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REVIEW

Neutrophil Extracellular Traps in Sepsis and Sepsis-Related Organ Dysfunction

Wenbo Yan[1,2,*], Xiyuan Xu[2,*], Xiaojuan Li[1], Yushu Ma[1], Lining Guo[3,4], Jingping Yang[2], Zhipeng Jin[1], Jie Zhang[3–5], Tiewei Li[1]

[1]Department of Clinical Laboratory, Zhengzhou Key Laboratory of Children's Infection and Immunity, Henan Children's Hospital, Children's Hospital Affiliated to Zhengzhou University, Zhengzhou, Henan, People's Republic of China; [2]Department of Respiratory and Critical Care Medicine, Inner Mongolia Baogang Hospital, Baotou, Inner Mongolia, People's Republic of China; [3]Department of Otorhinolaryngology Head and Neck Surgery, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, Beijing, People's Republic of China; [4]Beijing Key Laboratory for Pediatric Diseases of Otolaryngology Head and Neck Surgery, Beijing, People's Republic of China; [5]Department of Otorhinolaryngology Head and Neck Surgery, Henan Children's Hospital, Children's Hospital Affiliated to Zhengzhou University, Zhengzhou, Henan, People's Republic of China

*These authors contributed equally to this work

Correspondence: Jie Zhang; Tiewei Li, Email stzhangj@263.net; litieweind@163.com

Abstract: Sepsis is a systemic inflammatory response triggered by infection, which can result in multiple organ dysfunctions, including disseminated intravascular coagulation (DIC) and acute lung injury (ALI), ultimately leading to patient mortality. The pathophysiology of sepsis is intricate, involving excessive immune activation, cytokine storms, endothelial damage, and microcirculatory dysfunction. Dysregulated host responses frequently give rise to severe complications, markedly elevating mortality rates. Neutrophil extracellular traps (NETs) are web-like structures consisting of DNA, histones, and granular proteins, released by neutrophils upon activation. Ongoing research into NETs has uncovered their significant pathophysiological roles in clinical conditions, including sepsis. This review outlines the mechanisms of NET formation, release, classification, detection methods, and relevant biomarkers. Additionally, it delves into the signaling pathways involved in NET generation, their pathophysiological implications in sepsis and its complications, and evaluates their potential utility in clinical laboratory diagnostics.

Keywords: sepsis, neutrophil extracellular trap, mechanism, biomarker, detection techniques

Introduction

Sepsis is a severe systemic inflammatory response syndrome typically triggered by infection. When infectious agents such as bacteria, viruses, or fungi enter the bloodstream and release toxins, the body mounts an excessive inflammatory response,[1] resulting in widespread tissue damage and organ dysfunction, including the lungs, heart, kidneys, and brain.[2] This systemic inflammation induces microthrombosis and can lead to complications such as disseminated intravascular coagulation (DIC), septic shock, and acute lung injury (ALI).[3] Recent data from 2025 indicate an overall mortality rate of 35% in the general population, with a significantly higher rate of 66% in high-risk groups.[4–6] Survivors often face long-term sequelae, including muscle atrophy, immune dysregulation, and the need for extended care.[7,8]

Neutrophils, as key players in the body's early defense against infection, play a critical role in sepsis. In addition to their functions of phagocytosis[9] and degranulation,[10] neutrophils were first recognized by Brinkmann et al in 2004 for their involvement in a novel immune mechanism, the formation of neutrophil extracellular traps (NETs).[11,12] NETs are a distinct form of cell death and have since become an established component of the innate immune response.[13] However, beyond their established role in immune defense, NETs may also contribute to organ damage and exacerbate disease through a spectrum of mechanisms, including cytotoxicity,[14] amplification of inflammatory responses,[15] and physical induction of thrombosis.[16] NETs contribute to various clinical conditions, including infectious diseases, autoimmune disorders, thrombotic conditions, and cancer.[2,17] During early infection, NETs trap pathogens through the release of histones[18] and DNA, which prevents pathogen spread, disrupts bacterial membranes, enhances antimicrobial defense, and

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supports immune and tissue homeostasis.[19–21] However, excessive NET release can exacerbate inflammatory responses. In sepsis, NETs interact with platelets to promote aggregation and thrombosis, which further contribute to DIC, septic shock,[22] and other complications.[11] Additionally, NETs compromise the integrity of alveolar epithelial cell junctions, leading to pulmonary edema and ALI.[23] There are several classification schemes for NETs, with two commonly accepted ones. One divides NETs into NOX-dependent and NOX-independent types, based on whether their formation relies on nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX) activity in the upstream signaling cascade.[24] Another classification, based on neutrophil morphological changes during NET formation, distinguishes suicidal NETs, vital NETs, and mitochondrial NETs.[25,26] Various detection methods for NETs are available, including immunofluorescence microscopy for DNA and ELISA for NET-associated proteases.[27]

This review summarizes the formation, release, and classification of NETs, along with the regulatory mechanisms and interactions among related signaling pathways.[28] It also evaluates laboratory detection methods and biomarkers for NETs, highlights their pathophysiological roles in thrombosis and multi-organ injury during sepsis, and discusses their potential clinical implications.

NETosis and Related Signaling Pathways

Neutrophils in the body are activated by various agents, such as bacteria, viruses, lipopolysaccharide (LPS), and granulocyte-macrophage colony-stimulating factor (GM-CSF), at specific time points, each triggering distinct pathways for NET production and release.[29] The time required for NET formation and release varies with the stimulus, and the NETs produced exhibit differing abilities to capture pathogens.[25] The process by which neutrophils generate and release NETs is referred to as NETosis.[30] NET formation pathways are broadly categorized into two types: NOX-dependent NETosis, which relies on NOX, and NOX-independent NETosis.[31,32] NETs primarily consist of fibrous networks made up of DNA, histones (H1, H2A, H2B, H3, and H4), and granzymes, such as myeloperoxidase (MPO) and neutrophil elastase (NE)[33,34] The NETosis process involves several signaling pathways, with the proteases and DNA components differing based on the specific pathway, as illustrated in Figure 1.

NOX-Dependent NETosis

NOX-dependent NETosis refers to pathways where reactive oxygen species (ROS) are generated through NOX activation (specifically NOX2) during NET formation, with a relatively extended formation period of approximately 2 to 4 hours.[35] Following neutrophil stimulation, such as by phorbol myristate acetate (PMA), the enzyme peptidylarginine deiminase 4 (PAD4) induces histone citrullination. This process is also accompanied by nuclear membrane rupture and DNA release, triggered by downstream signaling, including extracellular signal-regulated kinases (ERK), Ak strain transforming (Akt) kinases, and endogenous Ca^{2+} that activate NOX enzymes, catalyzing ROS production, including superoxide.[36] Ras-related C3 botulinum toxin substrate 2 (Rac2), a small GTPase, regulates NOX in NOX-dependent NETosis by activating NOX to promote ROS generation.[37] Subsequently, the generated ROS further promote the formation of NETs through a cascade of events, including activation of enzymes such as MPO and NE, disruption of membrane integrity, and stimulation of PAD4-mediated citH3.[38] Additionally, p47phox and p67phox, regulatory subunits of the NOX complex, are critical for its activation and function.[36,39] For instance, Pieterse et al[22] demonstrated that NOX-dependent NETosis leads to the cleavage of the N-terminal tails of core histones by NE, while Yoko et al[40] further confirmed that singlet oxygen, a type of ROS, plays a key role in NOX-dependent NETosis formation. In patients with chronic granulomatous disease (a congenital ROS deficiency), NET formation is impaired.[41] This NOX-dependent NETosis pathway is commonly observed in pathogen defense responses and is also implicated in autoimmune diseases.[42]

NOX-Independent NETosis

Unlike NOX-dependent NETosis, NOX-independent NETosis does not rely on ROS generated by NOX enzymes but is triggered through alternative mechanisms. This process results in the rapid synthesis and release of NETs, typically occurring within 15 to 60 minutes.[35] Due to its swift response, NOX-independent NETosis is often observed during the early stages of acute inflammation.[43] It involves the production of mitochondrial ROS,[44] calcium influx,[31] specific metabolic pathways such as lactate production via glycolysis,[45] and direct chemical stimuli, such as uric acid.[22,46] For

