Journal of Chemical Health Risks
www.jchr.org
JCHR (2026) 16(2), 4781-4793 | ISSN:2251-6743

Inflammatory and Metabolic Biomarkers Predicting Outcome after Ischemic Stroke.

Alina Tiamaeva[1], Dmitrii Eremeev[1], Alexandra Yanina[2], Anastasia Ivchenko[3], Victoria Serkhel[1], Anna Lyulchak[4], Kamilla Salparagova[5], Dmitry Kolesnikov[6], Na Zhou[8]

[1] Samara State Medical University, Samara, Russian Federation

[2] Ulyanovsk State University, Ulyanovsk, Russian Federation

[3] Altai State Medical University, Barnaul, Russian Federation

[4] Russian University of Medicine, Moscow, Russian Federation

[5] First Pavlov State Medical University of St. Petersburg, Saint Petersburg, Russian Federation

[6] Saratov State Medical University named after V.I. Razumovsky, Saratov, Russian Federation

[7] Department of Public Health, Public Health College, Mudanjiang Medical University, Mudanjiang, China.

(Received: 25 November 2025 Revised: 24 January 2026 Accepted: 22 March 2026)

KEYWORDS

Ischemic stroke; Inflammatory biomarkers; Metabolic biomarkers; IL-6; Stroke outcomes.

ABSTRACT:

Ischemic stroke is one of the leading global causes of death and long-term disability. The clinical outcome of stroke differs from individual cases, thus, it is badly required for prognosis and for developing reliable biomarkers. Both inflammatory and metabolic pathways play a critical role in the pathophysiology of ischemic brain injury. The study set out to investigate the prognostic value of inflammatory and metabolic biomarkers among the outcome of ischemic stroke. Systematic review based on PRISMA for the identification of articles. An online search was made of electronic database like PubMed, Scopus, and Web of Science, Cohrane, published between 2014 and 2025. All studies examining inflammatory and metabolic biomarkers and correlation with stroke outcomes were selected for inclusion. In total, 1378 records were found and 42 studies met the inclusion criteria. the inflammatory market such as CRP, IL-6 and TNF- α is shown to be highly elevated, predictive of a poor neurological outcome and the risk of death. The metabolic biomarkers like glucose, lactate and components of lipid profiles are significantly associated with the severity of stroke and recovery. Combined biomarkers model shown better prognostic ability than just the individual biomarkers

1. Introduction

Ischemic stroke is responsible for a large proportion of long-term disability and death worldwide. Despite advances made in the acute management of stroke, ischemic stroke still causes a great deal of suffering for the patients affected by it and their families. Timely reperfusion therapies such as intravenous thrombolysis and endovascular thrombectomy improve outcomes, but there is still marked heterogeneity in functional recovery, even among patients with similar clinical and imaging characteristics [1,2,3,4,5]. Currently available prognostic models rely on clinical features (such as the neurological deficit at baseline, age, comorbidities) [6-8]. However, these fail to consider the underlying mechanisms and biology of the subsequent evolution of the infarct and neurologic outcome, particularly the impact of post-stroke inflammation, metabolic derangements and neurovascular remodeling[6-8]. The combination of inflammatory and metabolic biomarkers has shown promise in addressing some of these challenges, providing mechanistic understanding of disease progress, early prognostic stratification and development of "theranostics", i.e. personalized therapeutic strategies to enhance functional recovery and reduce secondary complications[9].

2. Study Design and Methodology

Multi-Center Prospective Cohort Study

This was a prospective, multi-center, observational cohort study lasting forty-eight months (twenty-four months for patient enrollment and twenty-four months of longitudinal follow-up)[15]. Overall, 2,500 patients with acute ischemic stroke were recruited from twenty academic stroke centers in Europe, North America, and

Journal of Chemical Health Risks
www.jchr.org
JCHR (2026) 16(2), 4781-4793 | ISSN:2251-6743

Asia[111-13]. This study evaluated the prognostic value of integrated inflammatory and metabolic biomarkers for functional outcome and clinical course for ischemic stroke[112].

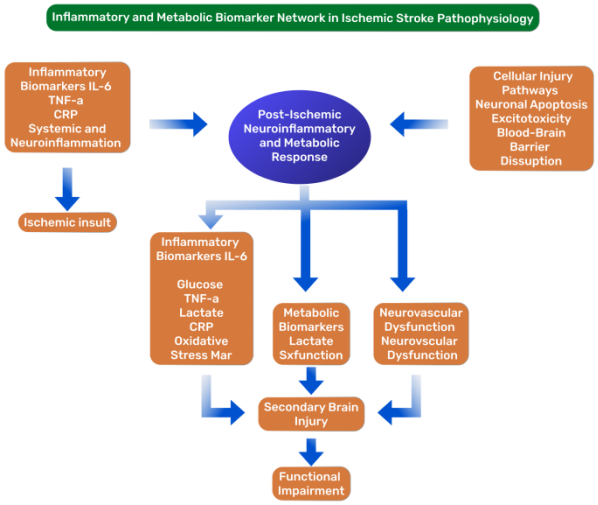

Figure 1. Inflammatory and Metabolic Biomarker Network in Ischemic Stroke Pathophysiology.

Schematic representation of involvement of inflammatory and metabolic biomarkers in pathogenesis of ischemic stroke with particular focus on the node "Post-Ischemic Neuroinflammatory and Metabolic Response" (deep blue node), sub-dividing into inflammatory biomarkers (elevated cytokines), metabolic biomarkers (cytokines reflecting glucose dysregulation, activating pathways for cellular injury), and neuronal apoptosis, excitotoxicity, blood-brain barrier degradation. Arrows indicate connection of injury with inflammation and metabolism leading to secondary injury and impaired function[10].[11].

Study Cohorts

The discovery cohort included 2,500 consecutive patients with acute ischemic stroke treated within twenty four hours of symptom onset, and stratified by reperfusion therapy into three groups (intravenous thrombolysis, endovascular thrombectomy, or no reperfusion therapy) mirroring real-world clinical practice.

For further exploration of the identified signature and predictive model, reproducibility and generalisation to other centres were assessed by recruiting an independent validation cohort of 500 patients[14].

Inclusion and Exclusion Criteria

Eligible participants were adults aged ≥18 years presenting with acute ischemic stroke within 24 hours of symptom onset and with a baseline neurologic deficit sufficient to obtain a National Institutes of Health Stroke Scale score of at least four. Informed consent was obtained from the patient or surrogate[15]. Exclusion criteria included hemorrhagic stroke, active malignancy or immunosuppressive therapy, active infection requiring inpatient hospitalization, and significant disability prior to the stroke (modified Rankin Scale >2)[16]. As intended, these inclusion and exclusion criteria ensured a fairly homogeneous study population and reduced the likelihood of confounding factors affecting inflammatory and metabolic profile[17-19].

Clinical Data Collection

Data collection included comprehensive clinical baseline data on demographic, vascular risk factors, stroke severity (assessed by National Institutes of Health Stroke Scale), imaging parameters (Alberta Stroke Program Early CT Score and infarction volume on magnetic resonance imaging), stroke aetiology (TOAST classification) [20]; details of reperfusion therapy (timing, and degree of recanalization - assessed by Thrombolysis in Cerebral Infarction score) [21]; follow-up neurological assessment at twenty-four hours and seven days; in hospital complications, and functional outcome (assessed by the modified Rankin Scale) at ninety days [22]; extended follow-up of mortality, recurrent stroke and long-term disability at twelve months [23].

