



Impact of Neutrophil Extracellular Traps on Clinical Outcome after Subarachnoid Hemorrhage: A Translational Narrative Review

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Abstract

Aneurysmal subarachnoid hemorrhage (aSAH) remains associated with substantial morbidity and mortality despite best medical treatment. Increasing evidence implicates thrombo-inflammation (TI), driven by neutrophils and neutrophil extracellular traps (NETs), in the pathogenesis of delayed cerebral ischemia (DCI) and cognitive impairment. This narrative review summarizes experimental and clinical data linking neutrophil activation and NETs formation to DCI after aSAH and outlines emerging therapeutic strategies. This review was structured according to the SANRA (Scale for the Assessment of Narrative Review Articles) guidelines and followed general recommendations for narrative reviews. A comprehensive PubMed and clinicaltrials.gov search identified experimental and clinical studies published in English without time window, focusing on TI, neutrophil activation, or NETosis in the acute phase of aSAH. Past and ongoing clinical trials were classified by mechanism of action. Experimental models and human data show early and sustained neutrophil activation within cerebral and systemic compartments after aSAH. NETs promote microvascular thrombosis, blood-brain barrier disruption, microglial activation, and neuronal injury, ultimately contributing to DCI and long-term cognitive impairment. Outside the brain, NETs may also aggravate neurogenic pulmonary edema and cardiac dysfunction. In animal models, deoxyribonuclease I (DNase I) effectively degrades NETs, improving perfusion, limiting neuronal apoptosis, and enhancing recovery. Several ongoing trials target TI pathways, including the RESET trial, which evaluates the impact of IV DNase I on clinical outcome after aSAH. NETs produced after neutrophil activation may be central to DCI. Targeting NETs represents a promising translational path to improve cerebral and systemic outcomes after aSAH.

Keywords Neutrophil Extracellular Traps · Subarachnoid Hemorrhage · Thrombo-Inflammation · Delayed Cerebral Ischemia · Cognitive Impairment

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Abbreviations

AIS	acute ischemic stroke
aSAH	aneurysmal subarachnoid hemorrhage
BBB	blood–brain barrier
CSF	cerebrospinal fluid
DAMPS	damage-associated molecular patterns
DCI	delayed cerebral ischemia
DNA	deoxyribonucleic acid
(rh)DNase	(recombinant human) deoxyribonuclease
DSA	digital subtraction angiography
EBI	early brain injury
GCS	Glasgow coma scale
HMGB1	high-mobility group box 1
JAK2/STAT3	Janus kinase 2/signal transducer and activator of transcription 3
LTP	long-term potentiation
MMP	metalloproteinase
MPO	myeloperoxidase
MRI	magnetic resonance imaging
NETs	neutrophil extracellular traps
NF- κ B	nuclear factor-kappa B
NMDAR	N-methyl-D-aspartate receptor
NPE	neurogenic pulmonary edema
RCT	randomized clinical trial
ROS	reactive oxygen species
RSS	really simple syndication
SANRA	scale for the assessment of narrative review articles
tGCI	transient global cerebral ischemia
TI	thrombo-inflammation
TLR	Toll-like receptor

Introduction

Subarachnoid hemorrhage due to aneurysm rupture (aSAH) is associated with substantial morbidity and mortality. Mortality is estimated at 14% [1], while 19% of survivors [2] will not regain full autonomy, and 67% will report reduced quality of life [3]. More importantly, the proportion of patients unable to resume their usual activities after SAH ranges from 40% to 82% across series [4].

Many patients also experience a measurable decline in quality of life [5] and a substantial proportion, despite returning to work and maintaining apparent functional independence, requires specific accommodations [4].

Given these individual consequences, the broader societal impact is considerable: the disease affects people during their most productive years [6] and generates substantial economic losses, partly driven by persistent attentional deficits [7].

A substantial part of this morbidity and mortality (including fatigue [8]) may relate to thrombo-inflammation (TI), both cerebral [9] and peripheral [10] (i.e. pulmonary), arising in the acute and subacute phases of aSAH.

The best-known subacute cerebral and clinically noticeable phenomenon related to TI is delayed cerebral ischemia (DCI) [11], although as discussed below, low-grade and subclinical TI is also likely responsible for reported morbidity, notably cognitive [12]. DCI is defined as the appearance, between 4 and 21 days after aSAH, of a focal neurological deficit or a decrease in Glasgow Coma Scale (GCS; at least 2 points for at least 1 h) that does not occur immediately after aneurysm exclusion and is not attributable to another cause (ruled out by clinical, laboratory, and radiological means) [13]. The incidence of DCI is estimated to be around 30% [14]–37% [15], and is significantly associated with an unfavorable 3-month functional outcome [16] and with cognitive impairment [17]. Currently, the only proven preventive treatments for post-aSAH DCI aim to prevent vasospasm or its consequences, for example via nimodipine administration [18] but with overall limited efficacy. Furthermore, based on current evidences, vasospasm is not the sole effector of DCI: up to 21% of patients without vasospasm still develop DCI [19], while in 27% of patients, DCI occurs outside the vascular territory affected by vasospasm [19]. Equally compelling is the reverse observation: 57% of patients with moderate-to-severe vasospasm show no neurological worsening, calling into question a simple causal relationship [20]. TI -and neutrophils in particular- are therefore increasingly regarded as an additional mechanism contributing to DCI, with or without the involvement of concomitant vasospasm, by inducing microcirculatory impairment [21]. Among substances secreted by activated neutrophils, neutrophil extracellular traps, or NETs - a network of decondensed chromatin secreted with histones and pro-inflammatory enzymes - have recently been associated with DCI and clinical prognosis after aSAH [21].

With this as a background, the primary objective of this study was to provide a narrative review of experimental and clinical data regarding the contribution of neutrophils and NETs to TI and DCI following aSAH.

Methods

Objective

This review was structured and reported in accordance with the SANRA (Scale for the Assessment of Narrative Review Articles) guidelines [22] and followed general methodological recommendations for narrative reviews [23].

Search Strategy

The literature search was conducted in two complementary phases to ensure a comprehensive and up-to-date overview of the field.

In the first phase, a systematic search of PubMed was performed to identify relevant pre-clinical and clinical studies published in English without limit on publication date, focusing on TI mechanisms and neutrophil-related pathways in the subacute phase of aSAH, within the time window of DCI that is, up to day 21. The general search strategy as well as the inclusion/exclusion criteria and quality assessment methods are provided in Supplemental Data. A Really Simple Syndication (RSS) feed was also systematically monitored during the preparation phase to capture and integrate the most recent publications relevant to the topic.

In the second phase, we searched clinicaltrials.gov for phase 1 to 3 randomized clinical trials (RCTs) involving pharmacological treatments in the acute phase of aSAH whose mechanism of action targeted TI, at least in part. This complementary approach aimed to map both the published literature and ongoing clinical efforts in the field.

Study Selection and Data Extraction

Two independent reviewers (FD, JL) screened all titles and abstracts for relevance. We included RCTs, observational studies, preclinical and clinical studies, meta-analyses, and consensus statements addressing the role of neutrophils or NETs in the context of aSAH or related TI processes.

Only studies focusing on the acute or subacute phases of aSAH and investigating pharmacological or mechanistic aspects of neutrophil activation or NETs formation were retained. A few references have been added for clarification and educational purposes.

Classification of Trials

Completed RCTs were classified as either prematurely terminated (with reasons for discontinuation specified) or carried through to completion. In the latter case, they were further subdivided according to whether they demonstrated success, failure, or absence of published results. Ongoing trials were also identified and classified according to their presumed mode of action and targeted pathway, with their objectives and planned inclusion periods reported when available. The flowchart displaying all RCTs sorted by potential mechanism of action has been added as Supplemental Figs. 2 to 6. In case of multiple targets, the most significant TI pathway has been arbitrarily chosen by authors.

Methodological Considerations

As this work follows a narrative review design, it does not include a formal risk of bias assessment or quantitative synthesis. While this format allows for broader integration of experimental and clinical evidence, it may be subject to selection bias, which was minimized through comprehensive database searches and inclusion of both published and ongoing studies. This review is complementary to the article recently published by Wroe and colleagues [24], which focused more on biochemicals and intracellular pathways than on clinical data and that we have read with the greatest interest.

Results

Parenchymal Injury, its Relationship with Microcirculatory Impairment and Thrombo-inflammation

Recent reviews highlight a significant role of microvascular TI in the pathophysiology of DCI [25, 26]. In animal models, microvascular alterations have been documented immediately after aSAH [25] and are responsible for subsequent ischemia in downstream microvascular territories [27]. Microvascular injury leading to parenchymal lesions probably begins as soon as aSAH occurs [28, 29], triggered by transient global cerebral ischemia (tGCI) [30] during an acute process termed early brain injury (EBI), which is now thought to set the stage for subsequent DCI through activation of TI [31, 32].

In humans, microstructural parenchymal injury, including neuronal damage, has been demonstrated in autopsy series [33, 34], where it is spatially associated with microvascular occlusion. From a temporal perspective, a second peak of microcirculatory injury appears to occur during the DCI time window (7–14 days post-aSAH) [35].

Outside post-mortem studies, only two imaging approaches currently allow a highly imperfect *in vivo* assessment of microcirculatory and cellular alterations in humans. First, perfusion-based techniques available in digital subtraction angiography (DSA) provide an indirect evaluation of microcirculatory impairment through prolongation of the Time to Peak (TTP). Notably, TTP prolongation at day 9 has recently been identified as a prognostic factor for DCI, independent of the occurrence of severe proximal vasospasm [36]. Second, brain magnetic resonance imaging (MRI) allows the characterization of chronic parenchymal injury and its spatial distribution. In a study performed by Galea and colleagues, MRI at 6 months demonstrated a persistent cortical permeation by hemoglobin, which was correlated

with cognitive impairment [37]. Microstructural abnormalities revealed by lower mean kurtosis -the average deviation of water diffusion from a Gaussian distribution- in prespecified gray and white matter areas, are also still detectable on brain MRI 6 weeks after aSAH in patients with cognitive deficits [9]. In contrast, no persistent inflammation could be measured in the same regions at that time, supporting the hypothesis that an early inflammatory process leads to long-lasting microstructural damage [9].

Nonetheless, due to the lack of direct observation of TI phenomenon in humans, we must rely on pre-clinical, predominantly animal, models to elucidate the mechanisms linking microcirculatory dysfunction and parenchymal injury after aSAH.

In murine experimental models of aSAH, microvascular occlusion is persistent and spatially associated with neuronal cell loss [38]. This neuronal injury is particularly pronounced in the CA1 and CA3 regions of the hippocampus, the cerebral cortex, and cerebellar Purkinje cells [39], with maximal damage observed at day 14 [40], coinciding with the second peak of microcirculatory impairment [35] and the highest incidence of DCI.

At the cellular level, neuronal injury results from several complementary mechanisms. First, microvascular obstruction induces distal ischemia [27] and disrupts local autoregulatory capacity [41], both directly contributing to neuronal damage. Second, thrombus components release neurotoxic mediators such as glutamate that further exacerbate neuronal injury [38]. In parallel, microvascular TI induces microglial migration and polarization toward a pro-inflammatory (M1) phenotype [42, 43]. All the TI phenomenon described above create an inflammatory milieu that propagates neuronal death, notably through apoptotic pathways [44].

