Liu *et al. BMC Nephrology* (2025) 26:253
https://doi.org/10.1186/s12882-025-04179-z

BMC Nephrology

REVIEW Open Access

Molecular insights and clinical implications of DNA methylation in sepsis-associated acute kidney injury: a narrative review

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Abstract

Sepsis-induced acute kidney injury (S-AKI) is a life-threatening complication of sepsis, marked by dysregulated inflammation, metabolic derangements, and immune dysfunction, driving high mortality. Its multifactorial pathogenesis increasingly implicates DNA methylation-a core epigenetic mechanism-as a critical disease modulator. This review synthesizes current knowledge of DNA methylation in S-AKI, covering molecular mechanisms, cellular dysfunction, and translational potential. In immune cells, sepsis-induced aberrant DNA methylation promotes hypomethylation of pro-inflammatory genes and hypermethylation of anti-inflammatory loci, exacerbating cytokine storms and immunosuppression. In renal tubular epithelial cells, abnormal methylation disrupts apoptosis, oxidative stress responses, and mitochondrial bioenergetics, impairing repair and accelerating S-AKI progression. Renal vascular endothelial cells exhibit methylation-dependent dysregulation of vasoactive and inflammatory pathways, compromising microvascular homeostasis and renal hemodynamics. DNA methylation signatures offer promise as early S-AKI biomarkers, with cell-type-specific patterns reflecting severity, injury, and prognosis. Targeting DNA methyltransferases with epigenetic modifiers represents a novel therapy, though challenges arise from sepsis's complex epigenetic landscape-bidirectional methylation changes, histone crosstalk, and context-dependent responses. A key paradox lies in DNA methylation's dual traits: stability underpinning biomarker reliability and plasticity enabling dynamic inflammatory adaptation, yet introducing therapeutic heterogeneity. Future research should prioritize dissecting cell-specific methylation mechanisms, integrating multi-omics to identify epigenetic subnetworks, and developing real-time monitoring tools for precision diagnosis and tailored interventions. Advancing these frontiers may translate epigenetic insights into transformative strategies to improve outcomes for this devastating condition.

Clinical trial number

Not applicable.

Keywords Sepsis, Acute kidney injury, DNA methylation, Epigenetics, Inflammation, Biomarkers

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Introduction

Sepsis, a life-threatening condition, poses a substantial threat to human health. Characterized by inflammation, metabolic derangements, and immunosuppression, it often leads to a protracted clinical course and challenges in restoring physiological homeostasis [1]. The kidneys are frequently affected during sepsis progression, with manifestations including neutrophil infiltration, the massive release of pro-inflammatory cytokines, disrupted vascular permeability, and the onset of an uncontrolled inflammatory storm [2]. Studies have shown that 47.5% of acute kidney injury (AKI) cases in intensive care units are sepsis-related [3]. When severe AKI progresses to renal failure, the mortality rate increases significantly compared to non-septic AKI (70.2% vs. 51.8%) [4]. Currently, understanding of its pathogenesis remains limited, diagnosis is often delayed, and post-diagnostic medical interventions are insufficient.

DNA methylation, a key epigenetic regulatory mechanism, has emerged as a critical factor in sepsis and its associated renal injury [5]. In sepsis, systemic inflammatory responses induce aberrant hypomethylation of pro-inflammatory genes (e.g., TNF-α, IL-1β) in immune cells such as macrophages and neutrophils, leading to excessive release of inflammatory cytokines [6]. Concurrently, hypermethylation of anti-inflammatory genes (e.g., IL-10) impairs immune regulation, exacerbating the inflammatory storm. This epigenetic imbalance amplifies the risk of organ injury through signaling pathways such as TLR/NF-κB [7]. In the kidneys, aberrant DNA methylation disrupts the expression of apoptosis-regulating genes (e.g., the Bcl-2 family), oxidative stress-related genes, and genes involved in mitochondrial function within renal tubular epithelial cells, resulting in impaired cellular repair and the development of sepsis-associated acute kidney injury (S-AKI) [5]. Furthermore, DNA methylation patterns serve as early biomarkers for sepsis-induced renal injury, and intervention strategies targeting DNA methyltransferases (e.g., DNMT inhibitors) hold promise as novel therapeutic avenues [8].