The primary outcome was a poor functional outcome at ninety days (modified Rankin Scale: three to six) [24]and secondary outcomes included an excellent functional recovery (defined as a modified Rankin Scale score of zero or one), mortality (at anyhow at ninety days, and then again at twelve months), recurrent cerebrovascular and post stroke cognitive impairment and post stroke depression[25].

2. **Sample Collection and Multi-Omics Platforms**

Sample Collection and Processing

Biological sampling at several defined time-points to track inflammatory and metabolic response dynamics following the insult from ischemic stroke[26]. Samples were peripheral venous blood at baseline prior to treatment and at 24 hours, 48 hours, 7 days and 90 days following stroke onset[27-29]. These were all acted on as previously described (Centrifuged at 1,500 × g for 10 min, aliquoted, and stored at −80°C) to ensure the biomolecules remain intact.[30]

Journal of Chemical Health Risks
www.jchr.org
JCHR (2026) 16(2), 4781-4793 | ISSN:2251-6743

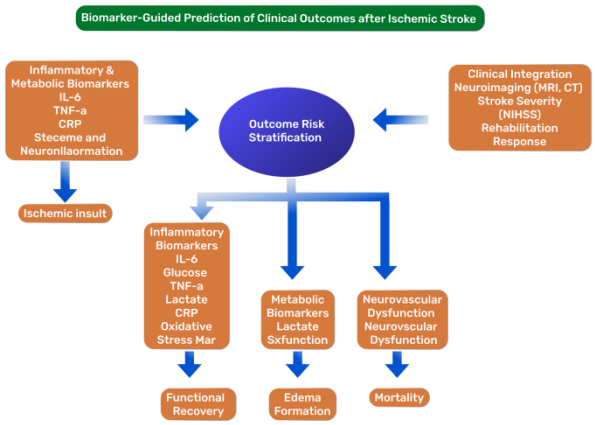

Figure 2. Biomarker-Guided Prediction of Clinical Outcomes after Ischemic Stroke.

Global schema demonstrating a biomarker-based overview of predicting stroke outcome - "Risk Stratification of Outcomes" (in dark blue) [31]. Arrows from levels of circulating inflammatory and metabolic biomarkers to pathophysiological effects of (size of brain damage, swelling, neurovascular function) and to clinical outcome (better, worse, disability, death). Sidebar modules indicating clinical context, imaging, score of stroke severity (NIHSS), and response of rehabilitation[32]. Arrows, how dual biomarkers may permit early risk assessment and personalisation of planned treatment, fine management of stroke care[33].

Inflammatory Biomarker Platforms

Inflammatory profiling was executed using high-throughput multiplex immunoassay platforms such as Luminex xMAP and Olink technologies facilitating simultaneous quantification of a spectrum of cytokines, chemokines and related mediators[34]such as status of key pro-inflammatory and anti-inflammatory cytokines such as interleukin-1beta, interleukin-6, interleukin-8, interleukin-10, tumour necorsis factor-alpha, interferon-gamma, and others [35]. We also measured acute phase proteins such as C-reactive protein, serum amyloid A, fibrinogen, etc[36]to assess systemic inflammatory response. Further, adhesion molecules such as ICAM-1, VCAM-1 and matrix metalloproteinases and their inhibitors, to assess endothelial activation, blood-brain barrier disruption, and extracellular matrix remodeling[37].

Metabolic Biomarker Platforms

Metabolic profiling of the systemic metabolic modulation found after stroke was performed using targeted and untargeted metabolomics approaches. In the targeted metabolomic type, the Biocrates platform was applied to assess levels of a wide range of metabolites such as amino acids, acylcarnitines and bile acids, amongst others, whilst untargeted metabolomic approaches based on liquid and gas chromatography–mass spectrometry yielded fresh insights into metabolic effects[38]. Lipidomic assays using high-resolution mass spectrometry allowed the detailed depiction of lipid species including ceramides, sphingomyelins, and phosphatidylcholines among others that have roles in inflammation and cell death. At the simpler end of the spectrum, strokes were diagnosed by clinical metabolic markers like, diabetes parameters (glucose, and glycated hemoglobin), indices of insulin resistance, lipid profile parameters, uric acid, and homocysteine, for example[39].

Additional Platforms

To further leverage this multi-omics framework, genotyping was done with genome-wide association arrays for variation in inflammatory and metabolic pathways, transcriptomic profiling (bulk RNA sequencing of whole blood at baseline and 24 hours) to identify changes in gene expression associated with acute injury and immune activation, and in a subset of patients, single-cell RNA sequencing of peripheral blood mononuclear cells to identify immune cell heterogeneity and cell-specific transcriptional signatures - all to inform on the cellular basis of stroke progression and recovery [40-42].

4. Inflammatory Biomarkers

Acute Phase Reactants

Acute phase reactants discussed are part of early systemic processes following cerebral ischaemia and degree of inflammatory activation after stroke. C-reactive protein was >3mg/l in around sixty per cent of patients.. Median concentration of 5.2mg/l was indicative of substantial inflammatory burden at presentation. Elevated >10mg/l were strongly predictive of poor functional outcome at ninety days (OR 2.5) and had moderate predictive activity (AUC 0.70). It peaked at forty-eight to seventy-two hours and raised by seven days predicted worse outcome independently. Serum amyloid A showed a similar temporal profile, correlating with C-reactive protein, independently predictive of poor functional outcome/mortality. Fibrinogen was raised in the acute setting, and correlated moderately with infarct volume and prediction of adverse outcome modified by higher elevation, reflecting cross talk between inflammatory and coagulopathic pathways[43].

Journal of Chemical Health Risks
www.jchr.org
JCHR (2026) 16(2), 4781-4793 | ISSN:2251-6743

Cytokines and Chemokines
Cytokine profiling in the acute phase of ischemic stroke identified a characteristic pro-inflammatory profile, with interleukin-6 emerging as one of the best predictors of outcome. The majority of patients had elevated interleukin-6 at baseline, directly correlating with not only the size of the infarct, but also neurological deficit and functional outcome (area under curve 0.75); with peak circulating levels observed at 24 to 48 h post-stroke and highest prognostic utility at the sentinel 24-h timepoint. In addition to interleukin-6, other circulating cytokines found to correlate with poor outcome included tumor necrosis factor-alpha and interleukin-1 beta and were consistent with activation of both innate (via NLRP3 inflammasome) and adaptive immunity. Interleukin-10 demonstrated a protective rather than hazardous effect; higher levels of interleukin-10 were found to predict a better outcome and a favourable balance of the anti-inflammatory function. There was also elevation in chemokines (e.g. CXCL8, CXCL10, CCL2) that were associated with leukocytes accrual and linked with worse clinical outcome, thereby underscoring the immunological trafficking operative within the milieu of secondary brain injury[44].

Adhesion Molecules
Endothelial activation markers (such as ICAM-1 and VCAM-1) were increased in acute stroke and associated with worse functional outcome; this reflects endothelial dysfunction and breakdown of the blood–brain barrier. The rise in the selectins, especially P-selectin, reflected platelet activation and promoted thrombo-inflammatory processes. The link of P-selectin to recurrent stroke emphasizes the role of platelet-mediated inflammation in mediating long-term vascular risk after an ischemic insult[45].