However, it has been said that neuronal injury confined to these regions is probably insufficient to fully account for the neurocognitive deficits observed in rats, suggesting a more diffuse pattern of damage [39]. Such injury may involve a broader cortical distribution [45] or reflect more subtle alterations. For instance, a reduction in synapse density within the dendritic layer of the CA1 region has been reported in mice following experimental SAH [12].

Neutrophils and NETosis

a. Preclinical evidence of neutrophil-driven thrombo-inflammation after aSAH.

During an experimental SAH, neutrophils [21] accumulate within microvessels [46], rapidly reaching the meninges and perivascular spaces [47], and subsequently infiltrating the brain parenchyma [48]. Neutrophils issued from the microcirculation enter perivascular spaces and then cerebral parenchyma via diapedesis through gaps formed by

blood-brain barrier (BBB) disruption [48], a pattern reminiscent of observations reported in autopsy series of acute ischemic stroke (AIS) [49]. According to preclinical models of aSAH, BBB function, normally maintained by adjacent endothelial cells bound by tight junction, is rapidly disrupted after aSAH [50], allowing immune cells infiltration [51]. Neutrophils likely play a direct role in BBB disruption, as inhibition of Toll-like receptor (TLR) 4, a key mediator of neutrophil NETosis, has been shown to attenuate BBB injury following experimental aSAH [52].

Recently, animal models have suggested that, in addition, a subset of neutrophils may be produced locally within the skull bone marrow before trafficking to the perivascular spaces and cerebrospinal fluid (CSF) via skull meningeal channels [53]. Notably, these neutrophils appear to exhibit a lower activation threshold for NETosis following aSAH [21].

In preclinical setting, adhesion of neutrophils to the microvascular endothelium [54] is promoted by increased expression of endothelial P-selectin [55], integrins [46], chemokines [56], and hemoglobin-degradation products [57] and occurs within 10 min after aSAH [58] before peaking on day 4 [59].

In the microvascular compartment, neutrophils contribute to microcirculatory occlusions [60], which, in animal models, leads to hypoperfusion in cortical territories [61]. As a surrogate marker of their detrimental activity, reducing neutrophil activation decreases early microvascular injury after aSAH in rats [54].

In preclinical models, neutrophil adhesion to the endothelium already promotes microglial polarization toward a pro-inflammatory (M1) phenotype and appears to drive microglial accumulation within the same brain regions [42].

In the microcirculation, CSF and parenchyma, neutrophils release pro-inflammatory mediators, myeloperoxidase (MPO), neutrophil elastase, metalloproteinase-9 (MMP-9), ROS, and NETs, responsible, beyond microthrombosis, for BBB disruption [54] and direct parenchymal injury [62]. Neutrophil activation is therefore associated with poorer neurological outcomes, especially cognitive impairment: in mice, neutrophil depletion improves memory, in part by restoring hippocampal N-methyl-D-aspartate receptor (NMDAR) function [63]. On the contrary, dysfunction of these receptors contributes to neuronal apoptosis after SAH [64] and to late long-term potentiation (LTP) deficits between 3 and 6 days after aSAH [63], whose role in memory consolidation is well known [65].

b. NETosis after SAH.

NETosis is defined as an active process of extrusion of decondensed chromatin fibers decorated with citrullinated histones and stabilizing proteins (i.e. chlorinated polyamines) into the interstitial and endovascular space

by neutrophils along with other enzymes such as elastase, cathepsin G or MPO [66, 67].

Two distinct pathways, which differ from necrosis and apoptosis, may result in NETosis: the classical or lytic pathway, resulting in the death of the originating cell, and the vital pathway, where DNA is encapsulated in vesicles secondary expelled in the extra-cellular space [68]. Interestingly, mitochondrial DNA sometimes secreted along with DNA in the *in vivo* pathway [69] may also play a significant role by acting as a Damage-Associated Molecular Patterns (DAMP), creating an amplifying loop [70]. Both pathways are presented in Fig. 1 and may be associated under certain conditions [71].

Initially described as a host defense mechanism against bacteria following neutrophil stimulation by pathogen-associated molecular patterns (PAMPs) [72], these structures are now recognized as key mediators of sterile inflammation such as AIS.

Within all compartments, neutrophils are attracted and activated by a wide range of triggering signals. Among them, the more relevant are likely to be DAMPs released passively and actively by injured cells, hemoglobin-degradation products, and cells activated within microvessels or

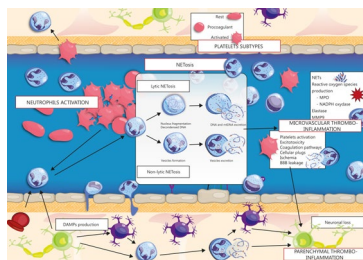


Fig. 1 An overview of neutrophil extracellular traps formation in the microvessels and brain parenchyma. In preclinical models, neutrophils and platelets adhere to the activated endothelium within minutes after SAH, because of the adhesion molecules overexpressed by the activated endothelium or chemokines produced by platelets or brain cells. Thereafter, they may stay in the microvessels, organizing homotypic or heterotypic cells aggregates, or enter the brain through lesions—they are partly responsible for—in the blood-brain barrier. In the brain and the microvessels, neutrophils activate in response to the damage associated molecular patterns (DAMPs) excreted by dying neurons or cytokines produced activated platelets and microglia. Upon activation, neutrophils excrete the so-called neutrophil extracellular traps (NETs), composed of decondensed deoxyribonucleic acid (DNA) decorated with histones and pro-inflammatory enzymes, by two distinct mechanisms. The lytic NETosis involves nucleus fragmentation and cell necrosis, while the non-lytic NETosis necessitates the formation and the excretion avec vesicles containing the NETs. When they enter the extracellular space, NETs activate primary hemostasis (including platelets) and coagulation pathway as well as microglia (promoting type 1), leading to neuronal cell death, secondarily responsible for delayed cerebral ischemia and cognitive impairment. Abbreviations: BBB: blood-brain barrier, DAMPs: damage associated molecular patterns, NADPH: (nicotinamide adenine dinucleotide phosphate, NETs: neutrophil extracellular traps, MMP: metalloproteinase, MPO: myeloperoxidase. Created in Adobe Illustrator

the brain parenchyma. Massive DAMPs release from injured cells is indeed a major activation signal. Among these, high-mobility group box 1 (HMGB1), produced locally [73] and immediately [74] by cells affected during early brain injury (EBI, during day 0 to 3 after SAH) [75] whose peripheral blood concentration is increased after SAH and correlates with DCI [76], potently stimulates neutrophil via activating receptors. Among them, the TLR superfamily, and notably the TLR4 [77] seems to be of paramount importance in NETosis triggering [78].

TLR4 is unique among pattern recognition receptors in its ability to activate both the myeloid differentiation primary response protein 88 (MyD88)-dependent and Toll/interleukin-1 receptor domain-containing adaptor-inducing interferon- β (TRIF - during the later phase of aSAH) signaling pathways and subsequent inflammatory reaction [79].

Heme present in subarachnoid clot degradation products (i.e. oxyhemoglobin [80, p. 4] and methemoglobin [81]) directly stimulates neutrophils TLR4 [80] signaling and activates the MyD88-dependent pathway during the early phase of SAH, which appears to be essential for NETs secretion [82]. MyD88 signaling induces nuclear factor- κ B (NF- κ B), which seems to be particularly active between days 3 and 5 after experimental aSAH in rabbits [83], as well as mitogen-activated protein kinase (MAPK) pathways, leading to apoptosis, pro-inflammatory gene expression [57], and NETosis [84]. Supporting the clinical relevance of this pathway during the early days of post-aSAH TI, pharmacological inhibition of TLR4 signaling reduced EBI in an experimental rat model of aSAH [85].

In parallel with TLR4 signaling, DAMPs also activate nicotinamide adenine dinucleotide phosphate (NADPH) oxidase [86], whose activation is required for NETs formation [87]. Erythrolysis degradation products also stimulate reactive oxygen species (ROS) [88] production, thus contributing to oxidative tissue damage and nitric oxide depletion (NO), leading to micro- and macro-vasospasm after SAH [89]. ROS themselves serve as potent triggering signals for NETs formation after hemorrhage [90].

Finally, peptidylarginine deiminase 4 (PAD4), which is essential for NETosis through histone citrullination [87], promotes chromatin decondensation and facilitates the extrusion of chromosomal deoxyribonucleic acid (DNA). PAD4 expression is increased in neutrophils after SAH [91], possibly in response to elevated intracellular calcium levels [92] secondary to NADPH oxidase-regulated ROS generation and subsequent Ca^{2+} influx [93].

Platelets, which aggregate in the microvasculature immediately after SAH [94] in animal models and whose binding to neutrophils is associated with vasospasm [95], are regarded as potent activators of neutrophils [96] and NETosis [97] [98] (Fig. 1). Neutrophil activation by platelets

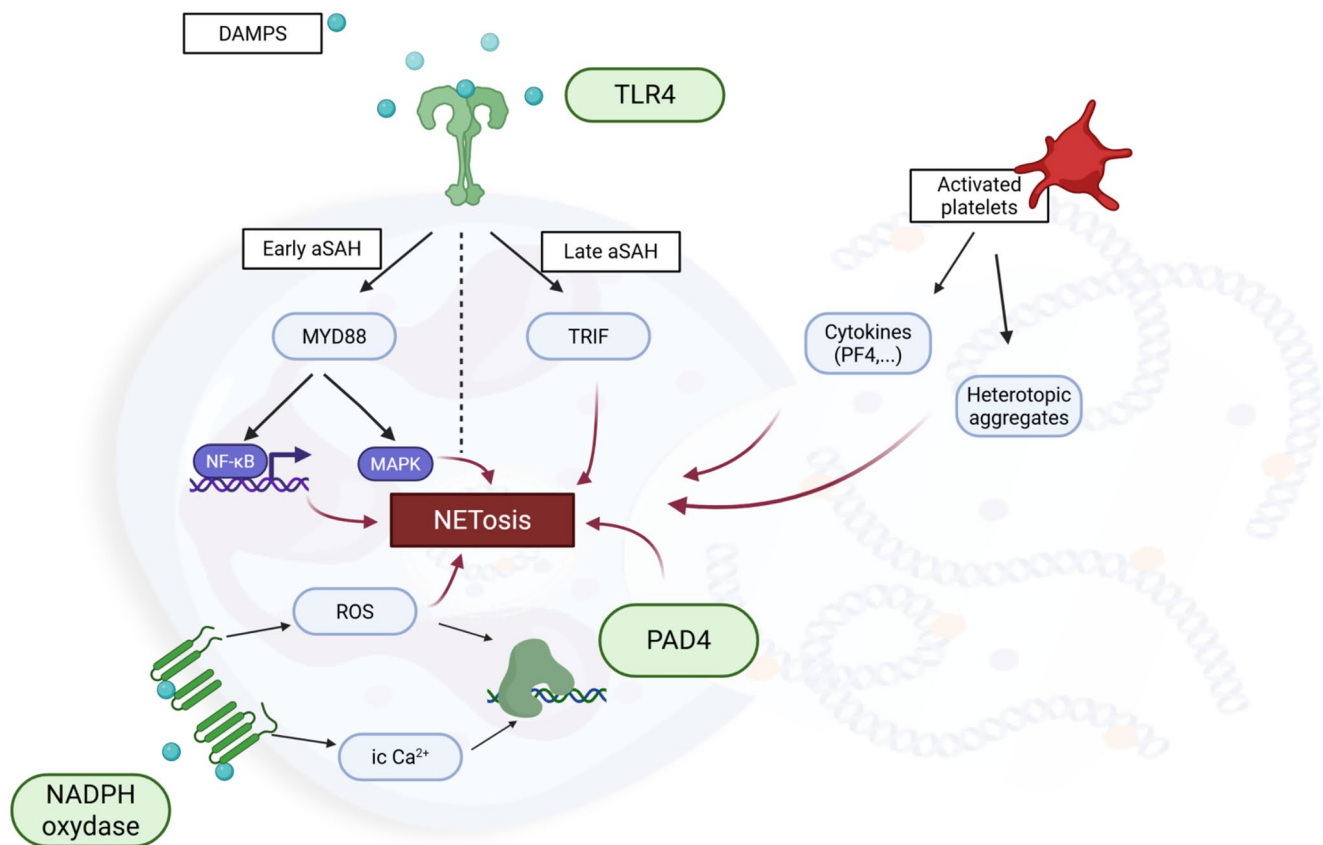


Fig. 2 An overview of intracellular pathways involved in neutrophil extracellular traps formation. Damage-associated molecular patterns (DAMPs) released by cells (particularly distressed neurons) activate toll-like receptor 4 (TLR4), which is unique in that it triggers two intracellular thombo-inflammatory pathways: MyD88 (predominantly within the first 5 days after SAH) and TRIF (activated later). Both pathways contribute to the induction of NETosis, with MyD88 acting via activation of NF-κB and MAPK signaling. DAMPs also stimulate NADPH oxidases, whose activation leads to reactive oxygen species (ROS) generation and increased intracellular calcium levels.

