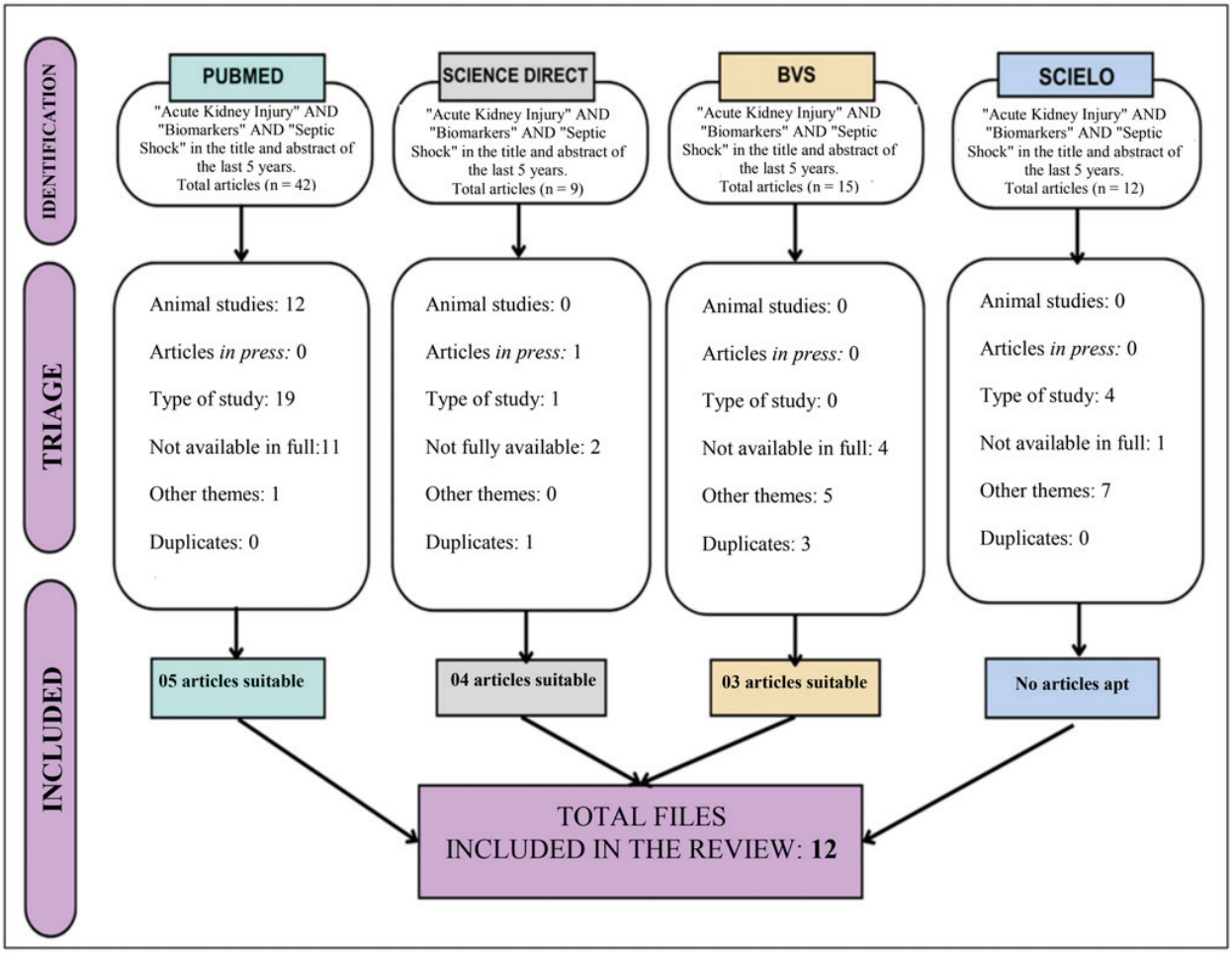

Figure 1. Flowchart of the selection of articles identified through the databases.