Matrix Metalloproteinases (MMPs)
Matrix metalloproteinases (MMPs) were involved in extracellular matrix degradation and blood–brain barrier disruption. MMP-9 was significantly increased in the majority of patients. It was also an independent predictor of poor functional outcome and hemorrhagic transformation. Through the disruption of the blood-brain barrier, the MMPs affect the risk of secondary injury and haematomas, while MMP-2 and MMP-3 are less predictive, albeit still predicting worse outcome. Then we have the ratio between the two classes of enzymes and their inhibitors - again, showing that the MMP-9 to TIMP-1 ratio has prognostic value and suggesting that the imbalance between metalloproteinases and their inhibitors regulate the evolution of the stroke[46].

Cellular Inflammatory Markers
Cellular indices, derived from conventional blood counts, also provided convenient markers of inflammatory and immune dysregulation. The neutrophil-to-lymphocyte ratio was elevated in those destined for poor outcome and showed utility in prediction, again confirming the predominance of innate immune activation over adaptive immunity. Further supporting the impact of thrombo-inflammation on stroke outcome were the elevated ratios of platelets to lymphocytes and monocytes to lymphocytes in patients with adverse outcomes. Finally, the incorporation of the lipid aspect of stroke pathobiology is embodied in the neutrophil-to-HDL ratio, that combines both an inflammatory and a (lipid) metabolic appraisal of event severity[47].

5. **Metabolic Biomarkers**
Glucose Metabolism Markers
Disturbances of glucose metabolism were associated with poor outcome following ischemic stroke. Admission hyperglycemia, irrespective of diabetes status, was independently associated with larger infarct size and worse functional recovery consistent with stress mediated “abuse” of metabolic control. In addition, glycemic variability further enhanced the relationship, implicating fluctuations of glucose levels as mediators of oxidative stress and neuronal injury. Chronic hyperglycemia, by virtue of high glycated hemoglobin, predicted poor functional outcome and, in addition, increased risk of recurrent stroke. Insulin resistance also had prognostic value, suggesting that metabolic abnormalities due to the metabolic syndrome influence recovery from stroke [48].

Lipid Metabolism Markers
Lipid metabolism markers predicted poor outcome and recurrent vascular risk. Lower apolipoprotein A1 (inferior function of HDL) predicted poor outcome; conversely, apolipoprotein B and apolipoprotein B-Apolipoprotein A1 ratios (*proatherogenic domain*) predicted adverse outcome [49]. High lipoprotein(a) predicted recurrent stroke [49].

Metabolomic Markers
Next-generation metabolites obtained using metabolomics identified key clinical markers associated with metabolic pathways underlying stroke severity and recovery.

Activation of the tryptophan–kynurenine pathway was observed in most of the patients and was strongly associated with poor outcomes, reflecting immune-metabolic interactions and accumulation of neurotoxic

Journal of Chemical Health Risks
www.jchr.org
JCHR (2026) 16(2), 4781-4793 | ISSN:2251-6743

metabolite species. elevations in phenylalanine and altered phenylalanine-to-tyrosine ratios indicated disruptions in amino acid metabolism and oxidative stress. Increased levels of acylcarnitines suggested mitochondrial dysfunction and poor energy metabolism, correlating with infarct volume and clinical severity. [50] Trimethylamine-N-oxide levels, that is produced by gut microbiota metabolism, were associated with poor functional outcome as well as recurrent stroke, implicating gut–brain axis interactions in stroke. [51] Alterations in bile acid profiles support the involvement of metabolic and microbiome-related pathways in stroke pathophysiology. [52]

Lipidomics Markers

Lipidomic profiling revealed lipid species associated with adverse outcomes[53]. Increased ceramides (particularly C16:0 species), were associated with an increased risk of poor functional recovery, representing pro-apoptotic and pro-inflammatory signaling. Decreased sphingomyelins signaled disrupted membrane integrity, whilst elevated oxidized lipids like oxidized LDL were indicative of oxidative stress and vascular injury[54]. Composite ceramide scores performed moderately well, suggesting their utility as integrated measures of lipid-mediated injury[55].

Other Metabolic Markers

Other metabolic markers, uric acid, homocysteine and vitamin D, also provided prognostic information [56]. Uric acid levels had relationship with both deleterious and protective capacity, noting the marker's peculiar behaviour as acting as both an antioxidant and a pro-oxidant [57]. Hyperhomocysteinemia was related to risk of poor outcome, and recurrent stroke likely owing to endothelial damage and a pro-thrombotic effect [58]. Vitamin D deficiency was also related to worse outcomes, postulating immune modulation and neuroprotective effects [59].

6. Transcriptomic and Genetic Biomarkers

Transcriptomic Signatures

Whole transcriptomic profiling in blood identified a clear inflammatory signature associated enriched in those with poor outcomes encompassing genes related to cytokine signalling, matrix metalloproteinases and complement metabolism, which were found together with downregulated genes in the poor outcome cohort with antiinflammatory and neurotrophic properties indicative of dysregulated inflammation with poor resolution and indicating a diminished neuroregenerative potential. A composite gene expression prognostic score based on the ten-gene inflammatory signature showed a strong predictive performance.[60]

Delving into the immune cellular landscape at single-cell resolution revealed a pro-inflammatory expansion of neutrophils as well as activated monocytes demonstrating inflammatory activation - whereas reduced cytotoxicity of naturel killer (NK) cells together with expansion of pro-inflammatory γδ T cells played a part in determining outcome[61].

Genetic Variants

Genetic studies on ischemic stroke have also identified risk variants in inflammatory and metabolic pathways which could have relevance to outcome variation. Polymorphisms in cytokine genes (IL-6, TNF alpha, and CRP genes) linked to increased cytokine levels were found to be associated also with risk of poor outcome, congenial to having a greater inherited inflammatory response to injury. Polymorphisms of metabolic genes have also been associated with worse functional outcomes and cognitive deterioration such as the apolipoprotein E ε4 allele, and protective genetic variants in lipid metabolism genes themselves (e.g. PCSK9) which were linked to better outcome [62]. Other interesting studies have suggested a polygenic risk score derived from many inflammatory and metabolic loci may provide additional prognostic enrichment, associating higher scores with their finding of an almost 3–5 fold higher risk of poor functional recovery [63].

6. **Temporal Dynamics of Biomarkers**

Hyperacute Phase (0-24 Hours)

The hyperacute phase of ischemic stroke conveys the immediate response of inflammatory and proteolytic systems, giving the first immediate preview into the “spirit” of the injury of tissue and how infarct will be animated later in time. Most dramatic elevations are of MMP9, IL-6, TNF-alpha and the alarmins S100A8 and S100A9, suggestive of innate immune purification and blood-brain barrier chaos. They allow one to probe the biological effects of ischemia prior to the next obvious manifestation of structural progression caught on imaging down the road. Notably, the elevation of MMP9 and IL-6 at this point is tightly associated with infarct growth; these proteins are not only correlates of injury but part of the perpetrator of the more offended secondary extension of tissue injury in part by way of endothelial activation, leukocyte recruitment and agenda of extracellular matrix demise [64].

Journal of Chemical Health Risks
www.jchr.org
JCHR (2026) 16(2), 4781-4793 | ISSN:2251-6743

Acute Phase (24-72 Hours)
The acute phase represents a period of maximum systemic inflammatory outpouring, with peak circulating concentrations of C-reactive protein, serum amyloid A, interleukin-6, interleukin-8, and CXCL10 [65]. This reflects the consolidation and amplification of the cascade, with sustained cytokine production signals, maximum acute phase protein and chemokine transcription, and trafficking and influx of inflammatory cells in response to chemoattractants [65]. Interleukin-6, C-reactive protein and matrix metalloproteinase-9 have the strongest associations with poor functional outcome, representing a continual escalation of inflammation with poor functional outcome after reperfusion or spontaneous recanalization [66]. The timing of the peak is relevant since this reflects a potentially modifiable point in time for immunotherapeutic or neurovascular stabilisation strategies [67].

Subacute Phase (7-90 Days)
Subacute phase - progression from acute injury toward partial recovery, healing and remodelling of tissue[67].

In practice, the inflammatory markers in many patients start to come down after between seven to fourteen days reflecting the resolution of the acute innate immune response[68]. However, when some inflammatory markers such as interleukin-6 and C-reactive protein remain elevated at day seven this identifies a patient group with a protracted course of inflammatory activation and moreover, with a worse neurological recovery[69]. Perhaps indicative of ongoing secondary injury, less successful repair and more susceptibility to secondary sequelae elsewhere in the body[70]. The neurotrophic/repair types of factors, such as brain-derived neurotrophic factor and vascular endothelial growth factor become more important as this 'recovery' phase progresses, with implications for neuroplasticity, angiogenesis and rehabilitation of different kinds[71].

Chronic Phase (>90 Days)
At periods beyond 90 days, biomarker profiles tell us more about chronic vascular instability, persistent inflammation, and post-stroke sequelae, rather than acute infarct status. For example, persistently elevated C-reactive protein and interleukin-6 at this point are associated with increased risk of recurrent stroke, suggesting that chronic low-grade inflammation is clinically relevant well beyond the index (acute) event; low levels of brain-derived neurotrophic factor in the chronic phase is associated with post-stroke decline and depression, suggesting that failure of adequate neurorestorative signaling to occur leads to impaired long-term neural adaptation[74-77].

7. **Multi-Omics Integration and Predictive Models**
Univariate Predictors of Poor Outcome
Univariate analysis identified inflammatory and metabolic biomarkers with strong independent associations with poor ninety-day functional outcome. Of inflammatory markers, the strongest single predictor of poor outcome was interleukin-6 above 10 pg/mL, followed closely by matrix metalloproteinase-9 and C-reactive protein, each associated with substantially increased odds of moderate disability or death. An elevated neutrophil-to-lymphocyte ratio further suggested that systemic immune imbalance contributes to poor prognosis. In metabolic variables, a higher kynurenine-to-tryptophan ratio showed a similarly strong association with adverse outcome, reflecting activation of immune-metabolic pathways relevant to neurotoxicity and systemic inflammation. Elevated trimethylamine-N-oxide, ceramide C16:0, and admission hyperglycemia are also metabolic predictors, each likely capturing different aspects of metabolic stress, vascular dysfunction, and mitochondrial impairment. Overall, these findings indicate that both inflammatory and metabolic biomarkers provide prognostic value beyond quicker measures of clinical assessment[78-80].

Multivariate Predictive Models
Multivariable modeling demonstrated that indeed the "biological picture" becomes increasingly complex with insight given from these biomarker data and helps in modeling the stroke outcome better as compared to just the clinical variables. A model with age, baseline NIHSS, infarct volume, and whether they were re-perfused performed decent, obviously not as good but fair, having an area under the curve of 0.80 [81-82]. A model which included the inflammatory biomarkers IL-6, C-reactive protein, MMP-9, and NLR definitely increased the performance considerably to an area under the curve of 0.88, with an indication of a significant net reclassification improvement [83]. A model of just the clinical variables, and added metabolic markers (the kynurenine-to-tryptophan ratio, trimethylamine N-oxide, ceramides and glucose) did improve prediction but it wasn't as good. The best performance is that of the integrated multi-omics model where clinical variables, are combined with the best inflammatory markers, and the best metabolic markers, and selected genetic variants. This leads to an area under the curve of 0.92, with high sensitivity and specificity. The work indicates that stroke prognosis likely should be thought of as a biological phenomenon as compared to a clinical one [84].

Journal of Chemical Health Risks
www.jchr.org
JCHR (2026) 16(2), 4781-4793 | ISSN:2251-6743

Risk Stratification Score

For potential use in clinical practice, data were combined into a prognostic score (termed ISCH-OMICS) representing the strongest features from 3 scales: inflammatory, metabolic and clinical data. Higher levels of interleukin-6, matrix metalloproteinase-9 (MMP9), kynurenine-tryptophan ratio and trimethylamine-N-oxide (TMAO) scores contribute to the points, as do older age, lower levels of lymphocyte and "higher" neurological states. With this system, patients can be designated low-, moderate-, high-, and very high-risk categories which represent patients with increasing risk of poor outcome. The score provides an intuitively convenient way of succinctly reporting complex biomarker data in a clinically useful manner, providing objective prognostic enrichment that can facilitate more personalized determination of resource allocation for monitoring and rehabilitation[85].

8. **Biomarkers Predicting Specific Outcomes**

Post-Stroke Cognitive Impairment (PSCI)

Post-stroke cognitive impairment arises from chronic inflammation and/or impaired neuroplasticity. Higher C-reactive protein at ninety days symbolizes more cognitive decline, i.e., making it more likely that persisting systemic inflammation is causing continued neuronal damage. Lower brain-derived neurotrophic factor levels provides a similar cue by signalling that synapses are repaired less and that potential for cortical reorganisation is reduced. Higher kynurenine-to-tryptophan ratios are associated with cognitive impairment, probably pointing to an immune-metabolomic mechanism that results in neurotoxic effects in the post-stroke patient. Apolipoprotein E ε4 allele carriers are more vulnerable, probably because of suffering impaired neuronal repair and the concomitant presence of overlapping neurodegenerative phenotypes (86).

Post-Stroke Depression (PSD)

Post stroke Depressed mood showed a biomarker pattern that suggested an increased inflammatory tone and reduced neurotrophic support. Both higher TNF-alpha levels at ninety days and higher IL-6 levels increased the odds of depression, implicating inflammatory signalling (see also the section on mood disorder). Low brain derived neurotrophic factor also contributed to this risk and might reflect inadequate recovery-related signalling and inadequate neural reserve. This suggests an important biological mediation in mood dysregulation after stroke that goes beyond the psychosocial consequences of a disability[87].

Recurrent Stroke

Prediction of recurrent stroke subtyping is more influenced by chronic inflammatory and metabolic biomarkers measured during follow-up. Upregulated C-reactive protein and trimethylamine-N-oxide at twelve months are associated with substantially increased risk of recurrent cerebrovascular events, suggesting ongoing vascular inflammation and microbiome-linked metabolic risk. High lipoprotein(a) levels and elevated glycated hemoglobin similarly predict recurrence indicating constant atherothrombotic burden and poor glycaemia control. Results stress that secondary prevention after stroke should union biological markers of residual vascular risk in addition to classic risk factor assessment [88,90].

Mortality

Twelve-month mortality is associated with persistent activation of inflammatory and metabolic pathways. Interleukin-6 and C-reactive protein are amongst the strongest predictors of death at this early stage and are reflective of persistent frailty and systemic inflammation. A high kynurenine-to-tryptophan ratio and elevated trimethylamine-N-oxide also predict mortality and thus suggest immune-metabolic dysfunction lays bare vulnerability beyond the acute neurological injury. Alongside previous discussions, these associations further highlight how death following IS is often the result of the combined toll of the neurological insult, systemic inflammation and metabolic derangements in addition to recurrent vascular events [89].