These processes are directly and indirectly—via PAD4, which mediates histone citrullination and is essential for NETosis—involved in NETosis initiation. Activated platelets at the site of thrombosis also promote NETosis through aggregate formation and the secretion of pro-inflammatory cytokines, including PAD4. Abbreviations : BBB: blood-brain barrier, DAMPs: damage associated molecular patterns, NADPH: (nicotinamide adenine dinucleotide phosphate, NETs: neutrophil extracellular traps, MMP : metalloproteinase, MPO: myeloperoxidase, TLR: toll-like receptor. Created in Adode Illustrator and BioRender. Oury, C. (2026) <https://BioRender.com/40vbtws>

occurs through direct binding to neutrophils with formation of heterotypic aggregates [99], enhanced after aSAH [58] and correlating with NETs formation [100] or through secretion of platelet-derived pro-inflammatory cytokines [97]. Among cytokines, Platelet Factor 4 (PF4, a potent neutrophil activator in neurovascular diseases [101]) concentration in peripheral blood has been correlated with perfusion impairment after aSAH [102]. Activating pathways involved in NETosis are illustrated in Fig. 2.

While NETosis has previously been implicated in microcirculation-related diseases (such as lupus, infectious diseases or AIS) [103–105] it has more recently been associated with DCI [21]. In murine experimental models of SAH, NETs are produced between 24 and 48 h post-SAH within microvascular spaces - where they are associated with microthrombosis [106] - and in perivascular spaces [107]. Their concentration then rises in both hemispheres of the

brain until day 14 [108], paralleling the DCI window and the peak of neuronal death [40]. In mice, intravascular NETs correlate with microthrombi and with DCI [21], whereas perivascular NETs drive microvasospasm [107].

In humans, NETs concentration increases in CSF and blood after SAH [108] and correlates with aSAH severity [109]. In the recent paper of Schneider et al., their concentration rose until day 9 and then trended back down on day 10 [110]. In somewhat contradictory results, the occurrence of DCI relates either positively [110] or negatively [111] to the concentration of NETs, measured in peripheral blood as MPO-DNA complexes in the early phase of DCI (day 4 to 5 after SAH). The explanation proposed by the authors of the latter study is that NETs may have been consumed within thrombi, thereby reducing their measurable circulating levels. However, it should be noted that the method used to quantify NETs in this study is generally considered

imprecise and may not accurately reflect the true burden of NET formation [112].

By contrast, most correlation studies in humans have relied on citrullinated histone H3 (CitH3). Elevated CitH3 levels have been associated with aSAH severity when measured within the first 24 h after ictus [109], and with the subsequent development of DCI when assessed at 2, 7, and 10 days after aSAH [21, 110]. Of note, Sajjad et al. found no association between CitH3 levels and angiographic vasospasm of the large cerebral arteries [113]. This observation is not necessarily inconsistent with the currently proposed role of NETs, which are thought to exert their deleterious effects predominantly at the microcirculatory level rather than through large-vessel vasospasm.

The involvement of NETs in DCI aligns with their strong pro-coagulant and pro-inflammatory potential. Positioned at the core of TI networks, NETs potentiate multiple pathways simultaneously, spanning platelet activation, coagulation cascades, complement engagement, and broader immune-cell activation. First, they provide a scaffold for platelets and immune cells adhesion and for local concentration of coagulation factors [114, 115]. Furthermore, they directly promote coagulation by binding circulating von Willebrand factor (vWF) and fibrinogen [115], by providing a procoagulant cofactor template for the factors XII and XI-induced contact activation and amplification of blood coagulation [116]. Furthermore, they are also decorated with tissue factor under certain conditions [117] and finally, they strongly stimulate platelet TLR4, enhancing thrombin generation [118]. Activated platelets further amplify microthrombosis [115], microvasospasm [119] and directly promote NETs production [72], creating a potential feed-forward loop. Beyond their role in TI, NETs may directly stimulate microglia. As noted above, M1-microglia stimulation contributes to neuronal injury via multiple mechanisms and, thereby, to cognitive deficits. One putative mechanism is binding of NETs components to microglial TLR4 receptors [120], whose expression increases after SAH [121] and whose activation is strongly pro-inflammatory [122], essential for neuronal injury [123] and for cognitive impairment in animal models of aSAH [124], yet another amplification loop in which NETs may play a central role.

Providing indirect evidence for a role of NETs in microglial polarization, intraperitoneal (50 µg) followed by intravenous (IV, 10 µg) administration of DNase I 3 h after an experimentally induced SAH in mice significantly reduced the level of pro-inflammatory subtype transition of microglia (marked with CD16/32, IL1β) and neuronal injury [125], although the precise spatial distribution of neuronal lesions was not reported. Interestingly, this reduction in microglial activation is accompanied by a significant decrease in ex

vivo brain edema and a significant improvement in neurobehavioral tests (i.e. Garcia test).

Furthermore, reinforcing the concept of co-dependence between microcirculatory injury and microglial pro-inflammatory activation, microglial surface area—a proxy for microglial activation—is up to 40% greater (estimated marginal means [95% CI]; 6.1 [5.4–6.9] vs. 4.3 [3.6–5.0], $p < 0.001$) around thrombosed microvessels in patients, at a mean delay of 1 day [0.3–9] after aSAH [43], in an autopsy series comparing 11 aSAH and 10 control patients.

Finally, NETs have recently been involved in the development of a subacute hydrocephalus in a preclinical model of SAH. In this model of kaolin-induced hydrocephalus in rat, the intrathecal application of DNase I (3500UI during 3 days after hydrocephalus induction) prevented ventricular enlargement evaluated on T2-weighted MRI images 28 days after hydrocephalus induction [126]. The proposed mechanism is the reduction of the proliferation and differentiation of meningeal fibroblasts induced by NETs, otherwise contributing to aggravated subarachnoid fibrosis.

c. Systemic effects of NETs.

Despite their role in antibacterial defense, there is currently no demonstration that targeting NETs increases infection risk. On the contrary, it has been suggested that NETs secretion may limit immunoglobulin production by lymphoid organs, possibly by inducing B cell loss in Peyer's patches via activation of apoptosis pathways [127]. Even in the brain, NETs may worsen infections: their concentration correlates with severity of pneumococcal meningitis in patients, and DNase I reduces bacterial load in an animal model of meningitis [128], possibly by improving bacterial clearance.

Conversely, some animal data suggest a link between circulating NETs and neurogenic pulmonary edema (NPE) [109], associated with an increased 1-year mortality after aSAH [10] while DNase administration [129] as well as P2 × 7R inhibition [130] (involved, among other roles, in NETs formation [131]) and melatonin administration [132] reduce NPE after experimental SAH in rats. In the latter study, MPO and MMP9, often used as proxy for neutrophil activation level, were reduced in the lungs of the treatment group. Furthermore, peripheral neutrophil count (but not NETs directly) is also strongly correlated with left ventricular dysfunction after aSAH [133].

In a nutshell, neutrophils, activated by both local and systemic signals, therefore mediate vascular, perivascular, and parenchymal injury that is detectable in humans. Animal models further indicate that this injury contributes to parenchymal, and specifically neuronal damage during the subacute phase of aSAH. Among neutrophil-derived effectors, NETs, composed of extracellular DNA networks, have been repeatedly correlated with clinical outcomes in patients with

aSAH, while their therapeutic targeting in preclinical models attenuates the cognitive deficits associated with aSAH.

Effects of NETs Inhibition

Targeting NETs can be achieved through several strategies: reducing neutrophil activation (for instance by limiting DAMP–neutrophil interactions [134]), inhibiting NETs formation pathways (e.g., by inhibiting enzymes required for NETs production such as PAD4, NADPH oxidase, or MPO), or degrading extracellular DNA networks once released, through DNase administration [135].

Given the very large number of preclinical studies aimed at inhibiting—at least in part—the effects of neutrophils activation after aSAH, we chose to prioritize animal studies focusing on pathophysiological pathways that focus mainly on neutrophils and can already be targeted in humans, either with novel agents or through drug repurposing.

We thus examine, along the NETosis pathway, an example of a receptor stimulated by DAMPs (TLR 4), an enzyme required for NETs release (MPO), and an enzyme co-released with NETs by neutrophils (MMP-9), as well as the lysis of NETs themselves by DNase—all of which may represent targets for potential trials using existing drugs.

It should be noted that in these studies, the primary outcome rarely involves direct assessment of DCI, but rather relies on proxies—typically imaging or biological biomarkers or functional clinical assessments—that can be linked to the occurrence of DCI.

NETs Secretion Inhibition

TLR 4 inhibition, involved in NETosis in response to DAMPs [78, 81], has been evaluated in a positive phase 2 study in AIS [136]. In experimental aSAH models in mice, intraventricular administration of a TLR4 inhibitor 30 min after the SAH reduced BBB permeability in one study [52], and decreased cerebral edema while improving neurocognitive function in another [137]. Although NETosis was not directly investigated in either study, the inhibitors used may have exerted part of their effects through modulation of NET formation, potentially via the JNK pathway [138] in the first study and the MAPK and NF- κ B pathways in the second.

MPO, required for NETosis [139] and endowed with intrinsic TI activity [140], has already been investigated in several diseases [141], including neurodegenerative conditions [142]. In this context, intraperitoneal administration of an MPO inhibitor for 4 days after experimental aSAH in mice appears to inhibit intrathecal neutrophils translocation—remaining confined within meningeal vessels—and improves spatial memory [143]. Earlier work from the same group suggested that the effects of neutrophils and MPO

may be exerted indirectly through astrocyte dysfunction, with secondary neuronal injury [47].

MMP-9, co-released with NETs by activated neutrophils, contributes to BBB degradation. Its levels in CSF or blood following aSAH have been shown to predict the occurrence of DCI, vasospasm, and clinical outcome in several patient series [144–146].

Inhibition of MMP9 via minocycline administration in preclinical aSAH models in mice resulted in reduced vasospasm and improved neurobehavioral outcomes [147]. It is worth noting that minocycline is not only an inhibitor of MMP-9 but also of PAD4 [148], a key protein for NETosis [149].

