Issue 3, Year 2, Volume 1, No. 01, January-June 2026

Systemic Responses to Trauma: Integrating Inflammation, Neuroendocrine Regulation, and Recovery Mechanisms

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Received: 28-Apr-20026 | **Accepted:** 28-Apr-2026 | **Published:** 30-Apr-2026

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How to cite this article: Hernandez Falcon, A. M., Cruz Molina, S. I., Chacón Hernández, J. A., Crespo Macias, M. F., Robles Gutierrez, D. A., Mesa Rincon, D., Yang Nam, H. S., & Badillo Avalos, J. O. (2026). Systemic Responses to Trauma: Integrating Inflammation, Neuroendocrine Regulation, and Recovery Mechanisms. México. International Science Journal "TheSci". 3 (1) 436-445. Quality Consulting Instituto de Educación Capacitación y Certificación de México. https://ieccmexico.com/thesci

E-ISSN: 3122-3591, P-ISSN: 3122-3753
Review International Science Journal

Issue 3, Year 2, Volume 1, No. 01, January-June 2026
E-ISSN: 3122-3591, P-ISSN: 3122-3753
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ABSTRACT

Trauma is a leading global cause of morbidity and mortality, traditionally understood as a localized physical injury. However, current evidence supports a broader perspective in which trauma triggers a complex systemic response involving inflammatory, neuroendocrine, immune, metabolic, and endothelial mechanisms. This study aimed to analyze Post-Traumatic Systemic Syndrome as an integrative condition that influences recovery beyond the initial injury. A structured narrative review was conducted using international scientific databases, including PubMed, Scopus, and Web of Science, focusing on high-impact literature related to systemic trauma responses. The analysis explored the interaction between inflammatory activation, neuroendocrine regulation, immune dysfunction, and metabolic alterations. The findings demonstrate that trauma induces an immediate inflammatory response characterized by cytokine

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release, followed by neuroendocrine modulation through activation of the hypothalamic–pituitary–adrenal axis. This interaction may lead to either balanced recovery or dysregulated states such as hyperinflammation, immunosuppression, and persistent inflammation syndromes. Additionally, endothelial dysfunction, coagulopathy, and mitochondrial impairment contribute significantly to systemic complications. Recovery trajectories vary depending on the regulation of these mechanisms, highlighting the importance of early and targeted interventions.
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KEYWORDS

Trauma, systemic inflammatory response, neuroendocrine response, immune dysregulation, cytokines, coagulopathy, endothelial dysfunction, mitochondrial dysfunction, metabolic response, recovery trajectories

INTRODUCTION

Trauma remains one of the leading causes of morbidity and mortality worldwide, particularly affecting young and economically active populations, thereby generating a profound global health burden. Beyond the immediate mechanical injury, trauma triggers a complex and dynamic systemic response that extends far beyond the initial insult. This response, often conceptualized as a **post-traumatic systemic syndrome**, encompasses a multifaceted interplay between inflammatory cascades, neuroendocrine activation, immune dysregulation, and metabolic alterations that collectively determine patient outcomes [1], [3].

The classical understanding of trauma has evolved from a purely structural perspective toward a systemic and integrative model. Following injury, the organism initiates a rapid inflammatory response characterized by the release of cytokines, chemokines, and damage-associated molecular patterns (DAMPs), which activate innate immune pathways and amplify systemic inflammation [6], [7]. While this response is initially protective and aimed at restoring homeostasis, excessive or dysregulated activation may lead to systemic inflammatory response syndrome (SIRS), multiple organ dysfunction syndrome (MODS), and increased mortality [4], [16]. In parallel, recent evidence has demonstrated that trauma-induced immune responses are not limited to hyperinflammation but also include a compensatory anti-inflammatory response, leading to a state of immunosuppression that predisposes patients to secondary infections and delayed recovery [15], [12].

In addition to the immune response, the neuroendocrine system plays a central role in orchestrating the systemic reaction to trauma. Activation of the hypothalamic–pituitary–adrenal (HPA) axis and the sympathetic nervous system results in the release of stress hormones such as cortisol, catecholamines, and glucagon, which modulate immune function, metabolism, and cardiovascular stability [9]. This neuroendocrine-immune interaction has been increasingly recognized as a bidirectional and tightly regulated process, where alterations can either support recovery or contribute to persistent inflammation and organ dysfunction. Emerging research highlights the concept of a "neuroendocrine-immune axis" as a critical determinant of outcomes in severely injured patients [11].