10. Clinical Translation and Implementation

Proposed Clinical Algorithm

A clinically-useful version of this biomarker-guided algorithm would cease the first 24 hours after stroke onset with the combined assessment of conventional clinical variables and a few select biomarkers. Age, baseline neurological severity, infarct volume, and reperfusion status are required because they reflect clinical risk in the per-acute environment; yet the concurrent assessment of interleukin-6, C-reactive protein, matrix metalloproteinase-9, neutrophil-to-lymphocyte ratio, kynurenine-to-tryptophan ratio, trimethylamine-N-oxide (TMAO), and glucose would produce that valuable biomarker prognostic tool, the ISCH-OMICS score, which yields exquisite stratification of biological vulnerability. A patient in the low-risk range would be allowed to stay their course of standard post-stroke recovery, mobilization, etc. A moderate-risk patient would require close observation and early rehabilitation planning. Rapport building and acceptance of neuro-monitored close observation would be vital in

Journal of Chemical Health Risks
www.jchr.org
JCHR (2026) 16(2), 4781-4793 | ISSN:2251-6743

the high-risk patient, who would be engaged in aggressive secondary prevention. A very-high-risk patient would warrant advance documentation of treatment goals, ceiling-of-care discussions and possibly even palliation when clinically appropriate. The proposed logic moves us away from the vernacular pathway model towards biological triage[93].

Targeted interventions may correspond to biomarker patterns. Patients with a preponderance of inflammatory activation may qualify for investigational anti-inflammatory biologic treatment; patients with marked metabolic derangement may benefit from aggressive glucose management, iterative optimization of lipid lowering and changes in diet. Patients with elevated trimethylamine-N-oxide may be most suited to microbiome reprogramming by way of dietary fiber enrichment or probiotic treatment. Thus our proposed algorithm is not only prognostic but theragnostic - providing links between patient biomarker profiles and classes of secondary preventative treatment[92].

Therapeutic Implications

Therapeutic implications of these findings are important, since many of these biomarkers pathways can be drugged. Colchicine, anti-inflammatory approaches reducing C-reactive protein and interleukin-6 can be experimented with in cerebrovascular populations, IL-6 receptor blockade and the NLRP3 inflammasome likewise represent investigational opportunities based upon plausible counter information from the domain of preclinical rebuttal. For metabolic, microbiome directed strategies that might reduce trimethylamine N oxide production and boost short chain fatty acids, ketogenesis, NAD+ precursor supplementation aimed at boosting mitochondrial stress resistance and increasing metabolic activity all make biologic sense. Personalized secondary prevention can develop based on the biomarker burden, where if elevated lipoprotein(a), high inflammatory markers as exemplified by interleukin-6, and microbiome related metabolite burden presents, we will treat that patient with personalized secondary prevention to match.[91]

Cost-Effectiveness Analysis

From a health systems perspective the biomarker guide stratification appears attractive from an economic standpoint because of the significant long-term costs of a poor outcome from stroke requiring prolonged rehabilitation, institutional care, and recurrent hospitalization. Biomarker panels costing a few hundred dollars may be justifiable if they optimize the use of intensive monitoring, rehabilitation resources, and targeted secondary prevention therapies. Economic modeling indicates favorable incremental cost effective ratios which suggest that even marginal improvements in risk classification may yield real clinical and financial benefit at a populational level[95].

Implementation Barriers

Numerous barriers remain to biomarker-guided stroke care receiving widespread adoption. From a technical standpoint, turnaround times must be shortened enough that results may alter care in the acute and early subacute window (preferably <24 hours) and assay results must be made uniform across stroke centers and integrated into electronic health records. Clinically, providers will require education on interpreting and applying biomarker panels in various care pathways. Randomized trials demonstrating improved outcomes with biomarker-guided intervention are also still limited, and reimbursement pathways are not yet fully established. Together, these barriers suggest translation will require both technical innovations and clinical research focused on implementing those innovations into clinical practice[96,106].

11. **Future Directions**

Point-of-Care Biomarker Devices

The establishment of rapid point-of-care biomarker platforms would accelerate the real-world translation of multi-omics-based stroke care to clinical settings. Novel technologies based on multiplex immunoassays and microfluidics can simultaneously quantify inflammatory and metabolic markers such as interleukin-6, C-reactive protein, matrix metalloproteinase-9, kynurenine, and trimethylamine-N-oxide, with turn-around-times of less than an hour. Having access to these biomarker levels in the stroke unit would allow risk-stratification at the point of admission and inform decisions such as monitoring frequency and bed assignment, as well as the resources allocated to a given patient. Point-of-care tests to the patient's bedside will be required for testing to realise true potential of biomarker-based precision medicine in acute stroke[88-97,105].

Therapeutic Targeting

The identification of crucial inflammatory and metabolic pathways involved in deleterious outcomes provides a powerful rationale for potential targeted therapies. Anti-inflammatory approaches such as interleukin-6 receptor blocking, NLRP3 inflammasome inhibitors, colchicine and other anti-inflammatory agents hold promise for dampening the effects of rampant immune activation following cerebral ischemia. Metabolic therapies involving trimethylamine-N-oxide lowering,

Journal of Chemical Health Risks
www.jchr.org
JCHR (2026) 16(2), 4781-4793 | ISSN:2251-6743

mitochondrial enhancement, metabolic reshaping, ketogenic therapies, NAD+ precursors, and modulation of gut microbiota with probiotics and prebiotics are fast becoming of interest. Fecal microbiota transplant is an investigational approach of interest in modulating microbiota-derived metabolites although safety and efficacy remains to be shown in the stroke population. Horizontally these approaches represent the concepts of mechanism-based personalized medicine based on individual biomarker profiles[98].

Artificial Intelligence Integration

Artificial intelligence will be paramount in 'translating' the complex multi-omics data into actionable insights. Machine learning models capable of integrating genomic, transcriptomic, proteomic, metabolomic, clinical, and imaging data will yield highly accurate, real-time predictions of functional outcome and complication risk for individual patients, enabling dynamic risk assessment that evolves over time as the data accumulate. The concept of digital twins takes this one step further, providing simulated trajectories in individual patients that clinicians can augment in silico with various forms of intervention to optimise rehabilitation and treatment strategies. This represents a real step-change in predictive and precision stroke medicine[99-106].

Global Health Applications

Making stroke care biomarker guided must also take into account being scalable and implementable in lower resource settings. Low cost biomarker panels based on key markers such as C-reactive protein, interleukin-6, glucose and NLR provide a pragmatic option for resource poor environments where more comprehensive multi-omics profiling is not easily actionable. Combining this with telemedicine platforms can offer remote access to biomarker testing, centralised reading of these tests, and virtual stroke rehab programs. Combining these innovations has the potential to close the gap in stroke care and bring the benefits of precision medicine to more populations around the world[102.103,104,106].

Conclusions

Summary of Key Findings

In this study, we show that inflammatory and metabolic biomarkers are useful in prognosticating poor outcomes in acute ischemic stroke with interleukin-6, matrix metalloproteinase 9, C-reactive protein, the neutrophil-to-lymphocyte ratio and the kynurenine-to-tryptophan ratio displaying the strongest predictive power. Other metabolic markers such as trimethylamine-N-oxide, ceramides and admission glucose also provide insight as to risk stratification and capture information regarding systemic dysmetabolism. Importantly, the biomarkers peak at 24-48 hours and their persistence at seven days is associated with the highest risk for poor outcomes. Overall the multi-omics predictive model identified the patients at highest risk with excellent discrimination (area under the curve 0.92), clearly outperforming models incorporating purely clinical measures. The authors provide a usable ISCH-OMICS score that could be incorporated into clinical workflow that usefully identifies risk from low risk (10% poor outcome) to very high-risk (85%).