NETs Degradation

As demonstrated in thrombus lysis experiments, where DNase effectively disrupts thrombi while leaving associated proteins and enzymes intact [103], the structural integrity of NETs appears to be fundamental to their deleterious effects. Consequently, degradation of this structure comes across as an interesting and somewhat critical therapeutic mechanism. As previously mentioned, NETs dismantling requires the action of a specific extracellular hydrolase—DNase—which hydrolyzes DNA phosphodiester bonds, followed by intracellular degradation by macrophages and monocytes [150] [151].

Two endogenous DNase families (DNase I and DNase II) exist; however, only DNase I functions in the extracellular compartment. The DNase I family comprises four members, DNase I, DNase1L1, DNase1L2, and DNase1L3, among which DNase I and DNase1L3 have been identified as the principal enzymes responsible for NETs degradation [150].

In the specific context of aSAH, several converging lines of evidence support the efficacy of DNase in reducing NETs burden and, beyond this, improving clinical outcomes. First, in humans, a reduction in endogenous DNase activity between days 0 and 4 after aSAH is associated with an increased risk of DCI [152], notably during the peaking of DCI risk. In mice, IV or intraperitoneal DNase administration after experimental SAH reduces NETs concentration and improves functional outcomes by directly enhancing cerebral perfusion through reduced microthrombosis [108, 109]. Within the parenchyma, NETs degradation also attenuates neuronal apoptosis [109].

In a striking study by Hao and colleagues, DNase reduced microthrombosis after experimental SAH in mice, leading to attenuation of brain edema, BBB disruption, neuronal injury, perfusion deficits, CSF flow dysfunction, and ultimately neurological impairment [153]. In another murine model, NETs targeting with DNase also reduced

microvasospasm [107]. Importantly, DNase administration reverses the M1-microglial activation described above in mice [125].

Zeineddine et al. reported contrasting findings in another murine study [21]. Although DNase administration effectively reduced circulating NET levels, it failed to improve cognitive outcomes. While the dose used was comparable to that employed in previous studies, the route of administration differed, being exclusively intraperitoneal rather than partially intravenous or intracisternal. In addition, the second dose was administered later than in earlier reports. These methodological differences may partly account for the lack of cognitive benefit observed despite successful NET reduction.

Beyond the brain, DNase may also mitigate systemic complications of aSAH. In particular, a mice model by Wu and colleagues suggested that DNase reduces NPE after experimental SAH [129], indicating that its benefits may extend beyond cerebral and cognitive outcomes.

Taken together, these data support the hypothesis of a potential efficacy of DNase in reducing TI after aSAH. Overall, there is growing consensus coming from preclinical and clinical data that the time has come for a randomized controlled trial targeting NETs to prevent or treat DCI and cognitive impairment following aSAH [154].

Clinical Trials

Thrombo-inflammation After aSAH

The research flowchart, along with all past and ongoing RCTs classified by outcome and target pathway, is provided as Supplemental Fig. 6.

To our knowledge, after our large review of trials dedicated to aSAH, the number of RCTs specifically targeting neutrophils in the acute phase of aSAH remains scarce, underscoring a significant contrast with the larger body of preclinical studies.

NETs Secretion Inhibition

Among currently ongoing clinical investigations, the compound most directly targeting NETs release appears to be SXN-CVS (NCT06138353), which inhibits the TLR4/NF- κ B signaling pathway. This phase 2 study, planned to enroll 50 patients, has not yet reported results (initial recruitment period planned for 2024–2025).

Beyond that, among notable trials partially targeting TI with published results, a monocenter phase 2 trial in 48 patients, showed that randomized, placebo-controlled dapson administration significantly reduced DCI (26.9% vs. 63.6%, $p = 0.011$) and emergent endovascular treatment of

vasospasm (15.4% vs. 45.5%, $p = 0.029$) [155]. Dapsone exerts part of its effect by inhibiting MPO [156], which is required for NETs formation [139]. The MASH study, targeting MMP-9, a predominantly neutrophilic secretion, showed a decrease in BBB permeability quantitated by contrast signal intensity ratios (0.23 vs. 0.28, $p < 0.01$) [157]. Although the effect is less direct, a randomized, placebo-controlled erythropoietin administration reduced cerebral infarcts as a secondary endpoint (32.5% vs. 2.5%, $p < 0.001$) [158], potentially by acting on microglia polarization [159].

NETs Degradation

Several clinical studies conducted in the 1950s evaluated high-dose IV bovine DNase in infectious diseases (meningitis, abscesses) without reporting major complications [160–163], yet no IV formulation of DNase has since reached the clinical market. The given dose in these studies is difficult to interpret, as it is expressed in units derived from a viscometric assay, reflecting enzymatic activity rather than a standardized mass. Dornase alfa (Pulmozyme[®], Roche), is a recombinant human DNase I (rhDNase), glycosylated and phosphorylated, authorized in many countries to improve pulmonary function by reducing bronchial congestion in patients with cystic fibrosis. In this indication, administration is by inhalation via nebulization. A 1999 study assessed IV Pulmozyme[®] in patients with lupus, including safety and pharmacokinetics, and reported no serious adverse events [104]. In this study, rhDNase was well tolerated without significant adverse events following administration of 2 series of 5 consecutive days with a 2-day washout in between, and treatment was not associated with the development of neutralizing antibodies to rhDNase. Serum rhDNase concentrations (80–100ng/mL) capable of hydrolytic activity of rhDNase were achieved up to 24 h following IV injections of 125microgr/kg.

RESET (NCT06723717) is currently the only reported RCT aiming to improve medium-term functional, especially cognitive, outcomes in patients with aSAH by targeting microvascular and parenchymal NETosis through IV rhDNase (Dornase alfa, Pulmozyme[®], Roche) daily administration. The primary objective of this phase 2b RCT is to evaluate the efficacy of daily IV infusion of dornase alfa (125 μ g/kg) up to 14 days post-aSAH on the occurrence of an excellent functional outcome at 6 months, defined as a score of 0 or 1 on the modified Rankin Scale (mRS) at 6 months. Patients may be included up to 48 h after the onset of symptoms related to aSAH. The inclusions are ongoing, and the results are expected in 2028.

Other Trials

Outside the scope of our review but intersecting the pathways cited above, it is worth noting the following RCTs: CIAO\@SAH (NCT06359782), a phase 2 study of a C1 esterase inhibitor (C1-INH) expected to complete in 2027; FINISHER (NCT04566991), giving dexamethasone (recruitment completion was expected in 2025); BLISS (NCT06439615), inhibiting the Janus kinase 2/signal transducer and activator of transcription 3 (JAK2/STAT3) pathway – involved in M1-type microglia promotion and inducible nitric oxide synthase, interleukin-1 β , and tumor necrosis factor- α after aSAH [164]– to prevent lung injury after aSAH (completion 2027) or THRIVE (NCT06863480), in which an interleukin-6 receptor (IL6R) blocker is given to reduce DCI (recruitment ends 2028).

To date, safety concerns about TI reduction after aSAH are limited. None of the halted trials were stopped for safety reasons or hemorrhagic excess (see Supplemental Fig. 3). Even administration of antiplatelet therapy in acute SAH (iSPASM, NCT03691727) has been shown to be safe, without excess of significant hemorrhage [165].

Perspectives

As the first clinical trial specifically aiming to degrade NETs in the acute phase of aSAH has only recently been initiated, clinical data remains limited, precluding definitive conclusions at this stage. However, as observed in other neurovascular disorders, future therapeutic strategies are likely to rely on a combination of targets and complementary mechanisms of action.

In this regard, the relatively recent demonstration of the efficacy of lumbar CSF drainage [166] and efficacy of intracisternal DNase administration in animal models [107], invites consideration of adjunctive therapeutic delivery via this route, in addition to the IV route. Such an approach could allow targeting intrathecal inflammation in parallel with intra- and perivascular inflammatory processes.

Moreover, the combination of multiple DNase isoforms active against extracellular DNA, such as DNase I and DNase1L3, has shown enhanced NETs-degrading activity in preclinical models [167]. Their combined use therefore warrants evaluation in a clinical setting.

Finally, longitudinal studies have demonstrated temporal fluctuations in the relative intrathecal concentrations of leukocyte subtypes, with neutrophils [168] and their activation markers increasing before day 4 [56], preceding a secondary rise in lymphocyte concentrations occurring between days 5 and 9 [169]. However, most longitudinal studies have focused on single cell lineages, with limited sampling timepoints and minimal clinical correlation. These limitations

are addressed by integrative cohorts such as RADICAL (NCT04971564) and TARGETS (NCT07354321), in which biological samples are collected at multiple timepoints during both the acute and chronic phases. Advanced analytical approaches, including spectral cytometry [170], will enable identification of leukocytes (and platelets) subpopulations specifically associated with clinical outcomes and thus representing priority therapeutic targets. In this context, the emergence of nanobodies, allowing highly specific and coordinated targeting of multiple markers of interest [171], appears particularly promising, both from a diagnostic and therapeutic point of view.

This review would be incomplete without addressing the numerous questions currently raised by translational research on post-aSAH TI. Indeed, several articles have been subject to an expression of concern [172] or retraction [173]. In some cases, the responses are still awaited, and the papers remain accessible. This situation — including the latency period during which the validity of the data has not yet been formally challenged — has itself been the subject of a recent publication [174]. As research on post-aSAH inflammation increasingly moves to the bedside, the acquisition of reliable and reproducible preclinical data has become a critical challenge.

Conclusion

The growing body of ongoing trials targeting complementary TI pathways highlights a paradigm shift: moving beyond vasospasm-centered interventions toward integrated modulation of neuroinflammation and microvascular thrombosis.

Among the identified TI phenomenon, NETosis emerges as a pivotal processes bridging vascular injury, coagulation, and neuroinflammation after aSAH. By promoting microvascular obstruction, BBB disruption, and microglial activation, NETs may orchestrate both early and delayed secondary brain injury, contributing to DCI and cognitive impairment.

Evidence from preclinical models consistently suggests that NETs degradation using DNase mitigates microthrombosis, reduces neuronal apoptosis, and improves both cerebral perfusion and neurological recovery, yet without apparent immunosuppressive risk. These findings converge with the rationale of the RESET trial (NCT06723717), aiming to translate DNase therapy into the clinical management of aSAH.

This trial, among others, may help to define the optimal timing, dosing, and combination of anti-NETs and anti-neutrophil activation strategies to improve both survival and long-term neurocognitive outcomes after SAH. In this regard, the rapid development of neutrophil activation after

aSAH could represent another paradigm shift, by redefining the degree of urgency required for the biological management of inflammation in this setting, bringing it closer, for instance, to that of AIS.

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

Declarations

Disclosures The authors have nothing to disclose.