Adapted from Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. DOI: 10.1136/bmj.n7110. **Source:** Authors (2025).

Author, Year and Country	Type of Study	Biomarker	Origin of the Biomarker	N	Objective
Tang et al., 2021[8], China.	Analytical study.	VMP1, SLPI, PTX3, TIMP1, OLFM4, LCN2, S100A9.	Differentially expressed genes in ATL.	90	To identify biomarkers and therapeutic targets for LTA associated with septic shock.
Olinder et al., 2024[9], Sweden.	Prospective cohort study.	Hepcidin, HBP.	Blood biomarkers in community septic shock.	140	To evaluate the ability of Hepcidin and HBP to predict ATL in septic shock.
Spoto et al, 2023[10], Italy.	Prospective cohort study.	MR-proADM.	Blood biomarker in sepsis.	301	To investigate whether MR-proADM can predict organ failure and sepsis prognosis.
Atreya et al, 2023[11], USA.	Prospective observational study.	Angpt-1 and 2, Endocan, ICAM-1, E-Selectin, TM (CD141).	Blood biomarkers in sepsis in pediatric patients.	414	To evaluate the prognostic and predictive capacity of biomarkers of endothelial dysfunction in ATL associated with sepsis.
Peerapornratana et al, 2020[12], USA.	Multicenter randomized clinical trial.	TIMP2, IGFBP, NGAL, KIM1, type IV collagen.	Blood and urine biomarkers in sepsis.	598	To identify and validate biomarkers for prognosis in sepsis.

Park et al, 2019[13], South Korea.	Retrospective observational study.	PCT, NGAL.	Blood and urinary biomarkers in ARF.	140	To evaluate NGAL as an early biomarker of ARF.
Titeca-Beauport, et al, 2020[14], France.	Prospective observational study	TIMP-2, IGFBP7	Urinary biomarkers.	184	To investigate the efficacy of TIMP-2 and IGFBP7 in differentiating between transient and persistent ARF in the context of early septic shock.
Ferrando et al, 2022[15], Sweden.	Prospective observational study.	sRTNF	Blood biomarkers of ATL.	122	To analyze plasma levels of soluble sTNFR 1 and 2 receptors in association with organ failure and outcome in critically ill COVID-19 patients.
Wu et al., 2020[16], China.	Retrospective observational study.	NGAL, PCT and Lactate.	Blood and urine biomarkers in ATL.	137	To evaluate the risk stratification and prognostic value of serum NGAL in patients with sepsis.
Stanski et al, 2020[17], USA.	Prospective cohort study.	CCL3, GZMB, HSPA1B, IL-8 and MMP-8	Blood biomarker.	461	To analyze the efficacy of PERSEVERE in predicting severe ARF associated with sepsis in children.
Pode-Shakked et al, 2023[18], USA.	Prospective cohort study.	ECA	Blood biomarker.	72	To explore the association between ACE concentrations and renal outcomes in pediatric septic shock.
Schneck et al., 2022[19], Germany	Prospective cohort study.	sDLL1	Blood biomarkers in ATL.	80	To explore the potential of sDLL1 as a biomarker for sepsis and ATL in surgical patients.

Table 2. Characterization and description of articles in terms of authors, year, country of origin, biomarker, sample number and proposed objectives.