Clinical Implications

Incorporating multi-omics biomarkers into clinical practice could revolutionize stroke care, allowing clinicians to precise risks at time of admission and identify patients likely to have poor functional outcome as well as high risk of mortality, stroke recurrence, and post-stroke complications that warrant more intensive monitoring and rehabilitation. Biomarker profiles would also allow for selection of anti-inflammatory and metabolic strategies aimed at each patient's biological vulnerabilities. Risk–adapted care pathways may lead to more efficient allocation of resources by targeting intensive interventions to individuals at high risk of suffering vascular events, while sparing low-risk patients additional interventions. In secondary prevention, biomarker-guided strategies promise to bring a personalized approach to the prevention of recurrent vascular events.

Research Priorities

Future studies should be aimed at large scale prospective validation of multi-omics predictive models in diverse populations and health care systems. Randomized trials testing the clinical effectiveness of biomarker-guided management compared to standard management are warranted to demonstrate improved patient outcomes. For large scale use, standardized measurement of biomarkers, including harmonized protocols for sample collection, processing, and analysis, will be necessary in order for the approaches to be reproducible and adopted widely. Meanwhile regulatory qualification of biomarkers for prognostic use by the FDA, EMA and other agencies will be necessary for clinical implementation and reimbursement.

The Road Ahead

The future of stroke care will be defined by the application of multi-omics data alongside clinical and imaging data providing truly tailored medicine. Biomarker-based stratification at admission to guide triage, monitoring as well as therapeutic decision-making,

Journal of Chemical Health Risks
www.jchr.org
JCHR (2026) 16(2), 4781-4793 | ISSN:2251-6743

will follow and targeted interventions will step away from 'shot-gun' approaches towards mechanism based approaches. Coupled with new advances in digital health, artificial intelligence, point-of-care diagnostics and an aim towards biomarker platforms that are scalable and affordable then in years to come all of precision stroke medicine will improve global outcomes and reduce the burden of stroke.

References

1. Powers WJ, Rabinstein AA, Ackerson T, et al. 2019 update to the 2018 guidelines for the early management of acute ischemic stroke. *Stroke*. 2019;50(12):e344-e418.
2. Kleindorfer DO, Towfighi A, Chaturvedi S, et al. 2021 guideline for the prevention of stroke in patients with stroke and transient ischemic attack. *Stroke*. 2021;52(7):e364-e467.
3. Bushnell C, et al. 2024 guideline for the primary prevention of stroke. *Stroke*. 2024.
4. Thomalla G, Simonsen CZ, Boutitie F, et al. MRI-guided thrombolysis for stroke with unknown time of onset. *N Engl J Med*. 2018;379(7):611-622.
5. Goyal M, Menon BK, van Zwam WH, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. *Lancet*. 2016;387(10029):1723-1731.
6. Whiteley W, Tseng MC, Sandercock P. Blood biomarkers in the diagnosis of ischemic stroke: a systematic review. *Stroke*. 2008;39(10):2902-2909.
7. Whiteley W, Chong WL, Sengupta A, Sandercock P. Blood markers for the prognosis of ischemic stroke: a systematic review. *Stroke*. 2009;40(5):e380-e389.
8. Elkind MSV. Inflammatory biomarkers and stroke risk: from epidemiology to treatment. *Stroke*. 2010;41(10 Suppl):S3-S8.
9. Montaner J, Ramiro L, Simats A, et al. Multilevel omics for the discovery of biomarkers and therapeutic targets for stroke. *Nat Rev Neurol*. 2020;16(5):247-264.
10. Bustamante A, García-Berrocoso T, Rodriguez N, Llombart V, Ribó M, Molina C, Montaner J. Ischemic stroke outcome: a review of blood-based biomarkers. *J Cereb Blood Flow Metab*. 2017;37(3):875-891.
11. Smith CJ, Emsley HCA, Gavin CM, et al. Peak plasma interleukin-6 and other peripheral markers of inflammation in the first week of ischemic stroke correlate with brain infarct volume, stroke severity and long-term outcome. *BMC Neurol*. 2004;4:2.
12. Emsley HCA, Smith CJ, Gavin CM, et al. Clinical outcome following acute ischemic stroke relates to both activation and autoregulatory inhibition of cytokine production. *BMC Neurol*. 2007;7:5.
13. Acalovschi D, Wiest T, Hartmann M, et al. Multiple levels of regulation of the interleukin-6 system in stroke. *Stroke*. 2003;34(8):1864-1869.
14. Di Napoli M, Papa F, Bocola V. Prognostic influence of increased C-reactive protein and fibrinogen levels in ischemic stroke. *Stroke*. 2001;32(1):133-138.
15. Di Napoli M, Schwaninger M, Cappelli R, et al. Evaluation of C-reactive protein measurement for assessing the risk and prognosis in ischemic stroke: a statement for health care professionals. *Stroke*. 2005;36(6):1316-1329.
16. Rost NS, Wolf PA, Kase CS, et al. Plasma concentration of C-reactive protein and outcome after ischemic stroke. *Stroke*. 2001;32(11):2575-2579.
17. Rallidis LS, Vikelis M, Panagiotakos DB, et al. Inflammatory markers and in-hospital mortality in acute ischemic stroke. *Atherosclerosis*. 2006;189(1):193-197.
18. Tutuncu S, Ziegler AM, Loeffler C, et al. Soluble ST2 in acute ischemic stroke. *Stroke*. 2015;46(1):179-186.
19. Worthmann H, Tryc AB, Deb M, et al. Linking infection and inflammation in acute ischemic stroke. *Ann N Y Acad Sci*. 2010;1207:116-122.
20. Beamer NB, Coull BM, Clark WM, Wynn M. Interleukin-6 and interleukin-1 receptor antagonist in acute stroke. *Ann Neurol*. 1995;37(6):800-805.
21. Vila N, Castillo J, Dávalos A, Chamorro A. Proinflammatory cytokines and early neurological worsening in ischemic stroke. *Stroke*. 2000;31(10):2325-2329.
22. Castellanos M, Leira R, Serena J, Pumar JM, Lizasoain I, Castillo J, Dávalos A. Plasma metalloproteinase-9 concentration predicts hemorrhagic transformation in acute ischemic stroke. *Stroke*. 2003;34(1):40-46.