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References

- Martino F, et al. Outcome of aneurysmal subarachnoid hemorrhage not altered with transatlantic airplane transfer: A bicentric matched case-control study. *J Neurosurg Anesthesiol*. 2025;37(3):279. <https://doi.org/10.1097/ANA.0000000000000984>
- Hop JW, Rinkel GJE, Algra A, van et J. Case-fatality rates and functional outcome after subarachnoid hemorrhage: A systematic review. *Stroke* (1970). 1997;28:660–4. <https://doi.org/10.1161/01.STR.28.3.660>
- Stienen MN et al. Predictors of in-hospital death after aneurysmal subarachnoid hemorrhage: Analysis of a nationwide database (Swiss SOS [Swiss Study on Aneurysmal Subarachnoid Hemorrhage]). *Stroke*. 2018;49(2):333–340. <https://doi.org/10.1161/STROKEAHA.117.019328>
- Al-Khindi T, Macdonald RL, Schweizer TA. Cognitive and functional outcome after aneurysmal subarachnoid hemorrhage. *Stroke*. 2010;41(8):e519–36. <https://doi.org/10.1161/STROKEAHA.110.581975>
- von Vogelsang A-C, Nymark C, Pettersson S, Jervaeus A. My head feels like it has gone through a mixer - a qualitative interview study on recovery 1 year after aneurysmal subarachnoid hemorrhage. *Disabil Rehabil*. 2023;45(8):1323–31. <https://doi.org/10.1080/09638288.2022.2057601>
- Rivero-Arias O, Gray A, Wolstenholme J. Burden of disease and costs of aneurysmal subarachnoid haemorrhage (aSAH) in the United Kingdom. *Cost Eff Resour Alloc*. 2010;8(6). <https://doi.org/10.1186/1478-7547-8-6>
- Wong GKC, et al. Cognitive domain deficits in patients with aneurysmal subarachnoid haemorrhage at 1 year. *J Neurol Neurosurg Psychiatry*. 2013;84(9):1054–8. <https://doi.org/10.1136/jnnp-2012-304517>
- Byun E, et al. Fatigue, toll-like receptor 4, and pro-inflammatory cytokines in adults with subarachnoid hemorrhage: A 6-month longitudinal study. *Biol Res Nurs*. 2024;26(2):192–201. <https://doi.org/10.1177/10998004231203257>
- Tack RW, et al. Neuroinflammation in long-term cognitive impairment after aneurysmal subarachnoid hemorrhage. *Int J Stroke*. 2025;17474930251362004. <https://doi.org/10.1177/17474930251362004>
- Junttila E, et al. Neurogenic pulmonary edema in patients with nontraumatic intracerebral hemorrhage: predictors and association with outcome. *Anesth Analg*. 2013;116(4):855–61. <https://doi.org/10.1213/ANE.0b013e3182811cc7>
- Rabinstein AA et al. (2004) Predictors of cerebral infarction in aneurysmal subarachnoid hemorrhage. *Stroke* (1970) 35(8):1862–1866. <https://doi.org/10.1161/01.STR.0000133132.76983.8e>
- Han SM, et al. Molecular alterations in the hippocampus after experimental subarachnoid hemorrhage. *J Cereb Blood Flow Metab*. 2014;34(1):108–17. <https://doi.org/10.1038/jcbfm.2013.170>
- Hoh BL. Guideline for the management of patients with aneurysmal subarachnoid hemorrhage: A guideline from the American Heart Association/American stroke association. *Stroke*. 2023;54(7):e314–70. <https://doi.org/10.1161/STR.0000000000000436>
- Kassell NF, Torner JC, Haley J, Jane JA, Adams HP. Kongable. The international cooperative study on the timing of aneurysm surgery. Part 1: Overall management results. *J Neurosurg*. 1990;73(1):18–36. <https://doi.org/10.3171/jns.1990.73.1.0018>
- Raatikainen E, et al. Prognostic value of the 2010 consensus definition of delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage. *J Neurol Sci*. 2021;420:117261. <https://doi.org/10.1016/j.jns.2020.117261>
- Rosengart AJ, Schultheiss KE, Tolentino J, Macdonald RL. Prognostic factors for outcome in patients with aneurysmal subarachnoid hemorrhage. *Stroke*. 2007;38(8):2315–21. <https://doi.org/10.1161/STROKEAHA.107.484360>
- Aydin S, Peker S. Long-term cognitive decline after subarachnoid hemorrhage: Pathophysiology, management, and future directions. *Stroke*. 2025;56(4):1106–11. <https://doi.org/10.1161/STROKEAHA.124.049969>
- Dorhout SM, et al. Calcium antagonists for aneurysmal subarachnoid haemorrhage. *Cochrane Database Syst Rev*. 2007;2007(3):CD000277. <https://doi.org/10.1002/14651858.CD000277.pub3>

19. Dankbaar JW, Rijdsdijk M, van der Schaaf IC, Velthuis BK, Wermer MJH, Rinkel GJE. Relationship between vasospasm, cerebral perfusion, and delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage. *Neuroradiology*. 2009;51:813–9. <https://doi.org/10.1007/s00234-009-0575-y>
20. Vergouwen MDI, Ildigwe D, Macdonald RL. Cerebral infarction after subarachnoid hemorrhage contributes to poor outcome by vasospasm-dependent and -independent effects. *Stroke*. 2011;42(4):924–9. <https://doi.org/10.1161/STROKEAHA.110.597914>
21. Zeineddine HA, et al. Neutrophils and neutrophil extracellular traps cause vascular occlusion and delayed cerebral ischemia after subarachnoid hemorrhage in mice. *Arterioscler Thromb Vasc Biol*. 2024;44(3):635–52 <https://doi.org/10.1161/ATVBAHA.123.320224>
22. Baethge C, Goldbeck-Wood S, Mertens S. SANRA—a scale for the quality assessment of narrative review articles. *Res Integr Peer Rev*. 2019;4(1):5. <https://doi.org/10.1186/s41073-019-0064-8>
23. Ferrari R. Writing narrative style literature reviews. *Med Writ*. 2015;24(4):230–5 <https://doi.org/10.1179/2047480615Z.000000000329>
24. Wroe WW, Zeineddine HA, Blackburn SL, Aronowski J, McBride DW. The role of neutrophils in vasospasm and delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage: Is it time for a SAH clinical trial targeting neutrophils? *J Cereb Blood Flow Metab*. 2025;0271678X251370858. <https://doi.org/10.1177/0271678X251370858>
25. Tso MK, Macdonald RL. Acute microvascular changes after subarachnoid hemorrhage and transient global cerebral ischemia. *Stroke Res Treat*. 2013;2013:425281. <https://doi.org/10.1155/2013/425281>
26. Chen Y, Galea I, Macdonald RL, Wong GKC, Zhang. Rethinking the initial changes in subarachnoid haemorrhage: Focusing on real-time metabolism during early brain injury. *eBioMedicine*. 2022;83. <https://doi.org/10.1016/j.ebiom.2022.104223>
27. Friedrich B, Müller F, Feiler S, Schöller K, Plesnila N. Experimental subarachnoid hemorrhage causes early and long-lasting microarterial constriction and microthrombosis: an in-vivo microscopy study. *J Cereb Blood Flow Metab*. 2012;32(3):447–55 <https://doi.org/10.1038/jcbfm.2011.154>
28. Friedrich V, Flores R, Muller A, Sehba FA. Luminal platelet aggregates in functional deficits in parenchymal vessels after subarachnoid hemorrhage. *Brain Res*. 2010;1354:179–87. <https://doi.org/10.1016/j.brainres.2010.07.040>
29. Friedrich V, Flores R, et, Sehba FA. Cell death starts early after subarachnoid hemorrhage. *Neurosci Lett*. 2012;512(1):6–11 <https://doi.org/10.1016/j.neulet.2012.01.036>
30. Sozen T, et al. Immunological response in early brain injury after SAH. *Acta Neurochir Suppl*. 2011;110(Pt 1):57–61. https://doi.org/10.1007/978-3-7091-0353-1_10
31. Zhang Z, et al. New mechanisms and targets of subarachnoid hemorrhage: A focus on mitochondria. *Curr Neuroparmacol*. 2022;20:1278–96. <https://doi.org/10.2174/1570159X19666211101103646>
32. Al-Mufti F, et al. Emerging markers of early brain injury and delayed cerebral ischemia in aneurysmal subarachnoid hemorrhage. *World Neurosurg*. 2017;107:148–59. <https://doi.org/10.1016/j.wneu.2017.07.114>
33. Neil-Dwyer G, Lang DA, Doshi B, Gerber CJ, Smith PW. Delayed cerebral ischaemia: the pathological substrate. *Acta Neurochir (Wien)*. 1994;131(1–2):137–45. <https://doi.org/10.1007/BF01401464>
34. Suzuki S, Kimura M, Souma M, Ohkima H, Shimizu T, Iwabuchi T. Cerebral microthrombosis in symptomatic cerebral vasospasm—a quantitative histological study in autopsy cases. *Neurol Med Chir (Tokyo)*. 1990;30(5):309–16. <https://doi.org/10.2176/nmc.30.309>
35. Stein SC, Browne KD, Chen X-H, Smith DH, Graham DI. Thromboembolism and delayed cerebral ischemia after subarachnoid hemorrhage: an autopsy study. *Neurosurgery*. 2006;59(4):781–7. <https://doi.org/10.1227/01.NEU.0000227519.27569.45>
36. Naraoka M, Matsuda N, Shimamura N, Ohkuma H. Role of microcirculatory impairment in delayed cerebral ischemia and outcome after aneurysmal subarachnoid hemorrhage. *J Cereb Blood Flow Metab*. 2022;42(1):186–96. <https://doi.org/10.1177/0271678X211045446>
37. Galea I, et al. Iron deposition in the brain after aneurysmal subarachnoid hemorrhage. *Stroke*. 2022;53(5):1633–42. <https://doi.org/10.1161/STROKEAHA.121.036645>
38. Bell JD, et al. Platelet-mediated changes to neuronal glutamate receptor expression at sites of microthrombosis following experimental subarachnoid hemorrhage. *J Neurosurg*. 2014;121:1424–31. <https://doi.org/10.3171/2014.3.JNS132130>
39. Jeon H, Ai J, Sabri M, Tariq A, Macdonald. Learning deficits after experimental subarachnoid hemorrhage in rats. *Neuroscience*. 2010;169(4):1805–14. <https://doi.org/10.1016/j.neuroscience.2010.06.039>
40. Heinz R, et al. Microglia as target for anti-inflammatory approaches to prevent secondary brain injury after subarachnoid hemorrhage (SAH). *J Neuroinflammation*. 2021;18(1):36. <https://doi.org/10.1186/s12974-021-02085-3>
41. Lidington D, Wan H, Bolz S-S. Cerebral autoregulation in subarachnoid hemorrhage. *Front Neurol*. 2021;12:688362. <https://doi.org/10.3389/fneur.2021.688362>
42. Atangana E, et al. Intravascular inflammation triggers intracerebral activated microglia and contributes to secondary brain injury after experimental subarachnoid hemorrhage (eSAH). *Transl Stroke Res*. 2017;8(2):144–56. <https://doi.org/10.1007/s12975-016-0485-3>
43. Koopman I, et al. Glial cell response and microthrombosis in aneurysmal subarachnoid hemorrhage patients: An autopsy study. *J Neuropathol Exp Neurol*. 2023;82:798–805. <https://doi.org/10.1093/jnen/nlad050>
44. Liu Y, et al. Acacetin inhibits activation of microglia to improve neuroinflammation after subarachnoid hemorrhage through the PERK signaling pathway mediated autophagy. *Hum Exp Toxicol*. 2024;43:9603271241251447. <https://doi.org/10.1177/09603271241251447>
45. Yamada H, et al. Subarachnoid hemorrhage triggers neuroinflammation of the entire cerebral cortex, leading to neuronal cell death. *Inflamm Regen*. 2022;42(1):61. <https://doi.org/10.1186/s41232-022-00236-4>
46. Gallia GL, Tamargo RJ. Leukocyte-endothelial cell interactions in chronic vasospasm after subarachnoid hemorrhage. *Neurol Res*. 2006;28(7):750–8. <https://doi.org/10.1179/016164106X152025>
47. Coulibaly AP, et al. Neutrophil enzyme myeloperoxidase modulates neuronal response in a model of subarachnoid hemorrhage by venous injury. *Stroke*. 2021;52(10):3374–84. <https://doi.org/10.1161/STROKEAHA.120.033513>
48. Li Z, et al. Blood-brain barrier permeability change and regulation mechanism after subarachnoid hemorrhage. *Metab Brain Dis*. 2015;30(2):597–603. <https://doi.org/10.1007/s11011-014-9609-1>
49. Perez-de-Puig I, et al. Neutrophil recruitment to the brain in mouse and human ischemic stroke. *Acta Neuropathol*. 2015;129:239–57. <https://doi.org/10.1007/s00401-014-1381-0>
50. Schöller K, et al. Characterization of microvascular basal lamina damage and blood-brain barrier dysfunction following subarachnoid hemorrhage in rats. *Brain Res*. 2007;1142:237–46. <https://doi.org/10.1016/j.brainres.2007.01.034>