The primary aim of this comprehensive review is to systematically synthesize current knowledge of the role of DNA methylation in S-AKI. By integrating research on the basic mechanisms of DNA methylation, its multifaceted interactions with sepsis, and the specific pathological processes of S-AKI, we aim to provide a clear and in-depth understanding of this complex topic. This effort will not only address existing knowledge gaps but also lay a robust foundation for future research and the development of innovative therapeutic strategies for S-AKI.

Overview of DNA methylation

Epigenetics refers to inheritance mechanisms independent of DNA sequence changes, regulating gene expression during mitotic and meiotic processes [9]. It comprises three primary categories: DNA methylation, histone modification, and non-coding RNA [10]. Its core function is to modulate gene expression patterns, governing the temporal and spatial regulation of gene expression and the underlying mechanisms that influence organismal growth, development, and disease responses [11]. Unlike genetic information encoded in DNA sequences, epigenetic markers can adapt to environmental changes such as diseases and undergo continuous adjustment [12]. This regulable and relatively stable property serves as a key mechanism in the formation of innate immune memory [13].

DNA methyltransferases

Among the five known DNA methyltransferase (DNMT) proteins, only DNMT1, DNMT3a, and DNMT3b exhibit high methylation activity [14]. DNMT1 is essential for DNA replication, ensuring the faithful transfer of methylation patterns from the template strand to the daughter strand, thereby maintaining the stability and continuity of methylation states across cell generations [15]. DNMT3a/3b are involved in DNA damage repair and can induce de novo DNA methylation through remethylation processes [16, 17].

DNA methylation mechanisms

Catalyzed by DNA methyltransferases, DNA methylation converts cytosine at the 5th carbon position to 5-methylcytosine [18]. This process regulates the distribution of DNA regions and gene expression levels, occurring primarily in cytosine-guanine dinucleotide (CpG) islands within gene promoters [19]. DNA methylation is central to maintaining cell function, genomic stability, chromosome inactivation, and genomic imprinting [20]. Notably, as a reversible physiological process, it significantly contributes to maintaining in vivo homeostasis [21]. Two main DNA demethylation mechanisms exist [22]: one involves the dilution of methylation marks during DNA replication until they are eliminated, and the other entails the conversion of methylated cytosines to their analogs under specific conditions, followed by the removal of methyl groups through DNA cleavage [22]. Generally, hypomethylation of CpG sites in promoter regions correlates with gene activation, whereas hypermethylation leads to gene silencing and suppressed gene expression [23]. DNA methylation balances stability (mitotically heritable, maintained by DNMT1, e.g., renal tubular function genes) and plasticity (stimulus-responsive, via DNMT3a/3b and TET enzymes, e.g., LPS-induced pro-inflammatory gene hypomethylation in macrophages).

This duality is critical for both long-term cellular identity and acute stress adaptation in S-AKI.

DNA methylation and sepsis

DNA methylation and host-pathogen interaction

Infection triggers sepsis, and host-pathogen interactions are fundamental to understanding its mechanisms [24]. Bacteria, viruses, fungi, and parasites manipulate the local microenvironment by synthesizing specific survival proteins [25]. During this process, epigenetic mechanisms are activated, generating specific epigenetic-modifying enzymes, modulating or inhibiting host endogenous epigenetic enzymes, and producing microRNAs (miRNAs) that interfere with protein translation [26]. These interactions disrupt host immune homeostasis, potentially leading to the emergence of multi-drug-resistant pathogens [27]. Although microorganisms and viruses are known to induce host immune changes, their precise roles and mechanisms in sepsis remain poorly understood.

DNA methylation and inflammatory response

The systemic inflammatory response in sepsis induces hypomethylation in the promoter regions of pro-inflammatory genes (e.g., TNF-α, IL-1β) within immune cells such as macrophages and neutrophils, culminating in excessive release of inflammatory mediators. This epigenetic alteration amplifies the inflammatory response via signaling cascades like the TLR/NF-κB pathway, triggering a "cytokine storm." Conversely, hypermethylation in the promoter regions of anti-inflammatory genes (e.g., IL-10) suppresses their transcriptional activity, diminishing immunomodulatory functions and exacerbating inflammatory dysregulation. Such methylation imbalance represents a pivotal mechanism underlying immune dysfunction in sepsis.

DNA methylation profiles of monocytes in sepsis patients correlate significantly with interleukin (IL) levels, including IL-6 and IL-10 [28]. This correlation is mediated through activation of the Toll-like receptor (TLR) pathway and downstream cytokine cascades, underscoring the close link between DNA methylation and the inflammatory response [29].

DNA methylation as a biomarker for sepsis

Biomarkers are essential for objectively assessing patient health, enabling accurate diagnosis, treatment evaluation, and personalized therapy monitoring. Due to its stability, DNA methylation has increasingly been used for early detection of major diseases, offering higher diagnostic value than conventional serological markers [30, 31]. Distinct methylation patterns-particularly those of immune-relevant genes-hold promise as biomarkers for early sepsis diagnosis and prognostic evaluation. At sepsis onset, gene reprogramming frequently occurs, heavily dependent on methylation mechanisms [32], accompanied by significant changes in gene expression and epigenetic modifications like DNA methylation and histone modification [32, 33]. Histone modifications (e.g., H3K27 acetylation, H3K4 methylation) regulate inflammation-related gene expression and T-cell differentiation [7, 34], while methylation status of PD-1 or HLA-DR genes in monocytes correlates with immunosuppression [35, 36].

Studies identify two critical aspects of epigenetic modifier therapy for sepsis: early intervention and bidirectional regulation. Early use of DNMT inhibitors or histone deacetylase inhibitors in LPS-induced mouse sepsis models improves outcomes [37–39], but sepsis-related epigenetic regulation is bidirectional [40, 41]. For example, while most genes show increased methylation in response to LPS, the TNF promoter region undergoes hypomethylation [42, 43], limiting the efficacy of single-agent therapies due to dynamic, context-dependent methylation changes and off-target effects on global methylation profiles. In type II alveolar epithelial cells, LPS induces inflammatory factor secretion via the DNMT1/miR-130a/ZEB1 regulatory pathway [44]. DNMT inhibitors reverse aberrant methylation, restoring anti-inflammatory gene expression and potentially improving sepsis prognosis. Combined with histone modification inhibitors (e.g., HDAC inhibitors), they may coordinate gene regulation to mitigate organ injury.

Notably, inter-individual variability in sepsis necessitates integrating multi-omics data (e.g., methylome, transcriptome) for accurate patient stratification [45]. Techniques enabling real-time methylation monitoring could effectively guide optimal therapeutic timing [46, 47], while elucidating interactions between methylation and other epigenetic modifications (e.g., histone acetylation) remains essential for understanding their combined impact on sepsis progression [32, 48].

S-AKI

AKI is a common clinical manifestation of sepsis, typically presenting as azotemia and oliguria, with high mortality, hospitalization rates, and poor prognosis. Traditional diagnostics rely on parameters such as urine output, creatinine, cystatin C, and blood urea nitrogen, but DNA methylation markers may aid early diagnosis of specific AKI forms, including S-AKI. As a severe complication, S-AKI threatens patient survival [49], yet its pathogenesis remains incompletely understood despite extensive research [50]. Multiple hypotheses have been proposed, with DNA methylation emerging as a key area of interest [51]. Focusing on specific cell types-renal tubular epithelial cells, renal vascular endothelial cells, and podocytes-may deepen understanding of DNA

methylation's role and inform targeted S-AKI prevention and treatment strategies [52, 53].

DNA methylation as a marker for S-AKI

DNA methylation, a hallmark epigenetic modification characterized by exceptional stability and dynamic adaptability, occupies a central role in the pathogenesis of S-AKI, offering dual promise as both a mechanistic target and a clinical biomarker. Preclinical evidence highlights the functional relevance of DNA DNMTs in S-AKI: LPS-induced rhabdomyolysis elevates DNMT1 expression in pulmonary tissues, while pharmacological inhibition of DNMTs with hydralazine attenuates renal dysfunction, underscoring the causal link between epigenetic dysregulation and kidney injury [54, 55]. In sepsis, pathogen-host interactions drive upregulation of DNMT activity and gene expression in epithelial, endothelial, and dendritic cells, promoting widespread DNA methylation that disrupts immune homeostasis and renal cellular function [24]. Renal-specific epigenetic alterations include reduced 5-hydroxymethylcytosine in the promoters of Cxcl10 and Ifngr2 during injury, which correlates with augmented transcription of pro-inflammatory mediators and exacerbation of S-AKI [56].

Contemporary research has deepened our understanding of DNA methylation in S-AKI. Stasi et al. demonstrated that mTOR inhibition mitigates LPS-induced acute kidney injury by reversing epigenetic hallmarks of cellular senescence in renal tubular epithelial cells, implicating DNA methylation in mechanisms of cellular aging and repair [54]. You et al. pioneered the use of kidney-specific cell-free DNA methylation markers for real-time monitoring of sepsis-induced AKI, showcasing their potential to reflect disease severity through non-invasive, circulating epigenetic signatures [57]. In vascular endothelium, septic shock triggers a STAT3-JunB-mediated transcriptional-epigenetic axis, where DNA methylation modulates vasoactive pathways and inflammatory signaling critical for maintaining renal microcirculatory integrity [58]. Complementary studies on endotoxin-induced rhabdomyolysis [59] and G-rich DNA in systemic lupus [60] provide cross-pathological insights into methyltransferase-dependent mechanisms of tissue injury and immune dysregulation, which are integral to S-AKI pathophysiology.

Taken together, these findings establish DNA methylation as a multifunctional biomarker for S-AKI, bridging roles in inflammatory dysregulation, renal hemodynamic compromise, and cellular dysfunction. Future investigations should prioritize single-cell methylomic profiling to define cell-type-specific epigenetic signatures and validate their utility in early diagnosis, prognostic stratification, and precision therapies for this life-threatening condition.

Changes in renal hemodynamics

Insufficient renal blood perfusion has long been considered a major factor in AKI development. Endotoxin can reduce the glomerular filtration rate by upregulating the expression of nitric oxide (NO) synthase [61]. However, recent studies challenge this, suggesting renal blood flow may not decrease in S-AKI [62]. For example, AKI occurs in stable-hemodynamics pneumonia patients [63], with conflicting findings attributed to animal model heterogeneity and sepsis induction method differences.

In renal tubular epithelial cells, DNA methylation is critical for cell repair and function. Pathogen-induced DNMT activity upregulation alters gene methylation status [48, 64]. Specifically, the hypermethylation of energy metabolism gene promoters leads to gene silencing. This silencing impairs the energy supply and disrupts the renal tubular reabsorption and secretion processes [65]. Research on S-AKI animal models has indicated that the abnormal methylation of genes associated with antioxidant stress in renal tubular epithelial cells weakens the cells' ability to resist oxidative damage. As a result, cell injury is exacerbated [66]. Furthermore, DNA methylation may interfere with the expression of tight-junction proteins in renal tubular epithelial cells. This interference undermines the integrity of the tubulo-interstitial barrier, which in turn promotes protein leakage. Ultimately, this process further aggravates kidney injury [67, 68].

Dysfunction of renal vascular endothelial cells is pivotal for abnormal renal hemodynamics. Septic shock induces endothelial cell injury, increasing endothelin release and microvascular thrombosis, leading to tissue ischemia-hypoxia, overproduction of reactive oxygen species and NO, and subsequent membrane/mitochondrial damage [69–71]. DNA methylation affects endothelial cell function: inflammatory mediators alter vasomotor gene methylation patterns [72], nitric oxide synthase gene hypermethylation reduces NO production, impairing vasodilation and perfusion [73], and pro-inflammatory gene promoter hypomethylation enhances mediator release, increasing vascular permeability and kidney injury [74–76].

Kidney injury related to cytokines

During sepsis, the presence of endotoxins in the bloodstream triggers AKI through three distinct signaling pathways. LPS binds to TLRs and interacts with CD14, inducing the production of inflammatory cytokines by neutrophils, monocytes/macrophages, and vascular endothelial cells [77]. TNF, in particular, can initiate a "cytokine storm" through interactions with other inflammatory mediators, resulting in kidney injury [78]. Upregulation of TLRs in renal tubular epithelial cells and local renal endothelial cells directly contributes to renal tubular injury [64]. Thus, cytokine-mediated inflammatory

cascades orchestrate sepsis-related kidney injury, often leading to multi-organ damage [2].

Abnormal coagulation function

In sepsis, the excessive release of inflammatory cytokines and immune cells activates coagulation factors, thereby initiating the intrinsic coagulation pathway [79]. This activation process causes fibrin to deposit in glomerular capillaries, which disrupts renal hemodynamics and decreases the glomerular filtration rate. Consequently, these cascading effects ultimately lead to prerenal renal failure. Apoptotic cells, encompassing those derived from red blood cells, platelets, monocytes, vascular endothelial cells, and vascular smooth muscle cells, release microparticles that contain procoagulant factors [80]. These microparticles have the potential to trigger disseminated intravascular coagulation and microvascular thrombosis during sepsis, which are crucial factors contributing to the development of AKI [81, 82].

Mitochondrial autophagy mechanism

Sepsis-induced oxidative stress leads to mitochondrial reactive oxygen species overproduction, activating repair or autophagic elimination of damaged mitochondria [83]. S-AKI animal models show early increased autophagosome levels, with higher levels correlating with less severe tubular injury [84, 85].

Changes in DNA methylation at different stages of S-AKI and their clinical significance

Metabolomic studies have demonstrated that the metabolome undergoes dynamic alterations at distinct time points following the onset of S-AKI, with these changes being closely correlated with disease progression and prognosis [66, 86]. Similarly, DNA methylation-a reversible and dynamic epigenetic modification-is likely to exhibit stage-specific patterns throughout the clinical course of S-AKI [87]. Such epigenetic alterations not only reflect underlying biological mechanisms but also offer potential for early disease detection and prognostic stratification. During the early phase of S-AKI, when inflammatory responses and immune activation dominate, DNA methylation actively regulates the expression of inflammation-related genes, thereby influencing cellular responses to inflammatory stimuli. As the disease progresses and tubulo-interstitial damage along with apoptotic processes intensify, DNA methylation further modulates genes involved in cellular repair and apoptotic pathways, directly impacting the severity of renal injury and the likelihood of functional recovery. In the convalescence phase of S-AKI, DNA methylation continues to play a critical role. Investigations have revealed that the methylation status of specific genes-including those associated with cellular energy metabolism and mitochondrial function-correlates significantly with renal functional recovery and tissue repair [88]. Collectively, these findings strongly indicate that DNA methylation represents a potential biomarker for early diagnosis and prognostic evaluation in patients with S-AKI.

Challenges and perspectives in DNA methylation-based diagnosis and DNMT-targeted therapy

The application of DNA methylation in diagnostic strategies and DNMT (DNA methyltransferase)-targeted therapies pose significant challenges alongside promising opportunities. In the realm of diagnostics, although DNA methylation signatures exhibit potential as biomarkers [89], key challenges include the variability of methylation patterns across different tissues and diseases, which limits their specificity. Technical obstacles-such as detecting low-abundance methylated DNA and standardizing assays across diverse platforms-further hinder clinical translation [90, 91]. For therapeutic interventions, DNMT inhibitors (e.g., 5-aza-2'-deoxycytidine) confront challenges like acquired resistance-evidenced by upregulated TET2 in DNMT1-deficient cancers-and off-target effects arising from global methylation disturbances [92]. Paradoxically, these inhibitors may induce hypermethylation in specific genomic regions, complicating therapeutic outcomes [92]. Additionally, the dynamic interaction between DNMTs and other epigenetic modifiers (e.g., histone methyltransferases) generates complex crosstalk that remains incompletely understood, thereby limiting the precision of targeted interventions [93, 94]. Looking ahead, integrating multi-omics datasets to identify patient-specific methylation biomarkers has the potential to enhance diagnostic accuracy. In therapy, combinatorial approaches-pairing DNMT inhibitors with histone deacetylase inhibitors or immunotherapies-show promise in overcoming resistance and improving treatment efficacy [95, 96]. Advancements in gene-targeted methylation editing technologies (e.g., CRISPR-based tools) may also enable precise modulation of pathogenic methylated loci, minimizing off-target effects [97, 98]. Understanding the evolutionary and tissue-specific dynamics of DNA methylomes will be critical for developing personalized approaches tailored to individual patients [99, 100]. Lastly, the paradox of DNA methylation stability (biomarker reliability) and plasticity (dynamic adaptability) necessitates integrating single-cell methylomics and longitudinal sampling to distinguish pathological signals from transient noise in S-AKI.

Limitation

Several critical limitations merit acknowledgment. First, although we discuss DNA methylation in immune, renal tubular, and endothelial cells, cell-type-specific methylation signatures and their functional roles in S-AKI

remain poorly characterized. This is primarily due to reliance on bulk cellular analyses rather than single-cell or subpopulation-level resolution-a shortcoming that hinders identification of nuanced epigenetic mechanisms driving pathogenesis and cell-specific regulatory networks. Second, while we highlight the potential of integrating methylomics with transcriptomics for patient stratification, current studies have underutilized multi-omics approaches to dissect interactions between DNA methylation, gene expression, and downstream pathways. This limits discovery of integrated biomarkers and subtype-specific therapies. Third, a key unaddressed caveat is the assumption that non-invasive biomarkers (e.g., urine, peripheral blood mononuclear cells) reflect renal epigenetics, despite evidence that peripheral blood rarely mirrors intrarenal microenvironmental changes. Renal biopsies offer direct tissue-specific insights into tubular, endothelial, and immune cell methylation but are invasive, necessitating studies to validate concordance between accessible biomarkers and renal tissue profiles. Additionally, the bidirectional nature of DNA methylation and its crosstalk with histone modifications introduce regulatory complexity, challenging translation of DNMT inhibitors due to context-dependent resistance and off-target effects on global methylation. Finally, despite the promise of dynamic methylation as temporal biomarkers, validated real-time monitoring tools are absent. Current retrospective, low-throughput, or invasive methods cannot inform timely interventions in critical care, limiting translation of epigenetic insights to clinical practice.

Conclusion

In summary, S-AKI remains a clinically complex condition associated with high morbidity and mortality, necessitating improved mechanistic understanding and innovative therapeutic strategies. DNA methylation, as a key epigenetic modifier, influences multiple pathogenic processes in S-AKI, encompassing host-pathogen interactions, inflammatory cascades, renal hemodynamic regulation, and cell-type-specific functions of renal tubular epithelial and vascular endothelial cells. The stage-dependent dynamic changes in DNA methylation patterns not only reflect underlying disease biology but also hold promise as biomarkers for early diagnosis and prognostic assessment. Future research should prioritize elucidating the cell-specific molecular mechanisms by which DNA methylation modulates S-AKI pathogenesis, including in-depth characterization of epigenetic regulation in key renal and immune cell populations. Additionally, the development of targeted therapies that modulate DNA methylation pathways-either alone or in combination with other epigenetic or immunotherapeutic approaches-represents a promising avenue for improving clinical outcomes. By addressing these scientific and translational gaps, we can harness the potential of DNA methylation research to develop more effective strategies for preventing, diagnosing, and treating S-AKI, ultimately reducing its global health burden.

Acknowledgements
None.

Author contributions
MQ and XJ did literature research and extracted the data. LL, SS, LN, and YY drafted the manuscript. LL designed the research and reviewed the manuscript. All authors reviewed the manuscript. All authors read and approved the final manuscript.

Funding
Zhejiang Province Medical and Health Technology Plan Project 2023KY1137.

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 25 March 2025 / Accepted: 13 May 2025
Published online: 22 May 2025

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