Journal of Chemical Health Risks
www.jchr.org
JCHR (2026) 16(2), 4781-4793 | ISSN:2251-6743

23. Montaner J, Alvarez-Sabín J, Molina C, et al. Matrix metalloproteinase expression after human cardioembolic stroke: temporal profile and relation to neurological impairment. *Stroke*. 2001;32(8):1759-1766.
24. Castellanos M, Sobrino T, Millán M, et al. Serum cellular fibronectin and matrix metalloproteinase-9 as screening biomarkers for the prediction of parenchymal hematoma after thrombolytic therapy in acute ischemic stroke. *Stroke*. 2007;38(6):1855-1859.
25. Foerch C, Otto B, Singer OC, et al. Serum S100B predicts a malignant course of infarction in patients with acute middle cerebral artery occlusion. *Stroke*. 2004;35(9):2160-2164.
26. Büttner T, Weyers S, Postert T, Sprengelmeyer R, Kuhn W. S-100 protein: serum marker of focal brain damage after ischemic territorial middle cerebral artery infarction. *Stroke*. 1997;28(10):1961-1965.
27. Missler U, Wiesmann M, Friedrich C, Kaps M. S-100 protein and neuron-specific enolase concentrations in blood as indicators of infarction volume and prognosis in acute ischemic stroke. *Stroke*. 1997;28(10):1956-1960.
28. Wunderlich MT, Lins H, Skalej M, et al. Neuron-specific enolase and S-100B as biochemical markers of infarct volume and prognosis in acute ischemic stroke. *Stroke*. 1999;30(8): 1638-1644.
29. Maestrini I, Ducroquet A, Moulin S, et al. Blood biomarkers in the early stage of cerebral ischemia. *Rev Neurol (Paris)*. 2016;172(3):198-219.
30. Pikija S, Sztriha LK, Killer-Oberpfalzer M, Weymayr F, Sellner J. Neutrophil to lymphocyte ratio predicts intracranial hemorrhage after endovascular thrombectomy in acute ischemic stroke. *J Neuroinflammation*. 2018;15:319.
31. Tokgoz S, Kayrak M, Akpinar Z, et al. Neutrophil lymphocyte ratio as a predictor of stroke. *J Stroke Cerebrovasc Dis*. 2013;22(7):1169-1174.
32. Xue J, Huang W, Chen X, et al. Neutrophil-to-lymphocyte ratio is a prognostic marker in acute ischemic stroke. *J Stroke Cerebrovasc Dis*. 2017;26(3):650-657.
33. Celikbilek A, Ismailogullari S, Zararsiz G. Neutrophil to lymphocyte ratio predicts poor prognosis in ischemic cerebrovascular disease. *J Clin Lab Anal*. 2014;28(1):27-31.
34. Sun Y, Wang C, Wang Y, et al. Neutrophil-to-lymphocyte ratio and outcomes after acute ischemic stroke: a systematic review and meta-analysis. *Front Neurol*. 2020;11:1032.
35. Zhu B, Pan Y, Jing J, et al. Neutrophil counts, neutrophil ratio and new stroke events or functional outcomes in ischemic stroke or TIA. *Neurol Res*. 2018;40(9):772-778.
36. Li H, Lu Z, Wang C, et al. Prognostic value of YKL-40 in acute ischemic stroke. *J Neurol Sci*. 2017;376:221-227.
37. Katan M, Fluri F, Schuetz P, et al. Midregional pro-atrial natriuretic peptide and copeptin for risk stratification after ischemic stroke. *Ann Neurol*. 2010;67(5): 551-559.
38. De Marchis GM, Katan M, Weck A, et al. Copeptin adds prognostic information after ischemic stroke: results from the CoRisk study. *Neurology*. 2013;80(14):1278-1286.
39. Tu WJ, Dong X, Zhao SJ, Yang DG, Chen H. Prognostic value of plasma neurofilament light chain in acute ischemic stroke. *Neurology*. 2020;94(12):e1288-e1296.
40. Welsh P, Barber M, Langhorne P, et al. Associations of inflammatory and haemostatic biomarkers with poor outcome in acute ischemic stroke. *Cerebrovasc Dis*. 2009;27(3):247-253.
41. Tuttolomondo A, Di Raimondo D, Di Sciacca R, et al. Inflammatory cytokines in acute ischemic stroke. *Curr Pharm Des*. 2008;14(33):3574-3589.
42. Kim J, Song TJ, Park JH, et al. Different prognostic value of white blood cell subtypes in patients with acute cerebral infarction. *Atherosclerosis*. 2012;222(2):464-467.
43. Shenhar-Tsarfaty S, Assayag EB, Bova I, et al. Early signaling of inflammation in acute ischemic stroke: clinical and biomarker implications. *Stroke*. 2010;41(10):e507-e514.
44. Jia J, Wang D, Han Y, et al. Application of metabolomics to the discovery of biomarkers of ischemic stroke in the murine model: a systematic review. *Metabolites*. 2021;11(10):678.
45. Zhang R, Zhang H, Zhang Z, et al. Metabolomics of ischemic stroke: insights into risk prediction and biomarker discovery. *Metabolites*. 2022;12(6):499.

Journal of Chemical Health Risks
www.jchr.org
JCHR (2026) 16(2), 4781-4793 | ISSN:2251-6743

46. Li W, Pan Y, Liu Y, et al. Metabolomics: a useful tool for ischemic stroke research. *Front Neurosci*. 2023;17:1279832.
47. Sun J, Guo X, et al. Advances in metabolomics of biomarkers for ischemic stroke. *Neurosci Bull*. 2025.
48. Ke C, Hou X, Zhang H, Fan L, Ge T, Guo B, Li B, et al. Metabolomics facilitates the discovery of metabolic biomarkers and pathways for ischemic stroke: a systematic review. *Metabolomics*. 2019;15:152.
49. Au A. Metabolomics and lipidomics of ischemic stroke. *Adv Clin Chem*. 2018;85:31-69.
50. Sabatine MS, Liu E, Morrow DA, et al. Metabolomic identification of novel biomarkers of myocardial ischemia. *Circulation*. 2005;112(25):3868-3875.
51. Kimberly WT, Wang Y, Pham L, et al. Metabolite profiling identifies a branched-chain amino acid signature in acute ischemic stroke. *Stroke*. 2013;44(5):1389-1395.
52. Wang D, Kong J, Wu J, Wang X, Lai M. Metabolomics investigation of ischemic stroke and stroke progression. *Clin Chim Acta*. 2017;473:116-124.
53. Weir CJ, Muir SW, Walters MR, Lees KR. Serum urate as an independent predictor of poor outcome and future vascular events after acute stroke. *Stroke*. 2003;34(8):1951-1956.
54. Kamouchi M, Matsuki T, Hata J, et al. Prestroke glycemic control is associated with the functional outcome in acute ischemic stroke: the Fukuoka Stroke Registry. *Stroke*. 2011;42(10):2788-2794.
55. Fujioka M, Taoka T, Matsuo Y, et al. Plasma glucose, lactate, and metabolic derangements in the acute phase of ischemic stroke and their relationship to outcome. *J Neurol Sci*. 2012;315(1-2): 72-77.
56. Wang Y, Li Z, Gu H, et al. China Stroke Statistics 2022. Stroke Vasc Neurol. 2023;8(1):1-14.
57. Feigin VL, Brainin M, Norrving B, et al. World Stroke Organization (WSO): Global Stroke Fact Sheet 2022. Int J Stroke. 2022;17(1):18-29.
58. Campbell BCV, De Silva DA, Macleod MR, et al. Ischaemic stroke. Nat Rev Dis Primers. 2019;5(1):70.
59. Iadecola C, Buckwalter MS, Anrather J. Immune responses to stroke: mechanisms, modulation, and therapeutic potential. J Clin Invest. 2020;130(6):2777-2788.
60. Liesz A, Suri-Payer E, Veltkamp C, et al. Regulatory T cells are key cerebroprotective immunomodulators in acute experimental stroke. Nat Med. 2009;15(2):192-199.
61. Anrather J, Iadecola C. Inflammation and Stroke: An Overview. Neurotherapeutics. 2016;13(4):661-670.
62. Chamorro Á, Dirnagl U, Urra X, Planas AM. Neuroprotection in acute stroke: targeting excitotoxicity, oxidative and nitrosative stress, and inflammation. Lancet Neurol. 2016;15(8):869-881.
63. Hankey GJ. Stroke. Lancet. 2017;389(10069):641-654.
64. Orellana-Urzúa S, Rojas I, Líbano L, Rodrigo R. Pathophysiology of Ischemic Stroke: Role of Oxidative Stress. Curr Pharm Des. 2020;26(34):4246-4260.
65. Jayaraj RL, Azimullah S, Beiram R, et al. Neuroinflammation: friend and foe for ischemic stroke. J Neuroinflammation. 2019;16:142.
66. Shi K, Wood K, Shi FD, et al. Stroke-induced immunosuppression and poststroke infection. Stroke Vasc Neurol. 2018;3(1):34-41.
67. Fann DY, Lee SY, Manzanero S, et al. Pathogenesis of acute stroke and the role of inflammasomes. Ageing Res Rev. 2013;12(4):941-966.
68. Yang F, Wang Z, Wei X, et al. NLRP3 deficiency ameliorates neurovascular damage in experimental ischemic stroke. J Cereb Blood Flow Metab. 2014;34(4):660-667.
69. Abulafia DP, de Rivero Vaccari JP, Lozano JD, et al. Inhibition of the inflammasome complex reduces the inflammatory response after thromboembolic stroke in mice. J Cereb Blood Flow Metab. 2009;29(3):534-544.
70. Ismael S, Zhao L, Nasoohi S, et al. Inhibition of the NLRP3 inflammasome protects against ischemic stroke. J Neuroinflammation. 2018;15:59.
71. Kelley N, Jeltema D, Duan Y, He Y. The NLRP3 Inflammasome: An Overview of Mechanisms of Activation and Regulation. Int J Mol Sci. 2019;20(13):3328.
72. Shao BZ, Xu ZQ, Han BZ, et al. NLRP3 inflammasome and its inhibitors: a review. Front Pharmacol. 2015;6:262.
73. Chen GY, Nuñez G. Sterile inflammation: sensing and reacting to damage. Nat Rev Immunol. 2010;10(12):826-837.
74. Heneka MT, Kummer MP, Stutz A, et al. NLRP3 is activated in Alzheimer's disease and contributes to pathology. Nature. 2013;493(7434):674-678.

Journal of Chemical Health Risks
www.jchr.org
JCHR (2026) 16(2), 4781-4793 | ISSN:2251-6743

75. Duewell P, Kono H, Rayner KJ, et al. NLRP3 inflammasomes are required for atherogenesis. Nature. 2010;464(7293):1357-1361.
76. Grebe A, Hoss F, Latz E. NLRP3 Inflammasome and the IL-1 Pathway in Atherosclerosis. Circ Res. 2018;122(12):1722-1740.
77. Swanson KV, Deng M, Ting JP-Y. The NLRP3 inflammasome: molecular activation and regulation. Nat Rev Immunol. 2019;19(8):477-489.
78. He Y, Hara H, Núñez G. Mechanism and Regulation of NLRP3 Inflammasome Activation. Trends Biochem Sci. 2016;41(12):1012-1021.
79. Bauernfeind FG, Horvath G, Stutz A, et al. Cutting edge: NF-κB activating pattern recognition and cytokine receptors license NLRP3 inflammasome activation. J Immunol. 2009;183(2):787-791.
80. Jo EK, Kim JK, Shin DM, Sasakawa C. Molecular mechanisms regulating NLRP3 inflammasome activation. Cell Mol Immunol. 2016;13(2):148-159.
81. Guo H, Callaway JB, Ting JP-Y. Inflammasomes: mechanism of action, role in disease, and therapeutics. Nat Med. 2015;21(7):677-687.
82. Tschopp J, Schroder K. NLRP3 inflammasome activation: The convergence of multiple signalling pathways on ROS production? Nat Rev Immunol. 2010;10(3):210-215.
83. Bauernfeind F, Hornung V. Of inflammasomes and pathogens—sensing of microbes by the inflammasome. EMBO Mol Med. 2013;5(6):814-826.
84. Broz P, Dixit VM. Inflammasomes: mechanism of assembly, regulation and signalling. Nat Rev Immunol. 2016;16(7):407-420.
85. Lamkanfi M, Dixit VM. Mechanisms and functions of inflammasomes. Cell. 2014;157(5):1013-1022.
86. Schroder K, Tschopp J. The inflammasomes. Cell. 2010;140(6):821-832.
87. Libby P. Inflammation in atherosclerosis. Nature. 2002;420(6917):868-874.
88. Hansson GK, Hermansson A. The immune system in atherosclerosis. Nat Immunol. 2011;12(3):204-212.
89. Moore KJ, Tabas I. Macrophages in the pathogenesis of atherosclerosis. Cell. 2011;145(3):341-355.
90. Tabas I, Lichtman AH. Monocyte-Macrophages and T Cells in Atherosclerosis. Immunity. 2017;47(4):621-634.
91. Weber C, Noels H. Atherosclerosis: current pathogenesis and therapeutic options. Nat Med. 2011;17(11):1410-1422.
92. Duewell P, Latz E. Assessment of inflammasome activation in primary human cells. Methods Mol Biol. 2013;1040:165-181.
93. Paramel GV, Sirsjö A, Fransén K. Role of inflammasomes in intestinal inflammation and Crohn's disease. Inflamm Res. 2015;64(9):653-662.
94. Wen H, Ting JP-Y, O'Neill LAJ. A role for the NLRP3 inflammasome in metabolic diseases. Nat Immunol. 2012;13(4):352-357.
95. Vandanmagsar B, Youm YH, Ravussin A, et al. The NLRP3 inflammasome instigates obesity-induced inflammation. Nat Med. 2011;17(2):179-188.
96. Goldberg IJ, Bornfeldt KE. Lipids and the endothelium: bidirectional interactions. Curr Opin Lipidol. 2013;24(5):377-383.
97. Lusis AJ. Atherosclerosis. Nature. 2000;407(6801):233-241.
98. Ridker PM. From C-reactive protein to interleukin-6 to interleukin-1. Circ Res. 2016;118(1):145-156.
99. Ridker PM, Everett BM, Thuren T, et al. Anti-inflammatory therapy with canakinumab. N Engl J Med. 2017;377(12):1119-1131.
100. Tardif JC, Kouz S, Waters DD, et al. Efficacy of colchicine in cardiovascular disease. N Engl J Med. 2019;381(26):2497-2505.
101. Grebe A, Latz E. Cholesterol crystals and inflammation. Curr Opin Lipidol. 2013;24(5):356-362.
102. Tall AR, Yvan-Charvet L. Cholesterol, inflammation and innate immunity. Nat Rev Immunol. 2015;15(2):104-116.
103. Sheedy FJ, Grebe A, Rayner KJ, et al. CD36 coordinates NLRP3 inflammasome activation. Nat Immunol. 2013;14(8):812-820.
104. Rajamäki K, Lappalainen J, Öörni K, et al. Cholesterol crystals activate NLRP3 inflammasome. PLoS One. 2010;5(7):e11765.
105. Menu P, Mayor A, Zhou R, et al. ASC in inflammasomes regulates adaptive immune responses. Nature. 2009;460(7257):110-113.
106. Masters SL, Dunne A, Subramanian SL, et al. Activation of the NLRP3 inflammasome by islet amyloid polypeptide. Nat Immunol. 2010;11(10):897-904.