VMP1 (vacuolar membrane protein 1); SLPI (secretory leukocyte protease inhibitor); PTX3 (pentraxin 3); TIMP1 (tissue inhibitor of metalloproteinases 1); OLFM4 (olfactomedin 4); LCN2 (lipocalin 2); S100A9 (S100-A9 protein); HBP (heparin-binding protein); MR-proADM (pro-adrenomedullin intermediate region); Angpt-1 and 2 (angiopoietin 1 and 2); Endocan (endothelial cell-specific molecule 1); ICAM-1 (intercellular adhesion molecule 1); TM (CD141) (thrombomodulin); TIMP2 (tissue inhibitor of metalloproteinases 2); IGFBP (insulin-like growth factor binding protein); NGAL (neutrophil gelatinase-associated lipocalin); KIM1 (kidney injury molecule 1); PCT (procalcitonin); IGFBP7 (insulin-like growth factor binding protein 7); ARF (acute kidney injury); ATL (acute tubular injury); sRTNF (soluble receptor for tumor necrosis factor); CCL3 (CC receptor-binding chemokine 3); GZMB (granzyme B); HSPA1B (heat shock protein 1B); IL-8 (interleukin 8); MMP-8 (matrix metalloproteinase 8); PERSEVERE (Panel of Sepsis Biomarkers for Risk Stratification in Children with Infection); sDLL1 (soluble Delta-like protein 1). **Source:** Authors (2025).

This research included scientific articles compatible with the guiding question, open access, human studies, clinical trials and prospective and retrospective observational studies, available in full and published in English. Studies from the last five years were selected, covering the period from the second half of 2019 to the first half of 2024.

Studies that were not freely available in full were excluded in order to guarantee unrestricted access to the data. Letters, reports, commentaries, editorials, panels and other types of publications that do not represent rigorous scientific studies were also excluded from the research in order to maintain the quality and reliability of the data analyzed.

RESULTS

The search resulted in 12 articles in SciELO, 15 in the BVS platform, 42 in PubMed and 9 articles in the Science Direct database. Following the inclusion and exclusion criteria, 3 studies from the BVS were considered, 5 from PubMed and 4 articles from Science Direct. No articles from SciELO were included in this review. As a result, 12 articles were selected for analysis in this review (**Figure 1**).

Table 2 summarizes the selected studies with the names of the authors and year of publication, country of origin of the study, biomarker shown, biomarker site, number of patients and objectives.

The studies reviewed were conducted in different countries, with four studies carried out in the United States, two in China, five in European countries and one in South Korea. No studies were carried out in Brazil.

The methodological design of the articles in this review mostly involved three subgroups: patients with sepsis, patients with severe sepsis and patients with septic shock. Regarding the study population, three studies were in pediatric patients and one study in COVID-19 patients.

Table 3 summarizes the main results, conclusions and limitations of the studies analyzed in this review.

DISCUSSIONS

Biomarkers in ARF can be divided into three categories: stress biomarkers, damage biomarkers and functional biomarkers (Figure 2). By considering them together, it is possible to adopt a more precise approach than simply measuring serum creatinine levels (SCr) or urine output (UO) in isolation, suggesting more accurate diagnostic and therapeutic methods[17].

Urinary markers such as tissue metalloproteinase-2 (TIMP-2) and insulin-like growth factor binding protein 7 (IGFBP7), recently recognized as inducers of G1 cell cycle arrest and main indicators of ATL stress, have been shown to be more effective than already known biomarkers such as kidney injury molecule-1 (KIM-1) and neutrophil gelatinase-associated lipocalin (NGAL). Interleukin 18 (IL-18), a pro-inflammatory cytokine that stimulates the production of interferon gamma, is identified in urine after acute proximal tubular damage. The urinary concentration of KIM-1, a transmembrane glycoprotein, is a marker of ATL in adults. NGAL, a key polypeptide, is identified in the blood and urine during the development of ATL after ischemic damage or damage induced by renal toxicity[20].

Despite advances in the identification of ARF biomarkers (Chart 4), seven markers have yet to be fully explored in the context of ARF induced by sepsis and septic shock: alanine aminopeptidase, alkaline phosphatase, γ-glutamyl transpeptidase, cystatin C, proencephalin type A, fatty acid-binding protein and N-acetyl-β-D-glucosaminidase. Although these biomarkers are directly related to kidney damage, there are still no specific studies validating their efficacy and applicability in detecting and monitoring ARF in patients with sepsis and septic shock. Further research is needed to better understand their role and clinical potential in these critical conditions, which could improve the diagnosis and treatment of these patients[21].

Tang et al. (2021) identified several genes differentially expressed in ATL, such as vacuolar membrane protein (VMP1), secretory leukocyte protease inhibitor (SLPI), pentraxin-3 (PTX3), tissue inhibitor of metalloproteinases-1 (TIMP1), olfactomedin 4 (OLFM4), lipocalin-2 (LCN2) and S100A9, along with specific miRNAs, including miR--29b-3p, miR-152-3p and miR-223-3p. These biomarkers have the potential to be used in both early diagnosis and therapeutic targeting, although the study is limited by the small sample size and the need for further validation in larger and more diverse cohorts.

Several studies[9-13,15-19] have focused on biomarkers present in the blood. Olinder et al. (2024) highlighted heparin-binding protein (HBP) as a promising marker for predicting ATL in patients with septic shock, while hepcidin showed no prognostic relevance. Spoto et al. (2023) identified mid-region pro-adrenomedullin (MR-proADM) as a useful bio-

Article	Main results	Conclusions
Tang et al., 2021[8], China.	Genes VMP1, SLPI, PTX3, TIMP1, OLFM4, LCN2 and S100A9, predicted miRNAs -miR-29b-3p, miR-152-3p and miR-223-3p, as potential targets for the diagnosis and treatment of ARF associated with septic shock.	These biomarkers help in risk stratification and therapeutic targeting in ARF associated with septic shock.
Olinder et al., 2024[9], Sweden.	HBP was significantly higher in patients with sepsis and was associated with disease severity, renal dysfunction and mortality. Hepcidin does not appear to be a prognostic marker for ATL in patients with septic shock.	Hepcidin is not a reliable predictor of ARF in septic shock, unlike HBP.
Spoto et al, 2023[10], Italy.	MR-proADM can predict kidney and other organ damage, as well as the risk of imminent death in patients with septic shock.	MR-proADM can be used as a biomarker for prognosis in patients with sepsis.
Atreya et al, 2023[11], USA.	Increased concentration of sTM, Angpt, Tie-2, ICAM, VCAM, PECAM in endothelial dysfunction in patients with ATL associated with sepsis.	Prognostic and predictive stratification of endothelial dysfunction to assess the risk of ATL associated with septic shock.
Peerapornratana et al, 2020[12], USA.	The study showed that urinary NGAL measured within 6 hours of hospital admission significantly improved the prediction of kidney disease when added to the clinical model, with an area under the ROC curve of 0.74.	Early identification of urinary NGAL in patients at risk of developing ARF allows for early interventions.
Park et al., 2019[13], South Korea.	In patients with septic shock, serum procalcitonin and urinary NGAL concentrations were higher in patients with ATL than in those without ATL ($p = 0.006$, $p < 0.001$).	Urinary NGAL concentration can predict ATL in patients with sepsis in the emergency department.
Titeca-Beauport et al, 2020[14], France.	Baseline urine TIMP-2 and IGFBP7 values were higher in the persistent ARF group than in the transient ARF group.	Measurements of urine TIMP-2 and IGFBP7 at the onset of septic shock are not effective in differentiating between transient and persistent ARF.
Ferrando et al, 2022[15], Sweden.	Levels of sTNFR were higher in patients with severe COVID-19 compared to controls and were associated with disease severity scores (SAPS 3 and SOFA), inflammatory biomarkers such as IL-6, ferritin and PCT.	Plasma levels of sTNFR 1 and 2 were higher in COVID-19 patients compared to controls.
Wu et al., 2020[16], China.	sNGAL in sepsis patients who developed ATL was significantly higher compared to sepsis patients who did not develop ATL, sNGAL demonstrating the potential to predict the occurrence of kidney damage, being a relevant biomarker for assessing the severity of sepsis.	sNGAL and lactate were identified as independent risk factors for 28-day mortality in patients with sepsis.
Stanski et al, 2020[17], USA.	CCL3, GZMB, HSPA1B, IL-8 and MMP-8 allowed the identification of patients at increased risk of developing severe ATL.	Biomarkers from the PERSEVERE model are useful in the early identification of severe ATL and in the evaluation of renal recovery in children with septic shock.
Pode-Shakked et al, 2023[18], USA.	Association between ACE concentrations, ACE activity and renal outcomes in pediatric septic shock, implying modifiable mechanisms of RAAS derangement in these patients.	ACE dysfunction occurs in pediatric septic shock, potentially due to endothelial damage.
Schneck et al., 2022[19], Germany	Although sDLL1 has shown diagnostic potential for discriminating sepsis from systemic inflammatory reactions induced by surgery, its specificity has been limited, especially in cardiac surgical patients.	Plasma levels of sDLL1 have been identified as a significant predictor of sepsis and ALL in surgical intensive care patients.

Table 3. Description of the main results and conclusions of the articles listed (2019-2024).

VMP1 (vacuole membrane protein 1); SLPI (secretory leukocyte protease inhibitor); PTX3 (pentraxin 3); TIMP1 (tissue inhibitor of metalloproteinases 1); OLFM4 (olfactomedin 4); LCN2 (lipocalin 2); S100A9 (S100-A9 protein); miR-29b- 3p (microRNA-29b-3p); miR-152-3p (microRNA-152-3p); miR-223-3p (microRNA-223-3p); ATL (acute tubular injury); HBP (heparin binding protein); MR-proADM (intermediate region pro-adrenomedullin); sTM (soluble thrombomodulin); Angpt (angiopoietin); Tie-2 (angiopoietin receptor); ICAM (intercellular adhesion molecule); VCAM (vascular adhesion molecule); PECAM (platelet-endothelium adhesion molecule); IRA (IRA); NGAL (neutrophil gelatinase-associated lipocalin); CCL3 (CC receptor-binding chemokine 3); GZMB (granzyme B); HSPA1B (heat shock protein 1B); IL-8 (interleukin 8); MMP-8 (matrix metalloproteinase 8); PERSEVERE (Panel of Sepsis Biomarkers for Risk Stratification in Children with Infection); sNGAL (soluble neutrophil gelatinase-associated lipocalin); TIMP2 (tissue inhibitor of metalloproteinases 2); IGFBP7 (insulin-like growth factor binding protein 7); sTNFR1 (soluble TNF receptors 1); sTNFR2 (soluble TNF receptors 2); ICU (intensive care unit); IL-6 (interleukin 6); PCT (pro-calcitonin); sDLL1 (soluble Delta-like protein 1); ACE (Angiotensin Converting Enzyme); RAAS (Renin-Angiotensin-Aldosterone System). **Source:** Authors (2025).

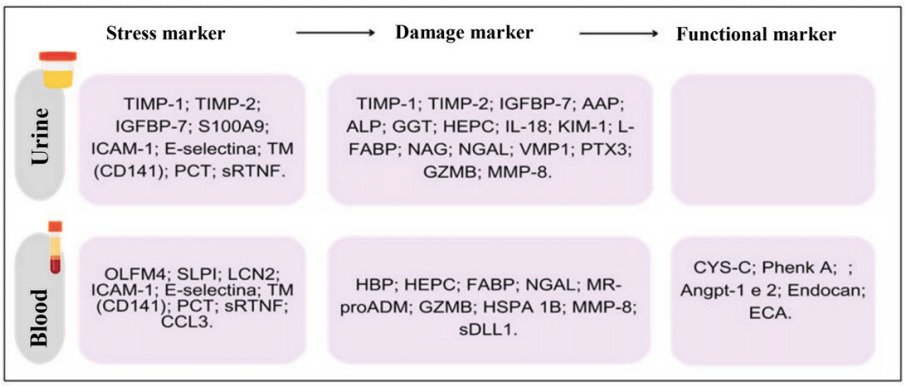

Figure 2 - Flowchart showing the classification of the types of ARF biomarkers in urine and blood listed in this review.

TIMP-1 (tissue inhibitor of metalloproteinases-1); TIMP-2 (tissue inhibitor of metalloproteinases-2); IGFBP-7 (insulin-like growth factor binding protein 7); ICAM-1 (intercellular adhesion molecule-1); TM (CD141) (thrombomodulin); PCT (procalcitonin); sTNFR (soluble tumor necrosis factor receptor); AAP (alanine aminopeptidase); ALP (alkaline phosphatase); GGT (γ-glutamyl transpeptidase); HEPC (hepcidin); IL-18 (interleukin-18); KIM-1 (kidney injury molecule-1); L-FABP (liver-type fatty acid binding protein); NAG (N-acetyl-β-D-glucosaminidase); NGAL (neutrophil gelatinase-associated lipocalin); VMP1 (vacuolar membrane protein 1); PTX3 (pentraxin-3); GZMB (granzyme B); MMP-8 (metalloproteinase-8); HEPC (hepcidin); FABP (fatty acid binding protein); NGAL (neutrophil gelatinase-associated lipocalin); MR-proADM (pro-adrenomedullin intermediate region); GZMB (granzyme B); HSPA1B (heat shock protein 1B); MMP-8 (metalloproteinase-8); sDLL1 (soluble form of delta-like ligand 1); OLFM4 (olfactomedin-4); SLPI (secretory leukocyte protease inhibitor); LCN2 (lipocalin-2); PCT (procalcitonin); sTNFR (soluble tumor necrosis factor receptor); CCL3 (CC-motif-binding chemokine 3); CYS-C (cystatin C); Phenk A (proencephalin type A); HBP (heparin-binding protein); Angpt-1 (angiopoietin-1); Angpt-2 (angiopoietin-2); ACE (angiotensin-converting enzyme). **Source:** Authors (2024).

Biomarker	Biological origin	Time	Limitations
Hepcidin	Produced in hepatocytes; freely filtered	Not specified.	Decrease in anemia and increase in inflammatory state (patients undergoing heart surgery; ICU patients).
TIMP-2; IGFBP7	MMP released during cell cycle arrest.	4h - 12h after injury.	High in diabetes (patients undergoing cardiac or non-cardiac surgery; ICU patients; emergency patients).
IL-18	Released in urine after LTA.	Not specified.	High in inflammatory states; lack of cut-off values (hospitalized patients; ICU and emergency patients; patients undergoing heart surgery).
KIM-1	Produced by proximal tubular cells; released in the urine after LTA.	12-24 hours after injury.	Elevated in chronic proteinuria and inflammatory diseases (hospitalized patients; emergency room patients; patients undergoing cardiac surgery; ICU patients).
NGAL	At least three different types: (1) produced by neutrophils and epithelial tissues, including tubular cells; (2) produced by neutrophils; and (3) produced by tubular cells.	Not specified.	High in sepsis, UTI and CKD; lack of specific cut-off values (patients undergoing cardiac or non-cardiac surgery; patients undergoing coronary angiography; ICU patients; post-transplant patients; emergency patients).
AAP; alkaline phosphatase; γ-GT	Localized in proximal tubular cells; released in urine after LTA.	Not specified.	Elevated in UTI, cardiovascular disease and stroke (ICU patients).
Cystatin C	Produced in nucleated cells; freely filtered.	12-24 hours after injury.	Confounded by age, gender, inflammatory state, diabetes, low albumin level, muscle mass and use of high doses of steroids (patients undergoing heart surgery or liver transplantation; hospitalized patients).
Penk A	Freely filtered.	Not specified.	ICU patients; patients undergoing heart surgery; hospitalized patients.
FABP	Freely filtered and released in the urine after LTA.	Not specified.	Associated with anemia in patients without diabetes (patients undergoing cardiac surgery; ICU or emergency patients).

NAG	Released in urine after LTA.	2-4h after injury	Elevated in diabetes and albuminuria (patients undergoing cardiac surgery; hospitalized patients).

Table 4. Characterization of ARF biomarkers in terms of biological origin, time of appearance after injury and main limitations.

AAP (Alanine aminopeptidase); γ-GT (γ-glutamyl transpeptidase); PENK A (proencephalin type A); FABP (fatty acid binding protein); NAG (N-acetyl-β-D-glucosaminidase); TIMP-2 (tissue inhibitor of metalloproteinases-2); IGFBP-7 (insulin-like growth factor binding protein 7); NGAL (neutrophil gelatinase-associated lipocalin); IL-8 (interleukin 8); KIM-1 (kidney injury molecule-1); ICU (Intensive Care Unit); CKD (Chronic Kidney Disease). Source: Translated and adapted from Zarbock et al., 2023.

marker for predicting organ damage and mortality in sepsis. Atreya et al. (2023) explored endothelial dysfunction through biomarkers such as soluble thrombomodulin (sTM), angiopoietin (Angpt), intercellular adhesion molecule (ICAM), vascular cell adhesion molecule (VCAM) and platelet-endothelium adhesion molecule (PECAM), highlighting their association with ARF in pediatric patients. These studies reinforce the importance of blood biomarkers in risk stratification and prognosis, although most need further validation and multicenter studies to confirm their clinical usefulness[5-7].

NGAL has consistently emerged as a promising biomarker in several studies. Park et al. (2019) and Wu et al. (2020) demonstrated that elevated urinary NGAL concentrations are strongly associated with ATL in septic patients, highlighting its predictive value. In addition, Titeca-Beauport et al. (2020) investigated the combination of TIMP2 and IGFBP7, showing that although they are useful for distinguishing between transient and persistent ARF, their initial measurements do not significantly improve clinical prediction.

Stanski et al. (2020) and Sancho et al. (2022) focused on inflammatory cytokines and proteins such as CC receptor-binding chemokine 3 (CCL3), granzyme B (GZMB), heat shock protein 1B (HSPA1B), interleukin 8 (IL-8), MMP-8 metalloproteinase 8 (MMP-8) and soluble tumor necrosis factor receptor (sTNFR), evidencing their ability to predict ATL and mortality in septic patients, including those with COVID-19. These findings underline the complexity of the inflammatory response in sepsis and the need for robust biomarkers to monitor disease progression and adjust treatment in a personalized way.

CONCLUSIONS

The studies analyzed in this integrative review highlighted several biomarkers that play important roles in predicting and diagnosing ARF in a septic context. Biomarkers such as NGAL, procalcitonin, KIM-1, TIMP-2, and IGFBP7 have shown promise in the early detection of kidney damage, while markers such as MR-proADM and HBP have been associated with disease severity and prognosis.

This review has shown that urinary and blood biomarkers offer a significant advantage over traditional diagnostic methods, such as measuring serum creatinine and urine output, which are less sensitive and specific. However, the studies reviewed also indicate the need for further validation in larger and more diverse cohorts to confirm the efficacy of these biomarkers and their clinical application.

Another noteworthy fact is the limitation observed in relation to the heterogeneity of the studies in terms of patient population, types of biomarkers investigated and methodologies used. In addition, many studies had relatively small sample sizes, which may limit the generalizability of the results.

In conclusion, the integration of biomarkers could represent a significant advance in early diagnosis and targeted treatment, im-

proving clinical outcomes. Future research, especially multicenter clinical trials, should focus on validating biomarkers and developing new indicators that can more accurately predict the occurrence and progression of ARF in patients with septic shock.

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