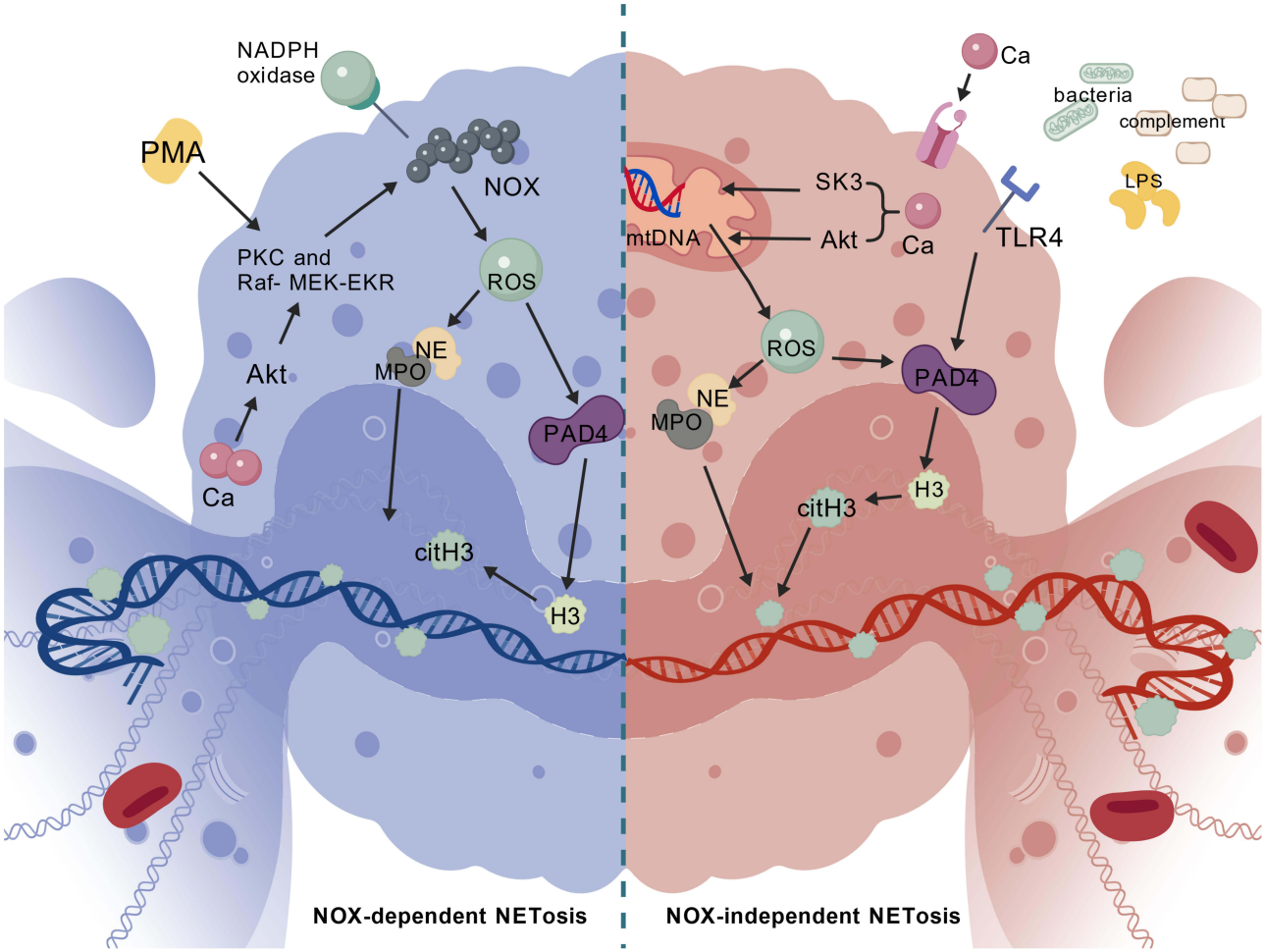

Figure 1 NETosis and associated signaling pathways. The formation mechanisms of NOX-dependent and NOX-independent NETs differ, although they share certain common pathways. The NOX-dependent pathway relies on NOX-mediated ROS production, Ca^{2+} influx, and the activation of Akt, PKC-MEK-ERK, and other signaling pathways. In contrast, NOX-independent NETosis involves Ca^{2+} influx that activates small conductance potassium 3 (SK3) and Akt signaling, leading to mitochondrial ROS production. This mitochondrial ROS generation triggers histone citrullination and NET formation. The activation and interaction of these signaling pathways are essential steps for neutrophils to respond to inflammatory signals and form NETs.

Abbreviations: Akt, Ak strain transforming; NETs, neutrophil extracellular traps; NOX, NADPH oxidase; ROS, active oxygen; SK3, small conductance potassium.

instance, Yutaka et al discovered that mitochondrial ROS plays a pivotal role in NOX-independent NETosis in cells with mitochondrial DNA deletion.[31] This finding is closely linked to autophagy studies, suggesting that autophagy, not only a regulatory mechanism for intracellular metabolism, may also be involved in NOX-independent NETosis.[47] Autophagosomes produced during autophagy can regulate intracellular ROS levels, thereby influencing NET formation.[48] However, Nina et al[49] found that NET formation does not depend on autophagy in human cells. Further research by Yasuyuki et al[46] revealed that high concentrations of uric acid can directly induce NETosis without activating NOX. Deepika et al[45] reported that lactate produced during glycolysis promotes NOX-independent NETosis. David et al[50] emphasized that calcium ion influx drives NET formation by activating mitochondrial ROS through the SK3 channel, independent of the ERK pathway. Moreover, Cristiane et al[44] demonstrated that shifts in local pH within inflammatory foci augment calcium influx and provoke the release of mitochondrial ROS. This mitochondrial ROS, in turn, serves as a key activator of PAD4, leading to chromatin citrullination and decondensation, thereby triggering NOX-independent NETosis.[51] This pathway is commonly observed in inflammatory diseases, such as dengue fever, where platelet activation and non-structural protein 1 (NS1) mediate NETosis.[52]

Currently, some researchers have isolated neutrophils from the peripheral blood of healthy donors and induced NET formation via high-dose ultraviolet (UV) light.[53] During this process, caspase-3 is activated in neutrophils exposed to UV,

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leading to mitochondrial ROS production and p38 phosphorylation.[54] Interestingly, UV-induced NET formation does not rely on histone citrullination[55] but occurs primarily through chromatin decondensation regulated at the transcriptional level. NETs induced by UV light may represent a distinct form of NOX-independent NETosis, but the detailed mechanism of their formation warrants further experimental investigation.

Cross-Sharing of the Two Generation Approaches

As depicted in Figure 1, the NETosis process involves multiple signaling pathways and substances, including DNA and proteases.[56] Between the two distinct NET formation pathways, several signaling elements are not independent but are instead mutually regulated and shared in various forms. These include: (1) ROS: ROS act not only as direct inducers of NET formation but also as critical components of the signaling cascade.[50] ROS generation initiates intracellular signal transduction and activates downstream transcription factors, thereby regulating NET formation.[57,58] For instance, ROS accumulation promotes histone citrullination, a key step in NET formation.[59] Moreover, ROS can facilitate NET release by impacting the integrity and dynamics of the cell membrane.[39] (2) Akt pathway: Inhibiting Akt activity with the MK-2206 inhibitor, David et al demonstrated that the synthesis of both types of NETosis was blocked. This further clarified that, despite differing activation levels of the Akt pathway during the synthesis of the two NETosis types, its activation is essential for both forms of NET generation.[50] (3) Glycolytic metabolism: Akt2 or calcium influx triggers lactate production, which either directly or indirectly activates pyruvate kinase muscle isozyme M2-lactate dehydrogenase (PKM2-LDH), driving NET formation through a series of cascade reactions.[45] (4) Histone citrullination: In NOX-dependent NETosis, ROS generated by NOX activation activate PAD4, catalyzing the conversion of arginine to citrulline residues on histone H3. In NOX-independent NETosis, calcium ion influx in an alkaline environment or ROS produced by mitochondria activate PAD4 to induce histone citrullination.[22,44] Since both types of NETosis involve the conversion of arginine to citrulline on histone H3, histone citrullination is regarded as a marker of NET formation.[34]

The Release of NETs

Building on the research regarding NET generation and signaling pathways (NOX-dependent and NOX-independent NETs), it is evident that the mechanisms of NET synthesis vary depending on the type of inducer involved.[60–62] Current evidence suggests that the phenotypic diversity of NETs stems from the activation of different upstream signaling cascades in neutrophils, triggered by various microenvironmental stimuli.[63] Notably, the downstream release process of NETs is not uniform,[63] and the remaining neutrophils exhibit distinct morphological changes post-release.[60] Some neutrophils die in a state between necrosis and apoptosis,[64] while others retain functional capabilities such as phagocytosis.[65] Based on these distinctions, NETs have been further classified into three categories: suicidal NETs, vital (also termed rapid or early) NETs, and mitochondrial NETs,[23] as illustrated in Figure 2.