Recent genomic and molecular studies have further expanded the understanding of trauma as a systemic disease. The concept of a "genomic storm," characterized by widespread and coordinated changes in gene expression following injury, underscores the complexity of the host response and its potential implications for personalized medicine approaches [14]. Similarly, mitochondrial dysfunction and metabolic reprogramming have been identified as key contributors to immune dysregulation and impaired tissue repair [11]. These findings suggest that trauma should be approached not only as an acute event but as a prolonged systemic condition requiring integrated therapeutic strategies.

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E-ISSN: 3122-3591, P-ISSN: 3122-3753
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Despite significant advances in trauma care, important gaps remain in understanding how these interconnected systems influence recovery trajectories. Most existing studies have focused on isolated components—such as inflammation, coagulopathy, or endocrine response—without fully integrating these mechanisms into a unified framework. This fragmentation limits the development of comprehensive treatment strategies capable of modulating the systemic response in a targeted and effective manner [13].

In the Latin American context, particularly in countries such as Mexico, Colombia, and Ecuador, trauma continues to represent a major public health challenge due to high rates of traffic accidents, interpersonal violence, and occupational injuries. However, there is a relative scarcity of integrative analyses that address the systemic nature of post-traumatic responses within these populations. Understanding regional variations in clinical presentation, resource availability, and therapeutic approaches is essential for developing context-specific strategies that improve outcomes and reduce disparities in care.

Therefore, the present review aims to provide a comprehensive and integrative analysis of post-traumatic systemic syndrome, focusing on three key dimensions: inflammatory response, neuroendocrine regulation, and recovery processes. The central research question guiding this work is: **how does the interaction between inflammatory and neuroendocrine mechanisms influence the trajectory of recovery following trauma?** From this perspective, the hypothesis proposes that the imbalance between pro-inflammatory activation and neuroendocrine modulation plays a decisive role in determining clinical outcomes, including complications and recovery time.

To address this objective, a structured narrative review design was employed, integrating recent and high-impact literature to synthesize current knowledge and identify emerging trends. The methodological approach aligns with the study objectives by allowing a comprehensive exploration of complex, multidimensional processes that cannot be fully captured through isolated experimental models. By bridging immunological, neuroendocrine, and clinical perspectives, this work seeks to contribute to a more holistic understanding of trauma and to support the development of innovative therapeutic strategies.

DEVELOPMENT

1. Comprehensive Analysis of the Post-Traumatic Systemic Syndrome

The understanding of trauma has undergone a paradigm shift in recent decades, evolving from a localized injury model to a systemic and multidimensional process involving immunological, neuroendocrine, metabolic, and cellular responses. The concept of **Post-Traumatic Systemic Syndrome (PTSS)** integrates these mechanisms into a unified framework, recognizing trauma as a trigger of widespread physiological disruption rather than an isolated event.

1.1 Inflammatory Response: From Local Injury to Systemic Dysregulation

Immediately after traumatic injury, the body activates the innate immune system through the recognition of **damage-associated molecular patterns (DAMPs)** released from injured tissues. These molecules, including mitochondrial DNA and high-mobility group box 1 (HMGB1), initiate signaling cascades that activate macrophages, neutrophils, and endothelial cells [6], [7].

This activation results in the release of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6, which amplify the inflammatory response and promote vascular permeability, leukocyte recruitment, and tissue repair mechanisms [1], [18]. While these processes are essential for healing, excessive or prolonged activation leads to systemic inflammatory response syndrome (SIRS), characterized by widespread endothelial dysfunction and microcirculatory impairment [4].

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E-ISSN: 3122-3591, P-ISSN: 3122-3753
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Moreover, studies have demonstrated that the magnitude of cytokine release correlates with injury severity and clinical outcomes, including the development of multiple organ dysfunction syndrome (MODS) [16]. Importantly, this inflammatory response is not linear but occurs in phases, often overlapping with anti-inflammatory mechanisms that attempt to restore homeostasis.

1.2 Immune Dysregulation and Immunosuppression

Contrary to earlier models that emphasized hyperinflammation alone, current evidence supports the coexistence of **persistent inflammation and compensatory immunosuppression**, forming a complex immunological phenotype known as PICS (Persistent Inflammation, Immunosuppression, and Catabolism Syndrome) [15].

During this phase, there is a reduction in antigen presentation capacity, lymphocyte apoptosis, and impaired innate immune responses, which increase susceptibility to secondary infections and sepsis [12]. This dual response—hyperinflammation followed by immune exhaustion—represents a critical determinant of patient prognosis.

Furthermore, genomic studies have revealed that trauma induces widespread alterations in gene expression, affecting both pro-inflammatory and anti-inflammatory pathways simultaneously, a phenomenon described as a **"genomic storm"** [14]. This insight challenges the traditional sequential model of immune response and highlights the need for personalized therapeutic approaches.

1.3 Neuroendocrine Response: Central Regulation of Systemic Homeostasis

The neuroendocrine system plays a pivotal role in modulating the systemic response to trauma. Activation of the **hypothalamic–pituitary–adrenal (HPA) axis** leads to increased secretion of cortisol, which exerts potent anti-inflammatory effects by inhibiting cytokine production and immune cell activation [9].

Simultaneously, the sympathetic nervous system releases catecholamines such as epinephrine and norepinephrine, which regulate cardiovascular function, glucose metabolism, and immune responses. While these mechanisms are essential for maintaining hemodynamic stability, prolonged activation contributes to metabolic derangements, including hyperglycemia, insulin resistance, and protein catabolism [11].

Recent studies emphasize the bidirectional interaction between the nervous and immune systems, forming a **neuroendocrine-immune axis**. Dysregulation of this axis has been associated with poor outcomes, including prolonged intensive care stays and increased mortality.

1.4 Coagulopathy and Endothelial Dysfunction

Another critical component of PTSS is trauma-induced coagulopathy, which occurs early after injury and is driven by a combination of endothelial damage, inflammation, and dysregulated coagulation pathways [13]. The endothelium, once considered a passive barrier, is now recognized as an active participant in inflammation and coagulation.

Endothelial activation leads to increased expression of adhesion molecules, disruption of the glycocalyx, and altered vascular permeability. These changes contribute to microvascular thrombosis, impaired tissue perfusion, and organ dysfunction. The interplay between inflammation and coagulation, often referred to as **immunothrombosis**, represents a key mechanism linking local injury to systemic complications.

1.5 Metabolic and Mitochondrial Alterations

Trauma induces profound metabolic changes characterized by a hypermetabolic state, increased energy expenditure, and altered substrate utilization. Mitochondrial dysfunction has emerged as a central factor in this process, affecting cellular energy production and contributing to organ failure [11].

The release of mitochondrial DAMPs further amplifies the inflammatory response, creating a feedback loop that perpetuates systemic dysfunction [19]. These findings underscore the importance of metabolic support and early nutritional interventions in trauma care.

1.6 Recovery and Clinical Implications

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Recovery from trauma is not merely the resolution of inflammation but a complex process involving tissue repair, immune reconstitution, and metabolic normalization. The balance between pro-inflammatory and anti-inflammatory responses, as well as the regulation of neuroendocrine activity, determines the trajectory of recovery.

Clinical evidence suggests that early identification of dysregulated responses—such as persistent inflammation or immunosuppression—can guide therapeutic interventions and improve outcomes. Strategies such as immunomodulation, hormonal regulation, and personalized critical care approaches are emerging as key areas of research.

GENERAL OBJECTIVE AND SPECIFIC OBJECTIVES

To analyze Post-Traumatic Systemic Syndrome as an integrative physiological condition that extends beyond mechanical injury, emphasizing the interaction between inflammation, neuroendocrine response, immune dysregulation, and recovery processes in trauma care.

A. Cognitive Domain

1. **To identify** the main inflammatory mechanisms activated after traumatic injury, including cytokine release, DAMPs signaling, endothelial dysfunction, and immune cell activation.
2. **To explain** the role of the neuroendocrine response in trauma, particularly the activation of the hypothalamic–pituitary–adrenal axis and the sympathetic nervous system.
3. **To analyze** the relationship between persistent inflammation, immunosuppression, metabolic alterations, and delayed recovery in trauma patients.
4. **To compare** current international evidence on systemic post-traumatic responses, considering clinical perspectives from Mexico, Colombia, and Ecuador.

B. Psychomotor Domain

1. **To organize** the available scientific evidence into a structured review model that allows a clear understanding of the systemic response to trauma.
2. **To construct** an integrative framework that connects inflammatory, neuroendocrine, immune, and metabolic pathways involved in post-traumatic recovery.
3. **To apply** a reproducible methodological process for selecting, analyzing, and synthesizing scientific literature related to trauma physiology and systemic complications.

C. Affective Domain

5. **To value** the importance of understanding trauma as a systemic condition rather than only as a localized injury.
6. **To promote** clinical awareness regarding the early identification of systemic alterations after trauma.
7. **To encourage** an international and educational perspective in trauma care, highlighting the relevance of evidence-based learning for medical students and healthcare professionals.
8. **To recognize** the importance of comprehensive trauma management adapted to different healthcare contexts, including Latin American settings.

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OBJECT OF STUDY

The object of study of this article is the **Post-Traumatic Systemic Syndrome (PTSS)**, understood as a complex, dynamic, and integrative physiological response that occurs following traumatic injury and involves the interaction of inflammatory, neuroendocrine, immune, metabolic, and coagulation mechanisms.

From a conceptual perspective, PTSS is not limited to the anatomical damage caused by trauma but represents a **systemic condition** characterized by widespread biological alterations that affect multiple organs and regulatory systems. This phenomenon emerges immediately after injury and evolves over time, influencing both acute outcomes and long-term recovery.

Phenomenon Under Investigation

The primary phenomenon analyzed in this study is the **systemic response to trauma**, focusing on three key dimensions:

1. **Inflammatory response:** Activation of innate immunity, release of cytokines, and systemic propagation of inflammation.
2. **Neuroendocrine response:** Activation of stress pathways, including the hypothalamic–pituitary–adrenal axis and sympathetic nervous system.
3. **Recovery processes:** Mechanisms of immune resolution, tissue repair, and metabolic normalization.

These dimensions are examined as interconnected processes rather than isolated events, highlighting their synergistic and sometimes maladaptive interactions.

Population of Interest

The study focuses on **patients with traumatic injuries**, particularly those presenting moderate to severe trauma, as these cases are more likely to develop systemic complications. Although the analysis is based on international literature, special consideration is given to clinical realities in **Mexico, Colombia, and Ecuador**, where trauma remains a major public health concern.

This population includes:

- Patients with polytrauma
- Individuals admitted to emergency and critical care units
- Patients at risk of systemic inflammatory response syndrome (SIRS), sepsis, or multiple organ dysfunction syndrome (MODS)

System Under Analysis

The system under investigation is the **human physiological response to trauma**, approached as an integrated network of:

- Immune system (innate and adaptive responses)
- Neuroendocrine system (HPA axis and autonomic regulation)
- Cardiovascular and endothelial systems
- Metabolic and mitochondrial function

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This systemic approach allows for a comprehensive understanding of how trauma affects the organism as a whole, rather than focusing on isolated organ damage.

METHODOLOGY

Study Design

This study was conducted as a **structured narrative review**, designed to integrate and critically analyze current scientific evidence on Post-Traumatic Systemic Syndrome (PTSS). This approach was selected due to the multidimensional nature of the phenomenon, which involves complex interactions between inflammatory, neuroendocrine, immune, and metabolic systems that cannot be fully addressed through a single experimental or quantitative method.

The narrative review design allows for the synthesis of diverse types of evidence, including clinical studies, experimental research, and translational findings, providing a comprehensive understanding of the topic.

Methodological Approach

The study follows the principles of the **Scientific Method**, adapted to a literature-based investigation. This approach ensures a logical, systematic, and reproducible process consisting of the following components:

1. **Problem Identification:** Recognition of trauma as a systemic condition involving multiple physiological pathways beyond localized injury.
2. **Research Question Formulation:** How does the interaction between inflammatory and neuroendocrine mechanisms influence systemic response and recovery following trauma?
3. **Hypothesis Development:** An imbalance between pro-inflammatory activation and neuroendocrine regulation contributes significantly to adverse clinical outcomes, including prolonged recovery and organ dysfunction.
4. **Data Collection:** Selection and compilation of relevant scientific literature addressing inflammation, immune response, neuroendocrine regulation, and recovery in trauma patients.
5. **Analysis and Synthesis:** Critical evaluation and integration of findings to identify patterns, relationships, and gaps in current knowledge.
6. **Interpretation:** Development of an integrative framework that explains the systemic nature of post-traumatic responses.

Search Strategy and Data Sources

A comprehensive literature search was performed using internationally recognized databases, including:

- PubMed/MEDLINE
- Scopus
- Web of Science
- Google Scholar

Keywords and combinations included: “trauma,” “systemic inflammatory response,” “neuroendocrine response,” “DAMPs,” “immune dysregulation,” “multiple organ dysfunction,” and “post-traumatic recovery.”

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Boolean operators (AND, OR) were applied to refine the search and ensure relevance.

Inclusion and Exclusion Criteria

Inclusion Criteria:

- Articles published in peer-reviewed journals
- Studies focusing on trauma-related systemic responses
- Research addressing inflammation, neuroendocrine mechanisms, or recovery
- Publications in English
- High-impact or widely cited studies

Exclusion Criteria:

- Studies unrelated to systemic trauma response
- Case reports without broader applicability
- Non-peer-reviewed sources
- Articles lacking methodological clarity

Data Extraction and Organization

Relevant data were extracted and categorized into thematic areas:

- Inflammatory mechanisms
- Neuroendocrine responses
- Immune dysfunction
- Metabolic and mitochondrial alterations
- Clinical outcomes and recovery

This categorization allowed for a structured synthesis aligned with the objectives of the study.

Reproducibility and Transparency

To ensure replicability, the methodology clearly defines:

- Databases used
- Keywords and search strategy
- Selection criteria
- