

Inflammatory Biomarkers as Predictors of Disease Severity and Prognosis in Patients with Guillain–Barré Syndrome

Vergina Wadiea Gayed Gabra, Elhady Ahmed Abdelgawad, Sabah Mohamed Lotfy and Noha Ali Hashim

Neurology Department, Faculty of Medicine, Zagazig University, Egypt

***Corresponding author:** Vergina Wadiea Gayed Gabra

Email: Gabragina7@gmail.com,

Abstract:

Guillain–Barré syndrome (GBS) is associated with complex immune and inflammatory responses that may influence disease severity and clinical outcomes. Easily obtainable blood-based inflammatory biomarkers have gained increasing attention because they reflect the balance between innate and adaptive immunity and may provide useful prognostic information. Among these markers, the neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), and platelet-to-lymphocyte ratio (PLR) are simple indices derived from routine complete blood counts and have been used as indicators of systemic inflammation. In GBS, elevated NLR has been associated with greater disability, poor prognosis, and respiratory failure, while increased PLR may reflect enhanced inflammatory activity and immune dysregulation. The leuko-glycemic index (LGI), which combines leukocyte count and blood glucose, may additionally reflect the interaction between systemic inflammation and metabolic stress, particularly in severe GBS and patients requiring ventilatory support. Therefore, these readily available biomarkers may have potential value in assessing clinical severity and prognosis in patients with GBS.

Keywords: Guillain–Barré syndrome; Biomarkers; Neutrophil-to-lymphocyte ratio; Monocyte-to-lymphocyte ratio; Platelet-to-lymphocyte ratio; Leuko-glycemic index; Inflammation; Disease severity.

Introduction:

Guillain–Barré syndrome is an acute immune-mediated disorder of the peripheral nervous system, characterized by rapidly progressive, usually symmetrical muscle weakness and decreased or absent deep tendon reflexes. It often occurs after an infection and may lead to respiratory muscle weakness and autonomic dysfunction. Biomarkers are objectively measured parameters used to assess normal biological processes, pathogenic conditions, or pharmacological responses to treatments. They represent changes in tissue or bodily fluid components and serve as tools for classifying diseases and risk factors, contributing to a deeper understanding of disease etiology (1).

the immune system is a unique configuration of many cells, tissues, and organs that collaborate to protect the body against infection and disease; its components are interconnected. Hematopoietic stem cells in the bone marrow give rise to all immune system cells, which eventually specialize in myeloid and lymphoid progenitors. Each further develops into several cell types, such as innate and adaptive immune cells (2).

Immune biomarkers are measurable signals found in blood, saliva, stool, urine, or tissues that reflect immune activity and balance. They can identify:

- Defense responses (e.g., white blood cell count during infection).

- Inflammatory signaling (e.g., C-Reactive Protein(CRP), Interleukin-6 (IL-6), Tumor Necrosis Factor- α (TNF- α)).
- Autoimmunity (e.g., Antinuclear Antibodies (ANAs), rheumatoid factor(RF), Thyroid Peroxidase antibodies (TPO antibodies)).
- Immunosuppression or exhaustion (e.g., persistently low lymphocytes or impaired Natural killer (NK) cell activity).

Unlike single diagnostic tests, immune biomarkers are dynamic, often providing early warning before overt disease develops (3).

Neutrophils are granulocytic leukocytes with multilobed nuclei. They are the first cells to phagocytose bacteria and other pathogens at the site of tissue injury. It is principally responsible for the increased levels of white blood cells associated with lupus, rheumatoid arthritis, sepsis and bone marrow damage. They increase in number in the bloodstream as a result of illness (4).

Neutrophils are responsible for the first line of host immune response against invading pathogens, through different mechanisms, including chemotaxis, phagocytosis, release of reactive oxygen species (ROS), granular proteins and the production and liberation of cytokines (5). Neutrophils also play an important regulatory role in adaptive immunity and are the main effector cells during the systemic inflammatory response (SIRS). As regulators of innate immunity, neutrophils recruit, activate and programme other immune cells, secreting an array of pro-inflammatory and immunomodulatory cytokines and chemokines capable of enhancing the recruitment and effector functions of other immune cells, such as dendritic cells (DCs), B cells, NK cells, CD4, CD8 and γ T cells, as well as mesenchymal stem cells (6).

Monocytes are a particular class of phagocytic cells in the bloodstream that develops into macrophages when they enter tissues. The most significant white blood cells, monocytes, make macrophages and dendritic cells (4). Macrophages ingest and digest infectious agents, cancer cells, and cell debris and participate in tissue regeneration, wound healing, and proinflammatory actions (7).

Lymphocytes originate from hematopoietic stem cells in the bone marrow, where immature lymphocytes are continuously produced and released into the circulation. Some migrate to the thymus and differentiate into T lymphocytes, which subsequently circulate through peripheral lymphoid organs and proliferate upon antigenic stimulation. Some lymphocytes remain in the bone marrow, where they differentiate into B lymphocytes, which migrate to peripheral lymphoid organs and proliferate upon appropriate stimulation. B cells mediate humoral immunity through antibody secretion, whereas T cells mediate cell-mediated immunity by directly targeting infected cells and regulating immune responses (8).

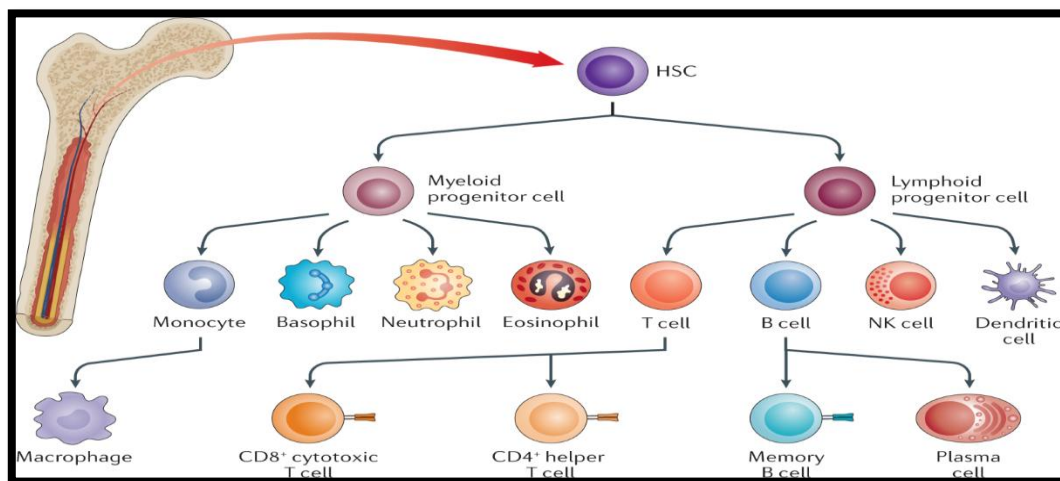


Figure (1): Hematopoiesis and differentiation of immune cells from hematopoietic stem cells. (9).

Neutrophil-to-lymphocyte Ratio

The neutrophil-to-lymphocyte ratio (NLR), calculated as a simple ratio between the neutrophil and lymphocyte count measured in peripheral blood, is a biomarker which conjugates two faces of the immune system: the innate immune response, mainly due to neutrophils, and adaptive immunity, supported by lymphocytes (10).

An isolated rise in neutrophil count, and, consequently, an elevated Neutrophil -to-Lymphocyte Ratio (NLR), can be observed in several conditions: bacterial or fungal infection, acute stroke, myocardial infarction, atherosclerosis, severe trauma, cancer, post-surgery complications and any condition characterized by tissue damage that activates Systemic Inflammatory Response Syndrome (SIRS). This is because the early hyperdynamic phase of infection is characterized by a proinflammatory state, mediated by neutrophils and other inflammatory cells. SIRS is associated with the suppression of neutrophil apoptosis, which augments neutrophil-mediated killing as part of the innate response. Thus, NLR is often characterized by an increase in neutrophils and a decline in lymphocytes (11).

Otherwise, lymphocytes, in their variety (B cells; T cells CD4-positive, CD4/CD8- negative or CD8-positive; natural killer T cells), are especially responsible for adaptive immunity, providing an antigen-specific response regulated by the major histocompatibility complex (MHC) class I. Lymphocyte activity is involved in host response to viruses, tumor cells, atopy and in SIRS too. Lower NLR is usually associated with favorable prognostic factors in every field of application, mirroring a preserved immune balance. (12).

NLR is a proven independent prognostic factor of morbidity and mortality in several diseases, its normal cut-off value is still under debate. **Forget et al. (13)**, in a large retrospective case-control study, observed that normal NLR values in an adult, non-geriatric population in good health may be between 0.78 and 3.53. In the Rotterdam study, it was observed that the mean NLR in the general population was 1.76, with a 2.5% limit at 0.83 and 97.5% limit at 3.92. Moreover, the mean NLR was significantly higher in males (mean of 1.88) than in females (mean of 1.68) and in elderly subjects >85 years of age (mean NLR of 2.13) compared with subjects aged 45–54 years (mean NLR 1.63) ($p < 0.001$) (14).

Karakonstantis et al. (15) found several factors that could determine a “false” increase in NLR, such as age, exogenous steroid intake, endogenous sexual hormones, active hematological disorders, such as leukemia, cytotoxic or granulocyte colony stimulating factor (G-CSF) chemotherapies, and HIV

The concept of the neutrophil-to-lymphocyte ratio (NLR), stands as a noteworthy outcome of these efforts. Just like the shock index, this new parameter, which is formulated by the ratio of two simple complete blood count parameters, has been found to provide better results in the prognosis of many critical conditions than its components, thus laying the foundation of a fairly extensive literature. (16).

Neutrophilia and lymphocytopenia, which are immune system responses to systemic inflammation, injury, and stress, are influenced by various factors. Neutrophils serve as precursors to the innate immune response, engaging in phagocytosis and releasing cytokines and mediators. They act as the main effectors in the early hyperdynamic phase of infection and contribute to adaptive immunity regulation. Conditions such as infection, acute stroke, myocardial infarction, atherosclerosis, severe trauma, burns, major surgery, and any situation involving tissue damage activating SIRS can lead to increased neutrophil counts (17).

Simultaneous yet opposite changes in neutrophil and lymphocyte counts reflect a multifactorial dynamic response, influenced by immunologic, neuroendocrine, humoral, and biological factors, adding a layer of complexity and interest to this phenomenon (18). In addition, the early change (<6 h) in neutrophil and lymphocyte counts following acute physiological stress endows them as earlier markers compared to other laboratory parameters (e.g., white blood cell count and C-reactive protein [CRP]).

The NLR was significantly higher in GBS patients with respect to healthy patients and it was also a poor prognostic factor. The early identification of GBS with poor prognosis will help patients to be treated with different doses, that NLR could be a prognostic factor for disability and respiratory failure. (19)

Monocyte-to-Lymphocyte Ratio (MLR):

Monocyte-to-lymphocyte ratio (MLR) is defined as absolute monocyte count divided by lymphocyte count. Given that the ratio reflects the opposite but complementary balance between the nonspecific inflammatory process and adaptive immune response in the body, several researchers suggested MLR as a competitive biomarker comparable to NLR or C-reactive protein (CRP) (20).

In healthy adults, MLR values typically fall within a low-to-moderate range, although reference intervals vary across laboratories and populations (often around 0.2–0.3). Lower MLR values generally reflect relative lymphocytosis or reduced monocyte counts and are commonly observed during acute viral infections, allergic conditions, or recovery phases following physiological stress, where adaptive immune responses predominate. In contrast, elevated MLR values may result from monocytosis, lymphopenia, or both, and have been associated with chronic inflammatory diseases, persistent infections such as tuberculosis, malignancies, cardiovascular disease, aging, malnutrition, and immunosuppressive states including steroid exposure and HIV infection (21).

Mechanistically, increased MLR may reflect enhanced monocyte activation and macrophage differentiation, contributing to sustained inflammatory signaling, endothelial dysfunction, and tissue damage. Conversely, reduced lymphocyte counts may indicate impaired adaptive immune surveillance. Clinically, elevated MLR has been linked to adverse outcomes in several conditions, including increased risk of cardiovascular events, disease severity in infections, and poor prognosis in various cancers. Despite its growing utility, MLR should be interpreted in the context of clinical findings, other inflammatory markers, and disease-specific factors (22).

Abnormally activated monocytes may play a role in the pathogenesis of inflammation, the role of monocytes in the immune system is cytokine expression, antigen presentation, or phagocytosis, there is a relationship between increased number of monocytes and disease and disease severity.(23). the blood–brain barrier is permeable to monocytes and monocytes can be

differentiate into microglia cells pass through this structure and this can demonstrate the important role of monocytes in the neuroinflammatory process. (23).

Platelet-to-Lymphocyte Ratio (PLR):

Platelets or Thrombocytes are a nucleated small blood cells, that originated in bone marrow from the megakaryocytes series, having a crucial role in thrombus formation, hemostasis and wound healing (24). However, as platelets retain many of capabilities possessed by the primordial hemocyte of invertebrates, it is perhaps not surprising that platelets have also been recognized to play a role as immune cells, directly linking coagulation and immunity.

Like hemocytes, platelets have been shown to be able to recognize pathogens through the expression of toll-like receptors (TLRs), release various cytokines, chemokines, and growth factors stored within their granules, and express cell adhesion molecules on their surface allowing for interaction with both the vasculature and immune cells, mainly neutrophils and monocytes (25).

Human platelets are also considered immune cells because of their ability to interact with the complement system. Platelets α granules have complement C3, C4a, C1-inhibitor (C1-I) and complement factor H that are released upon platelet activation. Platelets can activate both, the classical pathway of complement by the deposition of C1q and C4d in the platelet surface, and the alternative pathway of complement by the secretion of C3 (26). Importantly, C1-I not only inhibits the classical pathway of the complement cascade by interacting with activated C1 but also inhibits factor XIa and XIIa from the coagulation cascade, providing additional overlap between immunity and coagulation.

Platelets also express receptors for C1q, C3a, and C5a. C3a and C5a binds to their receptors and trigger platelet activation and aggregation, inducing exposure of P-selectin and the receptor for C1q (C1qR). C1q binds to its receptor further promoting P-selectin expression and platelet activation, adhesion, and aggregation, while C4a is able to bind PAR1 and PAR4 triggering platelet activation (27).

Recently, a new mechanism, called immunothrombosis, has been described, where coagulation and the immune response work together to trap and kill bacteria. This process involves prothrombotic mechanisms that operate within intact blood vessels to facilitate the recognition of pathogens, prevent their spread and enhancing clearance. In response to recognition of Pathogen-Associated Molecular Patterns (PAMPs), monocytes express tissue factor (TF) at sites of pathogen exposure, initiating the coagulation cascade (28).

Platelets participate in inflammation and immunity through multiple mechanisms including the storage of a wide variety of cytokines, chemokines, and adhesion molecules within their granules, their ability to interact with pathogens through membrane expression of TLRs and other Pattern Recognition Receptors (PRR), and by direct platelet interactions with other immune cells and the complement system (Fig. 2)

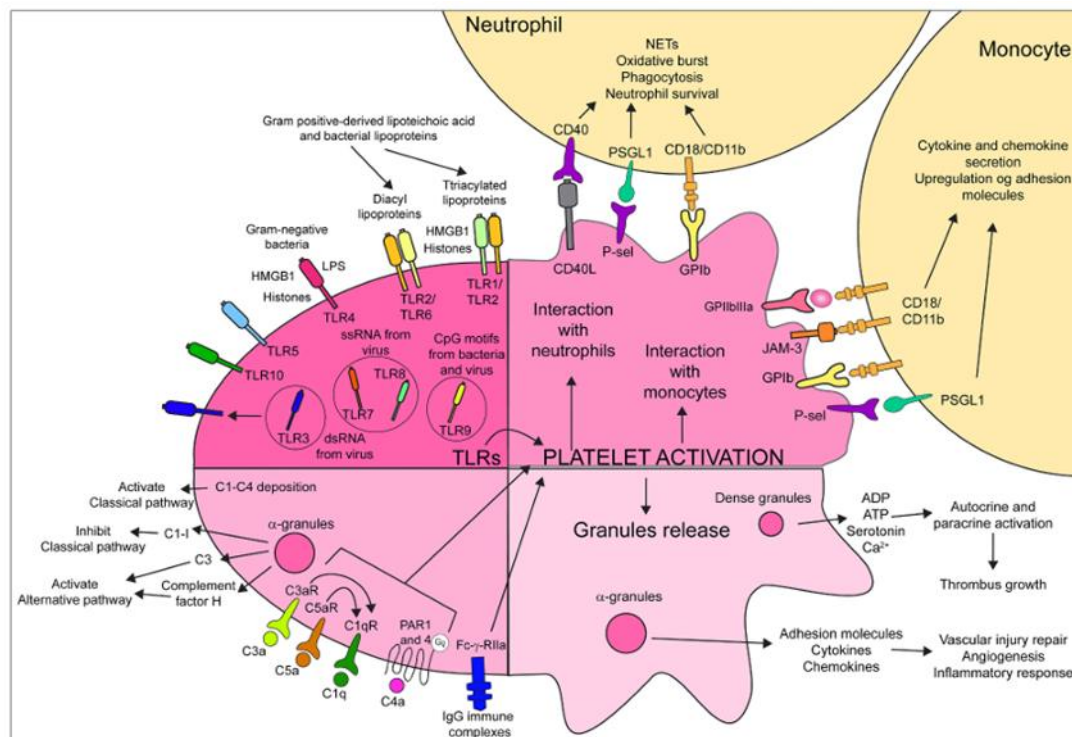


Fig. 2. Platelets as immune cells. Platelets act as immune cells through the expression of TLRs, their interaction with neutrophils and monocytes and the complement system and the release of molecules from their α and dense granules (29)

Evidence in mice indicates that the P-selectin–PSGL1 axis precipitates NETosis, which may provide another link between platelet–neutrophil aggregates and autoimmunity and thrombosis (30) (fig 3 a)

In the context of immune complex-mediated inflammation in mice, platelet activation through GPVI, which is targeted by antiplatelet antibodies, is responsible for increased recruitment of neutrophils to the site of inflammation and their increased degranulation and release of elastase and matrix metalloproteases, leading to tissue damage (31).

Mouse monocytes also express PSGL1 and interact with activated platelets in vitro and in vivo. Furthermore, P-selectin drives the maturation of monocytes to activated DCs with increased expression of CD80 and CD86, which results in increased T cell activation, including greater antitumour activity of CD8⁺ T cells in vitro. In the context of viral infection, activated platelets interact with monocytes through P-selectin–PSGL1 and CD40L–CD40, and promote the differentiation of monocytes towards a pro-inflammatory DC phenotype with increased production of the inflammatory cytokine IL-1 β (Fig. 3a). Importantly, platelets also contain large quantities of immunomodulatory molecules such as transforming growth factor- β (TGF β), and several reports indicate that the incubation of monocytes with platelet lysates or their secretome induces the differentiation of DCs with deficient

immunostimulatory activities (32). Overall, the interactions between platelets and innate immune cells, including DCs, lead to multiple and complex effects on adaptive immune cells.

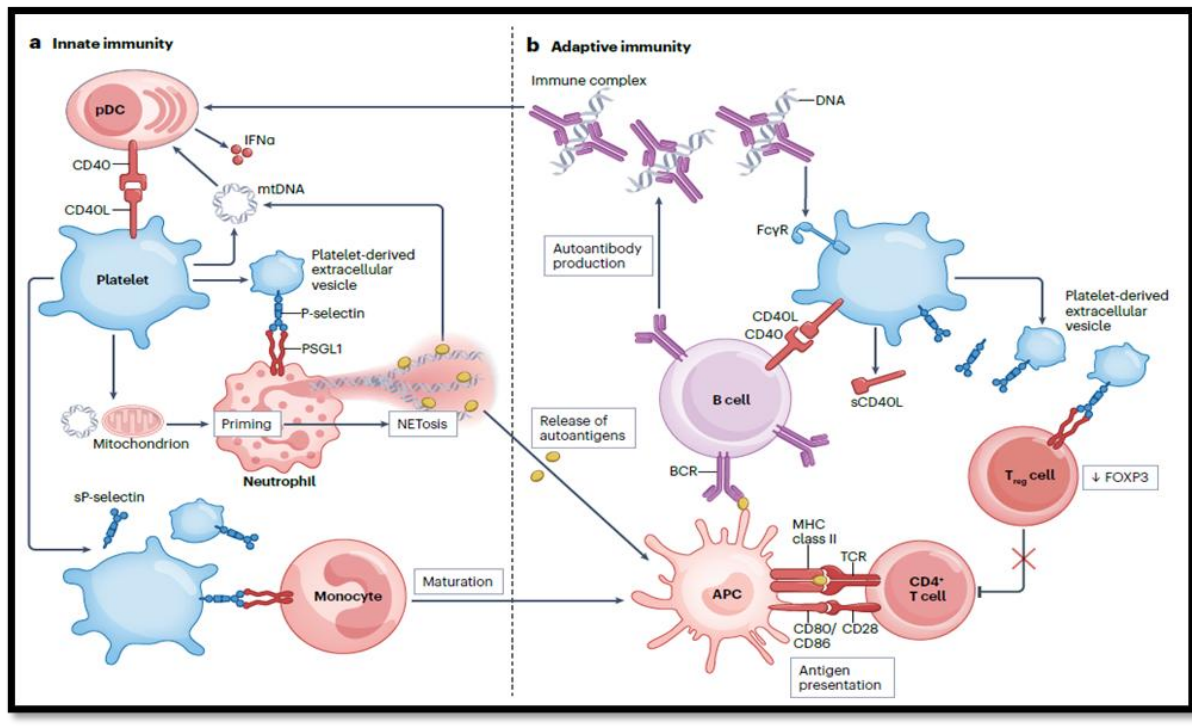


Fig.3| Activated platelets interact with and activate innate and adaptive immune cells. Activated platelets and platelet-derived extracellular vesicles physically interact with immune cells and stimulate an inflammatory response. **a**, Innate immunity. Platelets aggregate with plasmacytoid dendritic cells (pDCs) through CD40 ligand (CD40L)–CD40 interactions and stimulate interferon- α (IFN α) production in response to circulating immune complexes. Platelets also interact with monocytes and neutrophils through the P-selectin–P-selectin glycoprotein ligand 1 (PSGL1) axis, leading to the maturation of monocytes to antigen-presenting cells (APCs) and the priming of neutrophils. Platelets release mitochondria and mitochondrial DNA (mtDNA), which induce neutrophil activation and the production of neutrophil extracellular traps (NETosis). This leads to the release of autoantigens that are processed by APCs and presented to lymphocytes. **b**, Adaptive immunity. Activated platelets express membrane CD40L and soluble CD40L (sCD40L), which stimulate B cell responses and the production of autoantibodies. P-selectin-positive platelets and platelet-derived extracellular vesicles interact with regulatory T cells (Treg cells), leading to FOXP3 downregulation and Treg cell dysfunction. BCR, B cell receptor; Fc γ R, Fc γ receptor; sP-selectin, soluble P-selectin; TCR, T cell receptor. (33)

Colchicine is a drug classically prescribed to patients with gout and in some Immune-mediated inflammatory diseases IMIDs such as SLE pericarditis. It inhibits microtubule assembly and inflammasome activation. Interestingly, colchicine use is linked to reduced cardiovascular disease risk in a meta-analysis of randomized clinical trial. Multiple mechanisms are responsible for this effect, including inhibition of inflammasome assembly and IL-1 β production, and a direct effect on platelets. Indeed, colchicine prevents platelet activation in vitro and reduces the number of platelet–neutrophil and platelet–monocyte aggregates in healthy humans. Furthermore, the pharmacological inhibition of Bruton's tyrosine kinase (BTK) has been identified as an efficient approach to inhibit the NLRP3 inflammasome, and may therefore limit platelet activation (34).

Human, but not mouse, platelets express the low affinity receptor for immunoglobulin (Ig), Fc γ RII. IgG-containing immune complexes can trigger platelet activation in a Fc γ RIIa dependent manner. Depending on the IgG and the environmental stimuli as a result of infection severity, activation of Fc γ RIIa by IgG immune complexes may also contribute to the prothrombotic potential of platelets. This bridge, through FcR-mediated antibody binding, allows platelets to respond to a wide spectrum of pathogens, independent of specific PAMPs

and DAMPs, harnessing the immense diversity present within the adaptive arm of the immune system and taking advantage of this pre-existing pool of antibodies in the blood to rapidly detect and bind pathogens and immune complexes (35). (figure 3b)

Biomarkers such as the NLR, MLR, and PLR have been validated as indicators of systemic inflammation in various conditions, including neuromyelitis optica spectrum disorder, multiple sclerosis, optic neuritis, primary Sjogren's syndrome, and Graves' orbitopathy (36).

Elevated PLR in patients with GBS reflects an imbalance in systemic inflammation and immune responses, characterized by increased PLT activity and reduced lymphocyte counts, which suggests heightened inflammatory activity and potential immune dysregulation, both of which have been implicated in GBS pathogenesis. (37)

The leuko-glycemic index (LGI):

The leuko-glycemic index (LGI) is a composite biomarker that integrates peripheral white blood cell count and blood glucose levels, typically calculated by multiplying these two parameters and dividing by 1,000. Because leukocytes are key effectors of the innate immune response and systemic inflammation, and glucose levels reflect metabolic stress and stress-induced hyperglycemia, LGI captures the interplay between metabolic dysregulation and inflammatory activation at the time of clinical presentation (38).

Studies have shown a relationship between blood glucose levels and the progression of sepsis. Elevated glucose can exacerbate inflammatory responses and weaken immune defenses, potentially accelerating disease progression. As glucose concentrations rise, pro-inflammatory cytokines such as IL-6, TNF- α , and IL-1 β tend to increase, while the CD4⁺/CD8⁺ T-cell ratio generally decreases (39).

Higher LGI values have been associated with elevated levels of classical inflammatory mediators and endothelial dysfunction in conditions characterized by chronic low-grade inflammation, such as overweight and obesity, where LGI correlated positively with IL-6, TNF- α , and von Willebrand factor, markers of systemic inflammation and vascular perturbation (40).

The Leuko-Glycemic Index (LGI) has been associated with poor outcomes in various conditions, including acute myocardial infarction (MI), coronary artery disease (CAD), COVID-19, and arteriovenous fistula (AVF) failure in long-term dialysis patients (41).

Higher serum glucose levels on admission in GBS patients with ventilatory support is compared to those without support, increase in serum glucose levels might be directly related to the metabolic response to stress in acute inflammatory processes, there is the high prevalence of autonomic dysfunction in severe GBS cases and in patients with mechanical support (40).

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