Suicidal NETs

Suicidal NETosis is a NOX-dependent cell death process distinct from apoptosis and necrosis.[66] NOX-derived ROS activate NE and MPO, which translocate to the nucleus.[67] There, they collaborate with PAD4-mediated histone citrullination to drive chromatin decondensation.[68] Subsequent nuclear and plasma membrane rupture releases decondensed chromatin complexed with antimicrobial proteins over 2–4 hours, resulting in neutrophil lysis and functional loss.[69,70]

Vital NETs

Vital NETosis is TLR-mediated and involves PAD4 and calpain synergizing for nuclear envelope dissolution.[51,71] Calcium signaling can induce chromatin depolymerization independently of NOX.[51] NETs are expelled via nuclear budding or vesicles within 30 minutes to 2 hours, preserving plasma membrane integrity.[72,73] The resulting anucleated cytoplasts retain chemotactic and phagocytic capacities, enabling rapid pathogen containment during early infection.[72–75]

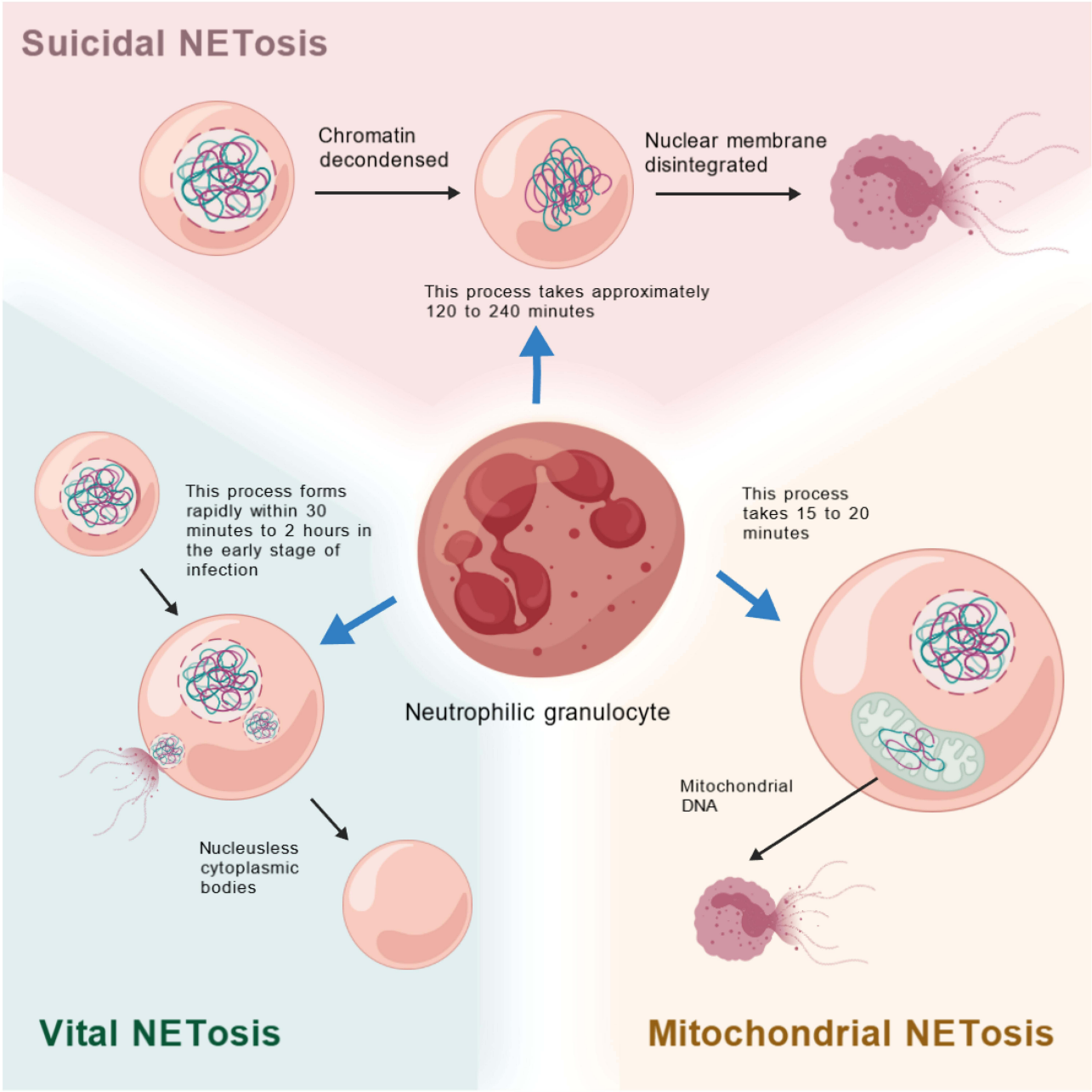

Figure 2 NET release and the three types of NETosis. The release mechanisms of suicidal, vital, and mitochondrial NETosis differ significantly. In suicidal NETosis, neutrophils are stimulated, leading to the disintegration of the nuclear membrane. Chromatin depolymerizes and combines with granular proteins, followed by cell membrane lysis, releasing NETs into the extracellular space. This process, which depends on NOX and ROS production, results in cell death and takes a relatively long time. In vital NETosis, neutrophils release chromatin and granular proteins via nuclear budding or vesicle-mediated blistering, without compromising cell membrane integrity. Despite losing their nucleus, neutrophils remain active. Mitochondrial NETosis likely involves mitochondrial DNA and mitochondria-derived ROS in the release mechanism.
Abbreviations: DNA, deoxyribonucleic acid; NETs, neutrophil extracellular traps; NOX, NADPH oxidase; ROS, active oxygen.

Mitochondrial NETs

Mitochondrial DNA-containing NETs (mtNETs), first described by Yousefi et al, consist of mitochondrial DNA released after GM-CSF priming and LPS/C5a stimulation.[29,76] Observed in ATC and post-trauma neutrophils, their ROS-dependent formation involves calcium-induced SK3 signaling, leading to mitochondrial permeability increase, swelling, and mtDNA release.[77–81] mtDNA-granule protein complexes are exported via vesicles or autophagy, with neutrophils remaining functional and release completing within 20 minutes.[82–84]

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Biomarkers and Detection Techniques Related to NETs

Laboratory biomarkers for detecting NETs can currently be categorized into two main types. The first type focuses on compositional analysis, measuring specific components such as nucleosomes, citH3, and MPO to indirectly assess NET formation. The second approach involves the direct visualization of NET structures through histological sectioning and fluorescence staining techniques combined with electron microscopy.[85] The second approach involves the direct visualization of NET structures through histological sectioning and fluorescence staining techniques combined with electron microscopy.[86]

Key Biomarker Characteristics, as Follows

(1) Nucleosomes/cfDNA/dsDNA: Nucleosomes, composed of histone octamers wrapped with 147 bp DNA, form the core scaffold of NETs.[87] During NETosis, chromatin depolymerization generates dsDNA fragments, which are the main source of cell-free DNA (cfDNA).[88,89] Elevated cfDNA levels thus closely reflect NET formation.
(2) CitH3: Generated by PAD4-mediated citrullination during NETosis, CitH3 promotes DNA binding and serves as a key chromatin component.[90] Its quantity in NETs correlates with sepsis severity, indicating prognostic value.[91]
(3) MPO and NE: MPO binds NET DNA to form MPO-DNA complexes,[92] while NE acts as a critical serine protease in neutrophil immunity.[93,94]
(4) Other Biomarkers: Glutathione peroxidase 3 (GPX3) synergizes with granular enzymes such as MPO and NE;[95] its overexpression can suppress NETosis and alleviate renal injury.[96] In transplant rejection, β2-microglobulin (B2M), CDK1, and MAP3K5 have emerged as novel NET biomarkers.[96]

Various detection techniques for NETs have been developed, with enzyme-linked immunosorbent assay (ELISA), flow cytometry, and fluorescent immunostaining being the most commonly employed laboratory methods. In tissues or cells, key biomarkers associated with NETs include double-stranded DNA (dsDNA), citH3, MPO, NE, NET-specific structures, and glutathione peroxidase 3 (GPX3). These biomarkers are primarily detected using advanced analytical techniques such as immunofluorescence microscopy[97] and Western blot analysis.[98] Imaging-based approaches utilize fluorescent DNA dyes (eg, Sytox Green) combined with MPO/NE immunofluorescence staining, allowing for direct visualization of NET structures via electron microscopy.[99,100] Imaging-based approaches utilize fluorescent DNA dyes (eg, Sytox Green) combined with MPO/NE immunofluorescence staining, allowing for direct visualization of NET structures via electron microscopy.[99–101] In peripheral blood, bronchoalveolar lavage fluid, or cerebrospinal fluid, circulating NET biomarkers include cfDNA, dsDNA, nucleosomes, MPO-DNA complexes, citH3, NE, and GPX3. These biomarkers are quantitatively measured using ELISA,[102] flow cytometry,[63] and quantitative real-time polymerase chain reaction (qPCR).[103] Notably, the assessment of MPO and NE level through ELISA provides indirect evidence of NET formation.[104] Despite significant advancements in NET detection technologies, several critical limitations remain. The primary challenge is the lack of standardized protocols, resulting in substantial variation in operational procedures and interpretation criteria across different studies.[100] Current methodologies are limited by their inability to provide real-time in vivo monitoring of NET dynamics, necessitating the reliance on static tissue sections or ex vivo sample analyses.[100] Additionally, the specificity of serum and plasma biomarkers, such as cfDNA, is questioned due to potential confounding factors from apoptotic or necrotic cellular processes. No single biomarker currently serves as a definitive indicator of NET formation. Emerging evidence indicates that multiplex biomarker detection significantly improves the specificity for NET identification. In this context, the colocalization of citH3+ and MPO+ has become the gold standard for NET verification.[105] However, while promising markers such as citH3 have shown utility in animal models and in vitro systems, their clinical validation remains incomplete, with additional constraints related to technical challenges and cost considerations. While current technologies have enhanced our ability to quantify enzyme activity and characterize molecular markers, significant challenges persist in methodological standardization, in vivo application, and clinical translation.

NETs are Involved in the Pathological Mechanism of Sepsis

The Formation of NETs in Sepsis

NETs often exhibit dual roles in the pathophysiology of diseases. On one hand, their unique fibrous network structure enables NETs to physically trap and eliminate pathogenic microorganisms.[20] Components such as citH3, MPO, and NE

within NETs also contribute to their bactericidal effects.[21] On the other hand, excessive NET release exacerbates inflammation-induced tissue damage.[106] Anurag et al[91] found that NOX-independent NETs exert a stronger pro-inflammatory effect compared to NOX-dependent NETs.

Recent studies examining NET-related markers in pediatric sepsis provide compelling evidence for NETs' involvement in the disease's pathophysiology. Quantitative analysis of plasma biomarkers (cfDNA, nucleosomes, NE, and citH3) alongside C-reactive protein (CRP) in children with early-onset and late-onset sepsis showed significantly elevated cfDNA levels in both patient groups.[104] These findings support cfDNA as a reliable marker for NETs formation and degradation during sepsis.[104] Serological analyses further demonstrated significantly higher concentrations of MPO-DNA complexes in patients with sepsis compared to healthy controls.[107] Although these results confirm NETs formation during early sepsis, they do not elucidate their functional role in disease progression. A more comprehensive study by Shuofei et al[108] quantified NETs biomarkers in three cohorts: 52 ICU patients with sepsis, 10 ICU patients without sepsis, and 40 healthy controls. Their analysis revealed markedly elevated levels of NET-specific markers (cfDNA, MPO-DNA, and NE) in patients with sepsis compared to both control groups.[108] Notably, plasma and platelet fractions from patients with sepsis were shown to stimulate enhanced NETs release from healthy neutrophils ex vivo.[108] These findings strongly implicate NETs as active contributors to the pathophysiological cascade of sepsis. Traditionally, the scientific community has emphasized NOX-dependent mechanisms in NETs generation. However, groundbreaking research by Elmar et al[22] has challenged this view. Their antibody-based detection of N-terminal histone tails in patients with sepsis conclusively demonstrated that NET formation in sepsis predominantly occurs via NOX-independent pathways.

Sofie et al[109] conducted a study in which 22 healthy volunteers were randomly injected with either LPS or normal saline to simulate the early inflammatory response of sepsis. Plasma samples were subsequently collected and analyzed using ELISA and flow cytometry.[109] Flow cytometry results revealed that citH3 could bind to the surface of microvesicles (MVs).[109] These MVs primarily expressed neutrophil markers (CD66b and MPO), with some also expressing platelet markers (CD42a).[109] The interaction between citH3 and MVs suggests a connection between platelets, neutrophils, and NETs.[109] Existing research indicates that platelet binding to neutrophils occurs as follows: platelets release chemokines and other factors to recruit neutrophils to the inflammatory site.[110,111] Platelets selectively adhere to neutrophil surfaces, forming platelet–neutrophil complexes (PNCs).[112] These complexes enhance the interaction of adhesion molecules (eg, integrin αIIbβ3 and CD11b/CD18), thereby accelerating neutrophil migration to the infected site and enhancing their pathogen-killing ability.[112–114]

Additionally, pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) bind to pattern recognition receptors (PRRs), triggering the release of inflammatory factors such as C-X-C motif chemokine receptor 2 (CXCR2).[115,116] Activated inflammatory factors bind to G protein-coupled receptors on neutrophil surfaces, leading to neutrophil recruitment.[117] PAMPs also interact with PRRs, such as TLRs on neutrophil surfaces, which stimulate the release of inflammatory mediators and NETs. The released NETs, along with PAMPs and other inflammatory mediators, further stimulate neutrophils, creating a cycle of excessive NET formation. This process exacerbates the inflammatory response, resulting in tissue damage[50] and regulatory imbalance, which amplifies the inflammatory response.[118] The pathological mechanism through which platelets and DAMPs promote NET formation in sepsis and contribute to related clinical complications is illustrated in Figure 3.

The pathways through which PNCs release NETs are as follows:

(1) P-selectin on platelet surfaces binds to PSGL-1 on neutrophils, stimulating the release of ROS, MPO, NE, and other factors from neutrophils.[110] Platelets also release high mobility group box 1 protein (HMGB1) and C3a, further enhancing neutrophil activity and promoting NET synthesis and release.[119]
(2) TLR4 on platelets detects TLR4 ligands in the blood, inducing platelet binding to adherent neutrophils and mediating increased NET release by polymorphonuclear neutrophils (PMNs).[24,120]
(3) Platelet-derived transforming growth factor-beta (TGF-β)[121] enhances neutrophil retention in organs such as the lungs and liver by regulating NET formation. However, this pathway amplifies the inflammatory response[122] and is often considered an aberrant activation mechanism for neutrophils.[112]
(4) Stimulation by LPS or DAMPs activates TLR4, triggering NET release via downstream signaling pathways, including the Raf-MEK-ERK pathway.[123]

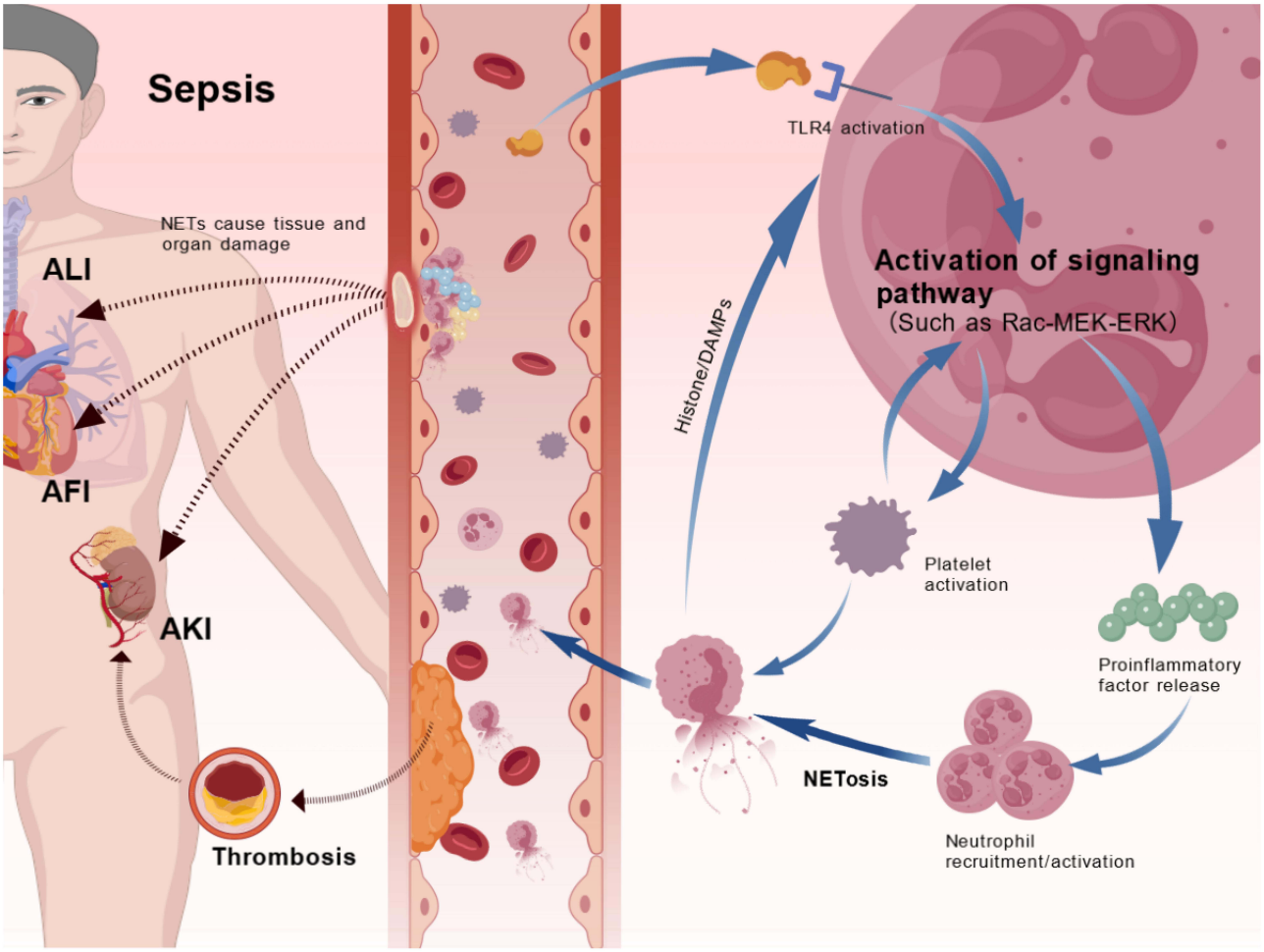

Figure 3 Pathological mechanism involving NETs. Activated TLR4 receptors on neutrophils mediate the release of inflammatory factors through the Rac-MEK-ERK signaling pathway, which also promotes neutrophil aggregation. Subsequently, neutrophils produce and release NETs. Additionally, activated platelets can further stimulate NET formation. Once formed, NETs activate neutrophils and amplify the inflammatory response. NETs can accumulate in microvessels, tissues, and organs. CitH3, a component of NETs, exerts cytotoxic effects on endothelial cells, and other enzymes and components of NETs contribute to these effects. These factors may lead to multiple organ damage, including thrombosis, ALI, AKI, and AFI.

Abbreviations: ALI, acute lung injury; AKI, acute kidney injury; AMI, acute myocardial injury; citH3: NETs, neutrophil extracellular traps; TLR4, toll-like receptor4.

NETs are Involved in Sepsis-Induced Thrombosis Formation

The synthesis and release of NETs lead to their binding with platelets, triggering the release of procoagulant factors. NETs also activate the extrinsic coagulation pathway by exposing tissue factor (TF) and inhibit the anticoagulation system, such as downregulating thrommoregulatory protein (TM), resulting in a systemic hypercoagulable state.[110,124] Platelet–NET complexes accumulate in microvessels, further damaging endothelial cells through obstruction and local inflammation, which includes complement activation and ROS release. This exposure of subendothelial collagen recruits additional platelets and neutrophils, perpetuating a vicious cycle.[121,125] Additionally, citH3 in NETs directly activates platelets and coagulation factor XII, thereby initiating the intrinsic coagulation pathway.[126] Histones also exert cytotoxic effects, exacerbating endothelial cell damage. PNCs further promote the synthesis and release of NETs, which act as scaffolds for thrombosis by recruiting red blood cells, von Willebrand factor (VWF), and fibrin, thus enhancing the positive feedback loop in coagulation and thrombosis formation.[111] P-selectin expressed on activated platelets binds to histones or DNA in NETs, while integrin αIIbβ3 adheres to the fibrous structure of NETs by binding to fibrinogen or VWF, stabilizing the platelet–NET complex.[114,127] In summary, NETs and platelets activate both extrinsic and intrinsic coagulation pathways and promote vascular endothelial cell injury through multiple mechanisms. These processes

culminate in microthrombi formation across various organs, depletion of coagulation factors, and the clinical manifestation of DIC, characterized by widespread hemorrhage and organ failure.

NETs are Involved in Sepsis-Associated ALI

Mengdi et al[128] found that levels of MPO-DNA and cf-DNA were significantly elevated in serological tests of adult patients with sepsis-associated ALI. Following induction with PMA, neutrophils from these patients exhibited an enhanced ability to generate NETs, providing evidence that NETs contribute to ALI induced by sepsis.[128] Sepsis pathogens activate the Raf-MEK-ERK pathway through TLR4 stimulation, promoting the release of inflammatory factors, which further recruit and activate neutrophils. These activated neutrophils release NETs within pulmonary microvessels. The DNA backbone and toxic components, such as citH3 and MPO, directly damage alveolar epithelial and endothelial cells, increasing vascular permeability, promoting microthrombi formation, and leading to pulmonary edema,[129] which exacerbates ALI. Additionally, TLR4 on platelets binds to TLR4 ligands, inducing PMNs to release more NETs.[24,120] The retention of PNCs in pulmonary capillaries facilitates fibrin deposition, triggering microthrombi formation, causing local ischemia, and worsening lung injury.[121,127] Histones and proteases in NETs damage the alveolar-capillary barrier, aggravating pulmonary edema and oxygenation deficits.[76] NETs further impair pulmonary microcirculation by activating platelets to form microthrombi.[130] Mitochondrial DNA (mtDNA) in NETs activates macrophages via the TLR9/STING pathway, resulting in the release of pro-inflammatory factors, such as interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α), which amplify inflammation and immune imbalance, thereby worsening lung injury.[131,132] In the mouse cecal ligation and puncture (CLP) sepsis model, deletion of programmed death-ligand 1 (PD-L1) significantly reduced neutrophil infiltration into the lungs and lung injury.[133] It also lowered plasma levels of pro-inflammatory factors like TNF-α and IL-6, while increasing the anti-inflammatory cytokine IL-10, leading to improved pathology.[133] Meanwhile, inhibiting PD-L1 function (eg, by blocking the PI3K/Akt pathway with anti-PD-L1 antibodies) accelerated neutrophil apoptosis, reduced lung tissue damage, and alleviated the inflammatory burden.[134] NETs contribute to ALI development in sepsis through immune thrombosis, inflammatory factor activation, disruption of signaling pathways, and endothelial injury.[135–137] Clinical data show that increased NETs and platelet aggregation markers correlate with the severity of ALI. Inhibiting NET formation or employing antiplatelet therapies (eg, $P2Y_{12}$ inhibitors) alleviates lung injury. Moreover, clinical trials have demonstrated that antiplatelet drugs, such as bellaprost, reduce the incidence of sepsis-ALI and ICU admissions.[138,139]

NETs are Involved in Sepsis-Associated Acute Myocardial Injury (SA-AMI)

Emerging evidence highlights the pivotal role of NETs in the pathogenesis of SA-AMI. Clinical studies consistently reveal elevated plasma NET levels in both pediatric and adult patients with sepsis,[140–142] with a significant correlation between NET concentrations and the severity of myocardial injury.[141,143] The harmful effects of NETs on myocardial tissue are mediated through several mechanisms:

(1) Prothrombotic Effects: NETs promote microvascular thrombosis by releasing histones and DNA, which activate coagulation factor XII, inducing platelet aggregation and fibrin deposition.[108] This exacerbates myocardial ischemic injury in sepsis.[144,145]
(2) Direct Cardiomyocyte Injury: CitH3 directly damages endothelial cells, increases myocardial permeability, and triggers cardiomyocyte apoptosis via TLR4/9-mediated pathways, leading to the release of cardiac enzymes.[141,143]
(3) Structural and Functional Impairment: In LPS-induced septic rat models, myocardial NET deposition correlates with significant structural damage and functional deterioration of cardiomyocytes.[143]
(4) Mitochondrial Dysfunction: NETs stimulate neutrophil-derived ROS production, reducing mitochondrial membrane potential and impairing ATP synthesis in cardiomyocytes.[146] Notably, ROS levels correlate positively with established markers of myocardial injury.[145]

The pathophysiological effects of NETs on myocardial conduction heterogeneity in sepsis are mediated by two key mechanisms: (1) Myocardial Fibrosis: NETs promote interstitial fibrosis and the formation of fibrous foci in myocardial

tissue.[143] PAD4-mediated histone citrullination induces atrial fibrosis and conduction heterogeneity.[145] (2) Ion Channel Dysfunction: Histones inhibit potassium channel activity, leading to prolonged action potential duration.[143] These alterations manifest clinically as a significantly increased risk of new-onset atrial fibrillation (NOAF) in patients with sepsis.[143] Cumulatively, the evidence highlights NETs as critical mediators of sepsis-induced cardiac dysfunction, suggesting potential therapeutic targets for mitigating SA-AMI.

NETs are Involved in Sepsis-Associated Acute Kidney Injury (SA-AKI)

The pathogenesis of SA-AKI involves a key mechanism centered around the lactate-HMGB1-NETs axis. Lactate induces the lactylation of HMGB1, which subsequently triggers NETosis, leading to renal tubular damage and oxidative stress.[147,148] Mechanistically, macrophages release lactylated HMGB1 via exosomes, activating neutrophils to release mitochondrial DNA and promoting NET formation.[148] Clinical studies of peripheral blood from patients with SA-AKI showed that NET formation and oxidative stress responses were linked to the downregulation of epithelial cell transforming 2 (ECT2) and chordin-like 1 (CHRDL1) gene expression, as well as the upregulation of platelet-activating factor receptor (PTAFR), colony stimulating factor 3 (CSF3), and FBJ murine osteosarcoma viral oncogene homolog (FOS) gene expression.[149] A 28-day follow-up study by Jian et al[150] involving 136 patients with SA-AKI revealed that non-survivors exhibited significantly higher plasma NET markers compared to survivors, with these markers correlating positively with inflammatory indicators. Moreover, Jonas et al demonstrated in a prospective study of 601 patients with sepsis that elevated plasma levels of heparin-binding protein (HBP) were significantly associated with an increased risk of AKI development.[151] Interestingly, a study of severely burned patients during the shock phase found that increased plasma HBP concentrations were associated with decreased NET release from neutrophils.[152] However, whether HBP, as a neutrophil chemotactic factor, functionally contributes to NET generation and release during sepsis remains unclear and warrants further investigation.

NETs are Involved in Sepsis-Associated Other Organ Damage

Laboratory analysis of patients with sepsis revealed markedly elevated plasma levels of cfDNA and histones, which showed significant positive correlations with hepatic injury markers such as alanine aminotransferase (ALT) and aspartate aminotransferase (AST). These findings suggest that NETs play an active role in sepsis-induced liver injury.[108,141] Mechanistic studies demonstrate that NETs contribute to hepatocyte damage through multiple pathways: (1) Released histones (H3 and H4) compromise plasma membrane integrity, induce oxidative stress, and disrupt mitochondrial function, ultimately triggering apoptotic or necrotic cell death;[141,145] (2) NETs activate platelets and facilitate the binding of coagulation factors, accelerating thrombin generation. Concurrently, histones inhibit protein C anticoagulant pathways, exacerbating coagulopathy and promoting microthrombus formation, which induces localized ischemia and hypoxia, further aggravating parenchymal injury;[108,153] (3) NET-associated proteases, particularly NE and MPO, activate Kupffer cells within the hepatic sinusoids, promoting the release of pro-inflammatory cytokines such as IL-1β and TNF-α, amplifying the inflammatory cascade and exacerbating tissue damage.[141,145]

In sepsis-associated brain injury, NETs contribute to neural dysfunction through dual mechanisms of inflammatory activation and coagulation cascade induction. Specifically, NETs exacerbate endothelial injury and disrupt blood-brain barrier integrity, promoting cerebral microvascular thrombosis.[145] Clinical evidence indicates that NETs enhance the hypercoagulable state in sepsis, with elevated plasma NET levels significantly correlating with thromboembolic events in patients with sepsis.[108] At the molecular level, NET formation upregulates pro-thrombotic and pro-inflammatory gene expression profiles. The subsequent release of inflammatory mediators traverses the compromised blood-brain barrier, activating microglia and leading to neuronal damage.[143,145]

Targeting NETosis in Sepsis: Therapeutic Strategies and Challenges

Recent studies have highlighted the critical role of NETs in exacerbating organ damage during sepsis. Concurrently, emerging evidence suggests that inhibiting NETosis to reduce NETs has emerged as a novel therapeutic strategy for sepsis, with the potential to mitigate multiple organ injury. The principal advantage of this approach lies in its direct intervention in NETosis, effectively lowering NETs levels and thereby attenuating inflammatory responses, thrombus

formation, and organ dysfunction. For instance, in a neonatal sepsis model, treatment with recombinant human DNase (rhDNase) reduced plasma NET concentrations and ameliorated organ injury.[141] In a neonatal mouse model of infectious peritonitis, DNase I directly degraded the DNA backbone of NETs, diminishing NET levels and inflammatory response.[154] Moreover, DNase I interfered with NETosis, thereby improving the hypercoagulable state and reducing thrombosis, which contributed to the alleviation of sepsis-associated atrial fibrillation.[108,143] Denorme et al[154] demonstrated that the neonatal NET-Inhibitory Factor (nNIF), an endogenous inhibitor of NET formation, directly blocked NET generation, decreased inflammatory cytokine levels, and improved survival in a translational model of neonatal infectious peritonitis. Beyond directly targeting NETosis, another strategy involves inhibiting the activity of PAD4, which suppresses histone citrullination and indirectly blocks NET synthesis and release. For example, in both infant and neonatal sepsis models, administration of PAD4 inhibitors significantly reduced NET formation and enhanced survival rates.[141,154] Additionally, Shirakawa et al[155] reported that hydrogen gas (H2) therapy directly inhibited PAD4, leading to decreased NET levels. Independently of PAD4 activity, Fang et al[135] showed that blocking macrophage-1 antigen (Mac-1) in an LPS-induced sepsis model suppressed direct contact between neutrophils and vascular endothelial cells, indirectly reducing NET formation.

However, targeting NETs presents several challenges. Although numerous studies suggest that excessive NET release exacerbates systemic inflammation and organ injury, NETs also serve as a crucial mechanism of neutrophil-mediated immune defense, particularly in early sepsis. Excessive inhibition of NETosis may therefore compromise antimicrobial immunity and increase infection risk.[144,145] Future investigations into NETs-targeting therapies should address this dual role. Furthermore, given the complex pathophysiology of sepsis and the indirect relationship between NETs and disease progression, monotherapy targeting NETs alone may be insufficient to fully resolve sepsis-induced damage.[108] A comprehensive therapeutic regimen, potentially combining NETs-targeting agents with antibiotics, may be necessary to form an integrated diagnostic and treatment framework.[156]

Potential Clinical Applications of Biomarkers of Nets in Sepsis

When sepsis occurs, tissue cells throughout the body are damaged, leading to the activation and death of immune cells, which results in the release of significant amounts of DNA into the bloodstream, forming cfDNA.[119] CfDNA levels notably increase at the early onset of sepsis in patients.[157] However, cfDNA can originate from various sources, including apoptotic cells, mitochondrial DNA, bacterial DNA, and others. It remains unclear whether cfDNA detected in the blood of patients with sepsis primarily originates from neutrophils or is associated with NETs. To investigate this, Nicholas et al[158] found in a study of 49 patients with sepsis that the plasma concentration of cfDNA was significantly positively correlated with MPO levels. Additionally, citH3 levels were significantly higher compared to the control group.[158] These findings suggest that the cfDNA detected in the serum of patients with sepsis primarily originates from NETs formed during NETosis.[158] Supporting this, Joshua's research on 14 patients with sepsis showed that cfDNA in 13 patients mainly came from neutrophils, although some patients had cfDNA derived from liver cells.[159] Further methylation profiling of cfDNA revealed that it not only serves as a diagnostic marker for sepsis but also reflects organ damage caused by the condition.

Currently, studies on the use of citH3 for the early diagnosis of sepsis are limited. However, existing research highlights its diagnostic potential in other infectious diseases. CitH3 may serve as a biomarker for clinical diagnosis when combined with other detection indicators. Among patients with sepsis, MPO-DNA levels showed significant correlations with inflammatory markers like PCT and CRP, as well as coagulation function indicators such as prothrombin time-international normalized ratio (PT-INR), further reflecting the dual role of NETs in systemic inflammation and coagulopathy.[160] The specific NET marker MPO-DNA was significantly elevated in the early stages (days 1, 3, and 7) of septic shock and can be detected by ELISA, providing evidence that MPO-DNA may serve as a diagnostic biomarker for sepsis.[161] MPO-DNA levels were significantly correlated with mortality rates on days 3, 7, and 28. They were also strongly associated with organ function impairment: MPO-DNA levels were negatively correlated with mean arterial pressure and PaO_2/FiO_2 ratio, and positively correlated with the SOFA score.[138] Moreover, neutrophil-derived exosomes, such as those containing MMP9, promote excessive NET formation, and their plasma levels are independently linked to the severity of sepsis and poor prognosis.[162]

A single biomarker is insufficient for the diagnosis of sepsis, as exclusive reliance on one marker increases the risk of false-positive results. Conditions such as trauma, surgery, ischemia-reperfusion injury, autoimmune diseases like rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE), atherosclerosis, and others can also trigger the release of NETs.[162–164] Therefore, detecting a single NET marker cannot reliably distinguish sepsis from these other conditions. Additionally, due to the multifaceted pathophysiology of sepsis, which involves inflammation, immune response, coagulation, and microcirculatory disturbances, measuring NETs alone does not fully reflect the complexity of the condition. NETs may represent only one aspect of sepsis' pathophysiological cascade. A combined measurement of multiple biomarkers provides more accurate clinical diagnostic support. For example, the simultaneous detection of inflammatory markers like MPO-DNA complexes and CRP offers a more comprehensive view of the abnormal inflammatory responses and coagulation dysfunctions that extend beyond sepsis. Moreover, cfDNA combined with CRP can serve as valuable biomarkers for assessing the severity of sepsis and is particularly useful in differentiating complex bloodstream infections from milder forms.[165] Additionally, citH3 and MPO co-localization staining has been employed to identify coronary thrombosis distribution in patients with ST-segment elevation myocardial infarction (STEMI).[105]

As discussed in Biomarkers and Detection Techniques Related to NETs, although a variety of biomarkers are available for NET detection, cfDNA, citH3, and MPO-DNA complexes are among the most frequently utilized diagnostic biomarkers in clinical settings. However, current clinical research predominantly compares patients with sepsis to healthy controls, without adequately addressing the distinction between septic and non-septic individuals within the same complication context. For example, in studies of ALI, most experimental designs have focused on comparing sepsis-induced ALI with healthy individuals, with a notable scarcity of studies comparing sepsis-induced ALI with non-sepsis-induced ALI. Thus, the reliability of these biomarkers in differentiating between these two distinct ALI etiologies remains uncertain and warrants further rigorous investigation. As shown in Table 1, NETs, as emerging biomarkers, hold substantial clinical potential in research on sepsis and its complications.

Table 1 Clinical Research of NET-Mediated Pathogenesis in Sepsis Complications (2019–2025)

Clinical Diagnosis	Cohort	Analysis of	Key Biomarkers of NETs	Detection Technology	Significance	Reference & Author
Sepsis (Organ damage is not specified)	Pediatric patients with sepsis and adult patients with sepsis	Plasma of patients	cf-DNA and citH3	ELISA	Plasma NET concentrations in children with sepsis were significantly higher than in adults.	Colon DF et al and 2019[141]
	Sepsis group, non-sepsis group and healthy people	Blood	NETs, CD66b, CD11b and CD177	Flow cytometry, Fluorescence microscopy	Patients with sepsis consistently show neutrophil phenotypic activation (upregulation of CD markers) and functional suppression (decreased NET formation) in clinical settings	Mulet, M et al and 2023[142]
	Patients with septic shock and healthy controls	Plasma of patients	dsDNA, MPO-DNA complexes	_____	NET levels are positively correlated with disease severity	Jiao, Y et al and 2020[166]
SA-ALI (ARDS)	Patients with ARDS in the ICU	Human neutrophils and biopsy samples ofthe patient's lung tissue (or autopsysamples)	cf-DNA, MPO-DNA and citH3	ELISA, DNA quantitative analysis, immunofluorescence microscopy (citH3/ MPO double staining)	In patients with ARDS, serum cf-DNA and MPO-DNA levels exceed those in healthy controls and correlate with severity. Lung biopsies reveal abundant CitH3-positiveNETs with neutrophil markers.	Qu M et al and 2022[128]
	Patients with ARDS and healthy controls	Human plasma andneutrophils	GGPPS, mRNA, GGPPS protein, dsDNA	qRT-PCR, Western blot, respectively.	In circulating neutrophils of patients with ARDS. GGPPS protein expression levels were significantly lower than in healthy controls, while plasma dsDNA concentrations were significantly increased.	Li L et al and 2025[167]
	Patients with ARDS and healthy controls	Human plasma and neutrophils	CitH3 and NETs	Western blotand Flow cytometry	NET formation was significantly reduced or absent in certain cases	Fang J et al and 2025[135]

(*Continued*)

Table 1 (Continued).

Clinical Diagnosis	Cohort	Analysis of	Key Biomarkers of NETs	Detection Technology	Significance	Reference & Author
Sepsis-DIC and Thrombosis	Confirmed, suspected and non-septic individuals in the ICU	Plasma samples were collectedintermittently	H3.1 Nucleosomeconcentration	ELISA	The H3.1 nucleosome concentration was highest in the sepsis group, followed by the unconfirmed sepsis group and the non-sepsis group.	Filippini et al and 2025[168]
	Patients with DIC and healthy controls	Human plasma	ZPI and NE	ELISA and Western blot	The mean plasma ZPI antigen concentration in patients with septic shock was 2.5 times higher than in healthy controls, suggesting that inflammation may inactivate ZPI, affecting coagulation and thrombosis through NETs.	Bianchini EP et al and 2022[169]
	Patients with sepsis	Patient plasma	IL-8	ELISA	NET formation driven by CXCR1/2 signaling is a therapeutic target in sepsis	Alsabani M et al and 2022[116]
	Patients with sepsis	Plasma samples were collectedintermittently	MPO-DNA, citH3-DNA, PAD4/PAD2 antigen, VWF antigen, etc	ELISA	NET levels were positively correlated with PAD4 and PAD2 levels, supporting the role NET formation.	Martens CP et al and 2023[170]
	Patients with sepsis in the ICU	Patient plasma	NETs, cfDNA, MPO, MPO-DNA complex	Semi-quantitative Detection, fluorescent staining, and ELISA	This is the first demonstration that NET formation ability at admission in critically ill patients is an independent predictor of DIC and mortality, providing experimental evidence for individualized treatment targeting the NET pathway.	Abrams ST et al and 2019[171]
SA-AKI	A total of 136 patients with AKI were divided into 76 survivors and 60 non-survivors.	Human plasma and serum	(citH3, NE-DNA, MPO-DNA complex) and (IL-6, IL-10, TNF-α)	_____	Plasma NET markers predict 28-day survival in patients with SAKI, possibly due to NET-related inflammation.	He J et al and 2024[150]
	Patients with SA-AKI and healthy controls	Patient serum	MPO-DNA Complex, Fn14 protein	ELISA	Serum Fn14 concentrations in patients were significantly increased and positively correlated with NETlevels, confirming the coexistence of FN14 and NETs in the pathological process.	Ni Y et al and 2021[172]
	Confirmed, suspected and non-septic individuals in the ICU	Plasma samples were collected intermittently	H3.1 Nucleosomeconcentration	ELISA	H3.1 concentrations were positively correlated with SOFA scores, indicating that higher concentrations are associated with more severe organ dysfunction. H3.1 concentration was significantly elevated in patients with AKI.	Filippini et al and 2025[168]
	Patients with SA-AKI and healthy controls	Venous blood	Blood lactate levels and HMGB1protein levels	ELISA and Western blot	Blood lactate levels in the SAKI group were significantly higher than in healthy controls, showing significant lactate accumulation.	Wei S et al and 2025[148]
	Patients with ADHF	Arterial blood	L-lactate	Arterial blood gas analysis	In patients with ADHF, higher lactate concentrations were significantly Positively correlated with the risk of AKI	Zhu L et al and 2024[147]
Sepsis-Liver dysfunction	Sepsis without liver injury group, liver injury group, non-sepsis group, healthy control group	Peripheral blood plasma of thepatient	cfDNA and NETs	PicoGreen fluorescence quantitative detection method, immunofluorescence staining method	WBC, PMN count, and cf-DNA /NET levels in the sepsis group (including those with and without liver injury) were significantly higher than in healthy controls and the non-sepsis group.	Gao F et al and 2019[173]
	Decompensated cirrhosis group, sepsis group, non-sepsis group, healthy control group	Plasma and whole blood cells	cfDNA	Flow cytometry and Q-pcr	Neutrophil dysfunction is associated with specific protein expressionchanges in sepsis individuals withdecompensated cirrhosis.	Sehgal R et al and 2022[174]

(*Continued*)

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Table 1 (Continued).

Clinical Diagnosis	Cohort	Analysis of	Key Biomarkers of NETs	Detection Technology	Significance	Reference & Author
Sepsis-SAE	Patients with sepsis	Human neutrophils	PD-L1 protein and GSDMD protein		PD-L1 and GSDMD are highly expressed in neutrophils from patients with sepsis, potentially contributing to the regulation of NET release via the PD-L1/STAT3/ GSDMD signaling axis.	Zhu CL et al and 2023[175]

Abbreviations: ADAMTS13, Metalloprotease that cleaves multimers of von willebrand factor; ADHF, Acute decompensated heart failure; AKI, Acute kidney injury; ARDS, acute respiratory distress syndrome; GGPPS, Geranyl diphosphate synthetase; GSDMD, Gasdermin D; Mac-1, Macrophage-1 antigen; SAE, Sepsis-associated encephalopathy; ZPI, Protein Z-dependent protease inhibitors.

Conclusion

Sepsis is a complex clinical syndrome, and research on NETs has highlighted their pivotal role in host immune responses and pathophysiological processes. NETs are fibrous DNA structures released by activated neutrophils, capable of capturing and eliminating pathogens. However, excessive NET release can lead to host tissue damage. In the context of sepsis, the relationship between NET formation and clinical complications is intricate. While NETs help contain infections, their overproduction can contribute to intravascular coagulation, thrombosis, DIC, ARDS (ALI), and multiple organ dysfunction. The excessive formation and release of NETs correlate closely with disease severity and poor prognosis. Recent advances in detection technology have enhanced our ability to assess NETs' presence and activity, offering new insights into both basic research and clinical diagnostics. For instance, NET formation can be indirectly evaluated by measuring plasma cfDNA levels and specific NET-associated proteins such as MPO, citH3, and NE. Clinical investigations have shown that the serum NET levels in pediatric patients with sepsis are significantly higher than in adult patients and healthy controls, suggesting an increased NET production in children with sepsis. Moreover, the level of NETs was found to correlate positively with the severity of sepsis in pediatric patients.[141]

Future research must further elucidate the mechanisms of NETosis in sepsis and develop therapies that balance the antimicrobial benefits of NET formation with the prevention of tissue damage. Establishing age-specific diagnostic criteria, particularly for pediatric populations, and optimizing rapid detection methods are critical for timely intervention. Standardizing NET quantification would enhance diagnostic accuracy. These advancements collectively offer: (1) A critical temporal window for life-saving interventions and (2) A foundation for personalized therapeutic approaches. The implementation of standardized NET assessment protocols could transform diagnostic practices, providing both prognostic value and therapeutic guidance in sepsis management.

Abbreviations

AST, aspartate aminotransferase; Akt, Ak strain transforming; AKI, acute kidney injury; ALT, alanine aminotransferase; ALI, acute lung injury; ATC, anaplastic thyroid carcinoma; AMI, acute myocardial injury; B2M, beta-2-Microglobulin; cfDNA, free deoxyribonucleic acid; citH3, histone H3 subunit citrullinated; CR3, complement receptor3; CDK1, cyclin-dependent kinase1; CRP, C-reactive protein; CXCR, C-X-C motif chemokine receptor; CLP, cecal ligation and puncture; CHRDL1, chordin-like 1 (CHRDL1); CSF3, colony stimulating factor 3; DIC, disseminated intravascular coagulation; dsDNA, double-stranded DNA; ECT2, epithelial cell transforming 2; ELISA, enzyme-linked immunosorbent assays; ERK, extracellular regulated protein kinases; FOS, FBJ murine osteosarcoma viral oncogene homolog; GTPases, guanosine triphosphatases; GPX3, glutathione peroxidase 3; GM-CSF, macrophage colony-stimulating factor; GSDMD, gasdermin D; HBP, heparin-binding protein; HMGB1, high mobility group box 1 protein; IL-1β, interleukin-1 β; LPS, lipopolysaccharide; mtDNA, mitochondrial DNA; MVs, microvesicles; MAP3K5, mitogen-activated protein kinase5; MPO, myeloperoxidase; MPO-DNA, myeloperoxidase DNA complex; NETs, neutrophil extracellular traps; NS1, non-structural protein 1; NADPH, nicotinamide adenine dinucleotide phosphate; NOX, NADPH oxidase; NE, neutrophil elastase; NOAF, new-onset atrial fibrillation; PKM2-LDH, pyruvate kinase muscle isozyme m2-lactate dehydrogenase; PAD4, peptidylarginine deiminase 4; PMA, phorbol myristate acetate; PD-L1, programmed death-ligand1; PNCs, platelet-neutrophil complexes; PAMPs,

pathogen-associated molecular patterns; PRR, pattern recognition receptors; PMN, polymorphic neutrophils; PT-INR, prothrombin time-international normalized ratio; PTAFR, platelet-activating factor receptor; Rac2, ras-related C3 botulinum toxin substrate 2; ROS, active oxygen; SK3, small conductance potassium; STEMI, ST-segment elevation myocardial infarction; SAE, sepsis-associated encephalopathy; SA-AMI, sepsis associated atrial fibrillation; SA-AKI, sepsis-associated acute kidney injury; TLR, toll-like receptor; TNF-α, tumor necrosis factor-α; TGF-β, transforming growth factor-beta; TF, tissue factor; TM, thrombomodulin; UA, high-dose ultraviolet light; VWF, von willebrand factor.

Data Sharing Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Ethical Approval

This review did not require ethical approval as it was based on previously published studies.

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