51. Fujimoto M, et al. Effects of tenascin-C knockout on cerebral vasospasm after experimental subarachnoid hemorrhage in mice. *Mol Neurobiol.* 2018;55(3):1951–8. <https://doi.org/10.1007/s12035-017-0466-x>
52. Okada T, Kawakita F, Nishikawa H, Nakano F, Liu L, Suzuki H. Selective toll-like receptor 4 antagonists prevent acute blood-brain barrier disruption after subarachnoid hemorrhage in mice. *Mol Neurobiol.* 2019;56(2):976–85. <https://doi.org/10.1007/s12035-018-1145-2>
53. Liu L, Zhang X, Chai Y, Zhang J, Deng Q, Chen X. Skull bone marrow and skull meninges channels: redefining the landscape of central nervous system immune surveillance. *Cell Death Dis.* 2025;16(1):53 <https://doi.org/10.1038/s41419-025-07336-2>
54. Friedrich V, Flores R, Muller A, Bi W, Peerschke EI, Sehba. Reduction of neutrophil activity decreases early microvascular injury after subarachnoid haemorrhage. *J Neuroinflammation.* 2011;8:103. <https://doi.org/10.1186/1742-2094-8-103>.
55. Sabri M, Ai J, Lakovic K, D'abbonanza J, Ildigwe D, Macdonald. Mechanisms of microthrombi formation after experimental subarachnoid hemorrhage. *Neuroscience.* 2012;224:26–37. <https://doi.org/10.1016/j.neuroscience.2012.08.002>.
56. Osuka K, Watanabe Y, Suzuki C, Iwami K, et S., Miyachi. Sequential expression of neutrophil chemoattractants in cerebrospinal fluid after subarachnoid hemorrhage. *J Neuroimmunol.* 2021;357:577610. <https://doi.org/10.1016/j.jneuroim.2021.577610>.
57. Akamatsu Y, Pagan VA, Hanafy KA. The role of TLR4 and HO-1 in neuroinflammation after subarachnoid hemorrhage. *J Neurosci Res.* 2020;98(3):549–56. <https://doi.org/10.1002/jnr.24515>
58. Ishikawa M, et al. Platelet and leukocyte adhesion in the microvasculature at the cerebral surface immediately after subarachnoid hemorrhage. *Neurosurgery.* 2009;64:546–53. <https://doi.org/10.1227/01.NEU.0000337579.05110.F4>
59. Solár P, Zamani A, Lakatosová K, Joukal M. The blood-brain barrier and the neurovascular unit in subarachnoid hemorrhage: molecular events and potential treatments. *Fluids Barriers CNS.* 2022;19(1):29. <https://doi.org/10.1186/s12987-022-00312-4>
60. Ishikawa M, et al. Leukocyte plugging and cortical capillary flow after subarachnoid hemorrhage. *Acta Neurochir (Wien).* 2016;158:1057–67. <https://doi.org/10.1007/s00701-016-2792-6>
61. Neulen A, et al. Neutrophils mediate early cerebral cortical hypoperfusion in a murine model of subarachnoid haemorrhage. *Sci Rep.* 2019;9(1):8460 <https://doi.org/10.1038/s41598-019-44906-9>
62. Guo Z, Sun X, He Z, Jiang Y, Zhang X. Role of matrix metalloproteinase-9 in apoptosis of hippocampal neurons in rats during early brain injury after subarachnoid hemorrhage. *Neurol Sci.* 2010;31(2):143–9 <https://doi.org/10.1007/s10072-009-0192-x>
63. Provencio JJ, et al. Neutrophil depletion after subarachnoid hemorrhage improves memory via NMDA receptors. *Brain Behav Immun.* 2016;54:233–42. <https://doi.org/10.1016/j.bbi.2016.02.007>.
64. Eyo UB, et al. The GluN2A subunit regulates neuronal NMDA receptor-induced microglia-neuron physical interactions. *Sci Rep.* 2018;8(1):828 <https://doi.org/10.1038/s41598-018-19205-4>
65. Morris RGM, Anderson E, Lynch GS, Baudry M. Selective impairment of learning and blockade of long-term potentiation by an N-methyl-D-aspartate receptor antagonist, AP5. *Nature.* 1986;319(6056):774–6 <https://doi.org/10.1038/319774a0>
66. Csomós K, et al. Protein cross-linking by chlorinated polyamines and transglutamylation stabilizes neutrophil extracellular traps. *Cell Death Dis.* 2016;7:e2332–2332. <https://doi.org/10.1038/cddi.2016.200>
67. Martinod K, Wagner DD. Thrombosis: tangled up in NETs. *Blood.* 2014;123(18):2768–76. <https://doi.org/10.1182/blood-2013-10-463646>
68. Tu H, Ren H, Jiang J, Shao C, Shi Y, Li P. Dying to defend: Neutrophil death pathways and their implications in immunity. *Adv Sci (Weinh).* 2023;11(8):2306457. <https://doi.org/10.1002/advs.202306457>
69. Yousefi S, Mihalache C, Kozłowski E, Schmid I, Simon HU. Viable neutrophils release mitochondrial DNA to form neutrophil extracellular traps. *Cell Death Differ.* 2009;16(11):1438–44. <https://doi.org/10.1038/cdd.2009.96>
70. Kayhanian S, et al. Cell-free mitochondrial DNA in acute brain injury. *Neurotrauma Rep.* 2022;3(1):415–20. <https://doi.org/10.1089/neur.2022.0032>
71. Pilsczek FH, et al. A novel mechanism of rapid nuclear neutrophil extracellular trap formation in response to *Staphylococcus aureus*. *J Immunol.* 2010;185:7413–25. <https://doi.org/10.4049/jimmunol.1000675>
72. Clark SR, et al. Platelet TLR4 activates neutrophil extracellular traps to ensnare bacteria in septic blood. *Nat Med.* 2007;13(4):463–9. <https://doi.org/10.1038/nm1565>
73. Zhao XD, Mao HY, Lv J, et, Lu XJ. Expression of high-mobility group box-1 (HMGB1) in the basilar artery after experimental subarachnoid hemorrhage. *J Clin Neurosci.* 2016;27:161–5. <https://doi.org/10.1016/j.jocn.2015.06.034>.
74. Balança B, Desmurs L, Grelier J, Perret-Liaudet A, Lukaszewicz AC. DAMPs and RAGE pathophysiology at the acute phase of brain injury: An Overview. *Int J Mol Sci.* 2021;22(5):2439. <https://doi.org/10.3390/ijms22052439>
75. Coulibaly AP, Provencio JJ. Aneurysmal subarachnoid hemorrhage: an Overview of inflammation-induced cellular changes. *Neurotherapeutics.* 2020;17(2):436–45. <https://doi.org/10.1007/s13311-019-00829-x>
76. Hemmer S, et al. Admission serum high mobility group box 1 (HMGB1) protein predicts delayed cerebral ischemia following aneurysmal subarachnoid hemorrhage. *Neurosurg Rev.* 2022;45(1):807–17. <https://doi.org/10.1007/s10143-021-01607-0>
77. Kim S-W, Lee H, Lee H-K, Kim I-D, Lee. Neutrophil extracellular trap induced by HMGB1 exacerbates damages in the ischemic brain. *Acta Neuropathol Commun.* 2019;7(1):94. <https://doi.org/10.1186/s40478-019-0747-x>
78. Maugeri N, et al. Activated platelets present high mobility group box 1 to neutrophils, inducing autophagy and promoting the extrusion of neutrophil extracellular traps. *J Thromb Haemost.* 2014;12(12):2074–88. <https://doi.org/10.1111/jth.12710>
79. Shen H, Tesar BM, Walker WE, Goldstein DR. Dual signaling of MyD88 and TRIF are Critical for Maximal TLR4-induced dendritic cell maturation. *J Immunol.* 2008;181(3):1849–58. <https://doi.org/10.4049/jimmunol.181.3.1849>
80. Wu Y, et al. Peroxisome proliferator-activated receptor gamma agonist rosiglitazone attenuates oxyhemoglobin-induced Toll-like receptor 4 expression in vascular smooth muscle cells. *Brain Res.* 2010;1322:102–8. <https://doi.org/10.1016/j.brainres.2010.1.073>.
81. Kwon MS, et al. Methemoglobin is an endogenous toll-like receptor 4 ligand-relevance to subarachnoid hemorrhage. *Int J Mol Sci.* 2015;16(3):5028–46 <https://doi.org/10.3390/ijms16035028>
82. Yipp BG, et al. Infection-induced NETosis is a dynamic process involving neutrophil multitasking in vivo. *Nat Med.* 2012;18(9):1386–93. <https://doi.org/10.1038/nm.2847>
83. You W-C, et al. Activation of nuclear factor-κB in the brain after experimental subarachnoid hemorrhage and its potential role in delayed brain injury. *PLoS ONE.* 2013;8(3):e60290. <https://doi.org/10.1371/journal.pone.0060290>
84. An Z, et al. Neutrophil extracellular traps induced by IL-8 aggravate atherosclerosis via activation NF-κB signaling in macrophages. *Cell Cycle.* 2019;18:2928–38. <https://doi.org/10.1080/15384101.2019.1662678>

85. Yan H, et al. Inhibition of myeloid differentiation primary response protein 88 provides neuroprotection in early brain injury following experimental subarachnoid hemorrhage. *Sci Rep*. 2017;7(1):15797. <https://doi.org/10.1038/s41598-017-16124-8>
86. Chaudhry SR, et al. Role of Damage associated molecular pattern molecules (DAMPs) in aneurysmal subarachnoid hemorrhage (aSAH). *Int J Mol Sci*. 2018;19(7):p2035. <https://doi.org/10.3390/ijms19072035>
87. Thiam HR, Wong SL, Wagner DD, Waterman CM. Cellular mechanisms of NETosis. *Annu Rev Cell Dev Biol*. 2020;36:191–218. <https://doi.org/10.1146/annurev-cellbio-020520-111016>
88. Wu F, et al. Inflammation and Oxidative Stress: Potential Targets for Improving Prognosis After Subarachnoid Hemorrhage. *Front Cell Neurosci*. 2021;15:739506. <https://doi.org/10.3389/fncel.2021.739506>
89. Akeret K, et al. The HeMoVal study protocol: a prospective international multicenter cohort study to validate cerebrospinal fluid hemoglobin as a monitoring biomarker for aneurysmal subarachnoid hemorrhage related secondary brain injury. *BMC Neurol*. 2022;22(1):1–267. <https://doi.org/10.1186/s12883-022-02789-w>
90. Kono M, et al. Heme-related molecules induce rapid production of neutrophil extracellular traps. *Transfusion*. 2014;54(11):2811–9. <https://doi.org/10.1111/trf.12700>
91. Weng W, Cheng F, Zhang. Specific signature biomarkers highlight the potential mechanisms of circulating neutrophils in aneurysmal subarachnoid hemorrhage. *Front Pharmacol*. 2022;13:1022564. <https://doi.org/10.3389/fphar.2022.1022564>
92. Kearney PL, et al. Kinetic characterization of protein arginine deiminase 4: a transcriptional corepressor implicated in the onset and progression of rheumatoid arthritis. *Biochemistry*. 2005;44(31):10570–82. <https://doi.org/10.1021/bi050292m>
93. Rohrbach AS, Slade DJ, Thompson PR, Mowen. Activation of PAD4 in NET formation. *Front Immunol*. 2012;3:360. <https://doi.org/10.3389/fimmu.2012.00360>
94. Sehba FA, Mostafa G, Friedrich V, Bederson. Acute microvascular platelet aggregation after subarachnoid hemorrhage. *J Neurosurg*. 2005;102(6):1094–100. <https://doi.org/10.3171/jns.2005.102.6.1094>
95. Clatterbuck RE, et al. Prevention of cerebral vasospasm by a humanized anti-CD11/CD18 monoclonal antibody administered after experimental subarachnoid hemorrhage in nonhuman primates. *J Neurosurg*. 2003;99(2):376–82. <https://doi.org/10.3171/jns.2003.99.2.0376>
96. Frontera JA, et al. The role of platelet activation and inflammation in early brain injury following subarachnoid hemorrhage. *Neurocrit Care*. 2017;26:48–57. <https://doi.org/10.1007/s12028-016-0292-4>
97. Carestia A, et al. Mediators and molecular pathways involved in the regulation of neutrophil extracellular trap formation mediated by activated platelets. *J Leukoc Biol*. 2016;99(1):153–62. <https://doi.org/10.1189/jlb.3A0415-161R>
98. Nakazawa D, et al. Activated platelets induce MLKL-driven neutrophil necroptosis and release of neutrophil extracellular traps in venous thrombosis. *Cell Death Discov*. 2018;4(1):1. <https://doi.org/10.1038/s41420-018-0073-2>
99. Denorme F, et al. Platelet necrosis mediates ischemic stroke outcome in mice. *Blood*. 2020;135:429–40. <https://doi.org/10.1182/blood.2019002124>
100. McDonald B, Urrutia R, Yipp BG, Jenne CN, Kubes P. Intravascular neutrophil extracellular traps capture bacteria from the bloodstream during sepsis. *Cell Host Microbe*. 2012;12(3):324–33. <https://doi.org/10.1016/j.chom.2012.06.011>
101. Kollikowski AM, et al. Platelet activation and chemokine release are related to local neutrophil-dominant inflammation during hyperacute human Stroke. *Transl Stroke Res*. 2022;13(3):364–9. <https://doi.org/10.1007/s12975-021-00938-w>
102. Khan D, Fischer I, Sahan S, Hewera M, Faust K, Muhammad. Platelet factor 4 and stromal cell-derived factor are novel prognostic biomarkers for cerebral vasospasm and mortality after subarachnoid hemorrhage. *Sci Rep*. 2025;15(1):32371. <https://doi.org/10.1038/s41598-025-18117-4>
103. Ducroux C, et al. Thrombus neutrophil extracellular traps content impair tPA-Induced thrombolysis in acute ischemic stroke. *Stroke*. 2018;49:754–7. <https://doi.org/10.1161/STROKEAHA.117.019896>
104. Davis JC, et al. Recombinant human Dnase I (rhDNase) in patients with lupus nephritis. *Lupus*. 1999;8(1):68–76. <https://doi.org/10.1191/096120399678847380>
105. Veras FP, et al. SARS-CoV-2-triggered neutrophil extracellular traps mediate COVID-19 pathology. *J Exp Med*. 2020;217(12):e20201129. <https://doi.org/10.1084/jem.20201129>
106. Zhou P, et al. Interactions between neutrophil extracellular traps and activated platelets enhance procoagulant activity in acute stroke patients with ICA occlusion. *EBioMedicine*. 2020;53:102671. <https://doi.org/10.1016/j.ebiom.2020.102671>
107. Nakagawa R, Itokazu T, Shibuya N, Kishima H, Yamashita T. Perivascular neutrophil extracellular traps exacerbate microvasospasm after experimental subarachnoid hemorrhage. *Stroke*. 2024;55:2872–81. <https://doi.org/10.1161/STROKEAHA.124.047574>
108. Früh A, et al. RNase A Inhibits Formation of Neutrophil Extracellular Traps in Subarachnoid Hemorrhage. *Front Physiol*. 2021;12:724611. <https://doi.org/10.3389/fphys.2021.724611>
109. Zeng H, et al. Neutrophil extracellular traps may be a potential target for treating early brain injury in subarachnoid hemorrhage. *Transl Stroke Res*. 2022;13(1):112–31. <https://doi.org/10.1007/s12975-021-00909-1>
110. Schneider H, et al. Neutrophil extracellular traps and delayed cerebral ischemia in patients with subarachnoid hemorrhage. *J Am Heart Assoc*. 2025;14(19):e041325. <https://doi.org/10.1161/JAHA.124.041325>
111. Witsch J, et al. Neutrophil extracellular traps and delayed cerebral ischemia in aneurysmal subarachnoid hemorrhage. *Crit Care Explor*. 2022;4(5):e0692. <https://doi.org/10.1097/CCE.0000000000000692>
112. Hayden H, et al. ELISA detection of MPO-DNA complexes in human plasma is error-prone and yields limited information on neutrophil extracellular traps formed in vivo. *PLoS ONE*. 2021;16(4):e0250265. <https://doi.org/10.1371/journal.pone.0250265>
113. Sajjad S, Hewera M, Rana M, Gliem M, Fischer I, Khan etD. Neutrophils extracellular traps myeloperoxidase and elastase predict cerebral vasospasms after aneurysmal subarachnoid hemorrhage. *Heliyon*. 2024;10(23):e40562. <https://doi.org/10.1016/j.heliyon.2024.e40562>
114. Fuchs TA, et al. Extracellular DNA traps promote thrombosis. *Proc Natl Acad Sci U S A*. 2010;107(36):15880–5. <https://doi.org/10.1073/pnas.1005743107>
115. von Brühl M-L, et al. Monocytes, neutrophils, and platelets cooperate to initiate and propagate venous thrombosis in mice in vivo. *J Exp Med*. 2012;209(4):819–35. <https://doi.org/10.1084/jem.20112322>
116. Kannemeier C, et al. Extracellular RNA constitutes a natural procoagulant cofactor in blood coagulation. *Proc Natl Acad Sci U S A*. 2007;104(15):6388–93. <https://doi.org/10.1073/pnas.0608647104>
117. Kambas K, et al. Autophagy mediates the delivery of thrombogenic tissue factor to neutrophil extracellular traps in human sepsis. *PLoS ONE*. 2012;7:e45427. <https://doi.org/10.1371/journal.pone.0045427>
118. Semeraro F. Extracellular histones promote thrombin generation through platelet-dependent mechanisms: involvement of platelet

- TLR2 and TLR4. *Blood*. 2011;118(7):1952–61. <https://doi.org/10.1182/blood-2011-03-343061>
119. Dienel A, Kumar P, Blackburn SL, McBride DW. Role of platelets in the pathogenesis of delayed injury after subarachnoid hemorrhage. *J Cereb Blood Flow Metabolism*. 2021;41(11):2820–30. <https://doi.org/10.1177/0271678X211020865>
 120. Da DE, Silva, et al. Extracellular mixed histones are neurotoxic and modulate select neuroimmune responses of glial cells. *PLoS ONE*. 2024;19(4):e0298748. <https://doi.org/10.1371/journal.pone.0298748>
 121. Zhang T, Su J, Guo B, Wang K, Li X, Liang. Apigenin protects blood-brain barrier and ameliorates early brain injury by inhibiting TLR4-mediated inflammatory pathway in subarachnoid hemorrhage rats. *Int Immunopharmacol*. 2015;28(1):79–87. <https://doi.org/10.1016/j.intimp.2015.05.024>
 122. Islam R, Vrionis F, Hanafy KA. Microglial TLR4 is critical for neuronal injury and cognitive dysfunction in subarachnoid hemorrhage. *Neurocrit Care*. 2022;37:761–9. <https://doi.org/10.1007/s12028-022-01552-w>
 123. Chen J, Zheng ZV, Lu G, Chan WY, Zhang Y, Wong KC. Microglia activation, classification and microglia-mediated neuroinflammatory modulators in subarachnoid hemorrhage. *Neural Regen Res*. 2022;17(7):1404–11. <https://doi.org/10.4103/1673-5374.330589>
 124. Hanafy KA. The role of microglia and the TLR4 pathway in neuronal apoptosis and vasospasm after subarachnoid hemorrhage. *J Neuroinflammation*. 2013;10:83. <https://doi.org/10.1186/1742-2094-10-83>
 125. Hanhai Z, et al. Neutrophil extracellular traps, released from neutrophil, promote microglia inflammation and contribute to poor outcome in subarachnoid hemorrhage. *Aging*. 2021;13(9):13108–23. <https://doi.org/10.18632/aging.202993>
 126. Ma C, et al. Neutrophil extracellular traps activate meningeal fibroblast to aggravate subarachnoid fibrosis in kaolin-induced hydrocephalus in rats. *Immun Inflamm Dis*. 2025;13(11):e70268. <https://doi.org/10.1002/iid3.70268>
 127. Tuz AA, et al. Stroke and myocardial infarction induce neutrophil extracellular trap release disrupting lymphoid organ structure and immunoglobulin secretion. *Nat Cardiovasc Res*. 2024;3(5):525–40. <https://doi.org/10.1038/s44161-024-00462-8>
 128. Mohanty T, et al. Neutrophil extracellular traps in the central nervous system hinder bacterial clearance during pneumococcal meningitis. *Nat Commun*. 2019;10(1) <https://doi.org/10.1038/s41467-019-09040-0>
 129. Wu X, Guo Y, Zeng H, Chen G. DNase-1 treatment exerts protective effects in neurogenic pulmonary edema via regulating the neutrophil extracellular traps after subarachnoid hemorrhage in mice. *J Clin Med*. 2022;11:4349. <https://doi.org/10.3390/jcm11154349>
 130. Chen S, et al. Role of P2X Purinoceptor 7 in Neurogenic Pulmonary Edema after Subarachnoid Hemorrhage in Rats. *PLoS ONE*. 2014;9(2):e89042. <https://doi.org/10.1371/journal.pone.0089042>
 131. Liu S, et al. Quercetin mitigates lysophosphatidylcholine (LPC)-Induced neutrophil extracellular traps (NETs) formation through inhibiting the P2X7R/P38MAPK/NOX2 Pathway. *Int J Mol Sci*. 2024;25(17):9411. <https://doi.org/10.3390/ijms25179411>
 132. Chen J, et al. Melatonin attenuates neurogenic pulmonary edema via the regulation of inflammation and apoptosis after subarachnoid hemorrhage in rats. *J Pineal Res*. 2015;59(4):469–77. <https://doi.org/10.1111/jpi.12278>
 133. Geraghty JR, Saini NS, Deshpande A, Cheng T, Nazir N, Tsetai FD. The role of serum monocytes and tissue macrophages in driving left ventricular systolic dysfunction and cardiac inflammation following subarachnoid hemorrhage. *Neurocrit Care*. 2024;40(3):1127–39. <https://doi.org/10.1007/s12028-023-01891-2>
 134. Chen J, et al. A β 1–40 oligomers trigger neutrophil extracellular trap formation through TLR4- and NADPH oxidase-dependent pathways in age-related macular degeneration. *Oxidative Med Cell Longev*. 2022;2022(1):6489923. <https://doi.org/10.1155/2022/6489923>
 135. Mutua V, Gershwin LJ. A review of neutrophil extracellular traps (NETs) in disease: Potential anti-NETs Therapeutics. *Clin Rev Allerg Immunol*. 2021;61(2):194–211. <https://doi.org/10.1007/s12016-020-08804-7>
 136. Hernández-Jiménez M, et al. A double-blind, placebo-controlled, randomized, Phase Ib/Ia clinical study of ApTOLL for the treatment of acute ischemic stroke. *Front Neurol*. 2023;14:1127585. <https://doi.org/10.3389/fneur.2023.1127585>
 137. Okada T, Lei L, Nishikawa H, Nakano F, Nakatsuka Y, Suzuki H. TAK-242, Toll-like receptor 4 antagonist, attenuates brain edema in subarachnoid hemorrhage mice. *Acta Neurochir Suppl*. 2020;127:77–81. https://doi.org/10.1007/978-3-030-04615-6_13
 138. Khan MA, et al. JNK Activation turns on LPS- and gram-negative bacteria-induced NADPH oxidase-dependent suicidal NETosis. *Sci Rep*. 2017;7(1):3409. <https://doi.org/10.1038/s41598-017-03257-z>
 139. Metzler KD, et al. Myeloperoxidase is required for neutrophil extracellular trap formation: implications for innate immunity. *Blood*. 2011;117(3):953–9. <https://doi.org/10.1182/blood-2010-06-290171>
 140. Ülken A, et al. Myeloperoxidase-derived oxidants induce blood-brain barrier dysfunction in vitro and in vivo. *PLoS ONE*. 2013;8(5):e64034. <https://doi.org/10.1371/journal.pone.0064034>
 141. Pravalika K, et al. Myeloperoxidase and neurological disorder: A crosstalk. *ACS Chem Neurosci*. 2018;9(3):421–30. <https://doi.org/10.1021/acscchemneuro.7b00462>
 142. Jucaite A, et al. Effect of the myeloperoxidase inhibitor AZD3241 on microglia: a PET study in Parkinson's disease. *Brain*. 2015;138(Pt 9):2687–700. <https://doi.org/10.1093/brain/awv184>
 143. Limon S, Coulibaly AP, Provencio JJ. Small molecule myeloperoxidase (MPO) Inhibition prevents delayed cerebral injury (DCI) After subarachnoid hemorrhage (SAH) in a murine model. *Neurocrit Care*. 2025;42:945–52. <https://doi.org/10.1007/s12028-024-02169-x>
 144. Triglia T, et al. Early matrix metalloproteinase-9 concentration in the first 48 h after aneurysmal subarachnoid haemorrhage predicts delayed cerebral ischaemia: An observational study. *Eur J Anaesthesiol*. 2016;33(9):662–9. <https://doi.org/10.1097/EJA.0000000000000494>
 145. Chou SH-Y, et al. Elevated peripheral neutrophils and matrix metalloproteinase 9 as biomarkers of functional outcome following subarachnoid hemorrhage. *Transl Stroke Res*. 2011;2(4):600–7. <https://doi.org/10.1007/s12975-011-0117-x>
 146. Mehta V, et al. Matrix metalloproteinases in cerebral vasospasm following aneurysmal subarachnoid hemorrhage. *Neurol Res Int*. 2013;2013:943761. <https://doi.org/10.1155/2013/943761>
 147. Vellimana AK, et al. Minocycline protects against delayed cerebral ischemia after subarachnoid hemorrhage via matrix metalloproteinase-9 inhibition. *Ann Clin Transl Neurol*. 2017;4(12):865–76. <https://doi.org/10.1002/acn3.492>
 148. Yao M, et al. Neutrophil extracellular traps mediate deep vein thrombosis: from mechanism to therapy. *Front Immunol*. 2023;14:1198952. <https://doi.org/10.3389/fimmu.2023.1198952>
 149. Zeineddine HA, et al. Neutrophils and neutrophil extracellular traps cause vascular occlusion and delayed cerebral ischemia after subarachnoid hemorrhage in mice. *ATVB*. 2024;44(3):635–52. <https://doi.org/10.1161/ATVBAHA.123.320224>
 150. Demkow U. Molecular Mechanisms of Neutrophil Extracellular Trap (NETs) Degradation. *Int J Mol Sci*. 2023;24(5):4896. <https://doi.org/10.3390/ijms24054896>

151. Santocki M, Kolaczowska E. On neutrophil extracellular trap (NET) Removal: What we know thus far and why so little. *Cells*. 2020;9(9):2079. <https://doi.org/10.3390/cells9092079>
152. Hendrix P, et al. Neutrophil extracellular trap biomarkers in aneurysmal subarachnoid hemorrhage: early decline of DNase 1 activity associated with delayed cerebral ischemia. *Front Neurol*. 2024;15. <https://doi.org/10.3389/fneur.2024.1354224>.
153. Hao X, et al. The role of neutrophil extracellular traps in early microthrombosis and brain injury after subarachnoid hemorrhage in mice. *Transl Stroke Res*. 2022;1–14. <https://doi.org/10.1007/s12975-022-01074-9>
154. Zhou J, Guo P, Hao X, Sun X, Feng H, Chen Z. Neutrophil extracellular traps (NETs): A new therapeutic target for neuroinflammation and microthrombosis after subarachnoid hemorrhage? *Transl Stroke Res*. 2022;1–3. <https://doi.org/10.1007/s12975-022-01039-y>
155. García-Pastor C, et al. Neuroprotective effect of dapsone in patients with aneurysmal subarachnoid hemorrhage: a prospective, randomized, double-blind, placebo-controlled clinical trial. *Neurosurg Focus*. 2022;(3):52. <https://doi.org/10.3171/2021.12.FOCUS21663>
156. Bozeman PM, Learn DB, Thomas EL. Inhibition of the human leukocyte enzymes myeloperoxidase and eosinophil peroxidase by dapsone. *Biochem Pharmacol*. 1992;44(3):553–63. [https://doi.org/10.1016/0006-2952\(92\)90449-S](https://doi.org/10.1016/0006-2952(92)90449-S)
157. Strickland BA, et al. Minocycline decreases blood-brain barrier permeability following aneurysmal subarachnoid hemorrhage: a randomized, double-blind, controlled trial. *J Neurosurg*. 2022;136(5):1251–9. <https://doi.org/10.3171/2021.6.JNS211270>
158. Tseng M-Y et al. Acute systemic erythropoietin therapy to reduce delayed ischemic deficits following aneurysmal subarachnoid hemorrhage: a Phase II randomized, double-blind, placebo-controlled trial. 2009. <https://doi.org/10.3171/2009.3.JNS081332>
159. Wu X, et al. Mechanism of erythropoietin-induced M2 microglia polarization via Akt / Mtor / P70S6k signaling pathway in the treatment of brain injury in premature mice and its effect on bio-film. *Bioengineered*. 2022;13(5):13021–32. . <https://doi.org/10.1080/21655979.2022.2073000>
160. Johnson AJ, Ayvazian JH, Tillett WS. Crystalline pancreatic desoxyribonuclease as an adjunct to the treatment of pneumococcal meningitis. *N Engl J Med*. 1959;260(18):893–900. <https://doi.org/10.1056/NEJM195904302601801>
161. Ayvazian JH, Johnson AJ, Tillett WS. The use of parenterally administered pancreatic desoxyribonuclease as an adjunct in the treatment of pulmonary abscesses. *Am Rev Tuberc*. 1957;76(1):1–21. <https://doi.org/10.1164/artpd.1957.76.1.1>
162. Johnson AJ, Goger PR, Tillett WS. The intravenous injection of bovine crystalline pancreatic desoxyribonuclease into patients. *J Clin Invest*. 1954;33(12):1670–86. <https://doi.org/10.1172/JCI113048>
163. Ayvazian JH. Ayvazian. Effect of intravenous administration of crystalline pancreatic desoxyribonuclease in patients with gout. *N Engl J Med*. 1960;263(20):999–1002. <https://doi.org/10.1056/NEJM196011172632005>
164. Wang Y, et al. SOCS1/JAK2/STAT3 axis regulates early brain injury induced by subarachnoid hemorrhage via inflammatory responses. *Neural Regen Res*. 2021;16(12):2453–64. . <https://doi.org/10.4103/1673-5374.313049>
165. Zanaty M, et al. Phase 1/2a Trial of ISPASM. *Stroke*. 2021;52(12):3750–8. <https://doi.org/10.1161/STROKEAHA.121.034578>
166. Musmar B, et al. Outcomes of external ventricular drainage and lumbar drainage in aneurysmal subarachnoid hemorrhage: A systematic review and meta-analysis. *Int J Stroke*. 2025;20(10):1201–13. . <https://doi.org/10.1177/17474930251361211>
167. Englert H, et al. Targeting NETs using dual-active DNase1 variants. *Front Immunol*. 2023;14. <https://doi.org/10.3389/fimmu.2023.1181761>
168. Koopman I, Zuithoff NPA, Rinkel GJE, D. I. Vergouwen. The course of cerebrospinal fluid parameters ≤20 days after aneurysmal subarachnoid hemorrhage. *J Neurol Sci*. 2020;415:116899. <https://doi.org/10.1016/j.jns.2020.116899>.
169. Roa JA, et al. Preliminary results in the analysis of the immune response after aneurysmal subarachnoid hemorrhage. *Sci Rep*. 2020;10(1):11809. <https://doi.org/10.1038/s41598-020-68861-y>
170. Spurgeon BEJ et, Frelinger AL. OMIP-097: High-parameter phenotyping of human platelets by spectral flow cytometry. *Cytometry A*. 2023;103(12):935–40. <https://doi.org/10.1002/cyto.a.24797>
171. Jank L, Pinto-Espinoza C, Duan Y, Koch-Nolte F, Magnus TB, Rissiek. Current approaches and future perspectives for nanobodies in stroke diagnostic and therapy. *Antibodies (Basel)*. 2019;8(1):5. . <https://doi.org/10.3390/antib8010005>
172. Expression of Concern for: Mechanisms of osteopontin-induced stabilization of blood-brain barrier disruption after subarachnoid hemorrhage in rats. *Stroke*. <https://doi.org/10.1161/STR.00000000000000510>
173. Retraction. Inhibition of NADPH oxidase attenuates vasospasm after experimental subarachnoid hemorrhage in rats. *Stroke*. 2011;42(7):2117. <https://doi.org/10.1161/STR.0b013e318222b160>
174. Aquarius R, van de Voort M, Boogaarts HD, Reesink PM, Wever KE. High prevalence of articles with image-related problems in animal studies of subarachnoid hemorrhage and low rates of correction by publishers. *PLOS Biol*. 2025;23(10):e3003438. . <https://doi.org/10.1371/journal.pbio.3003438>

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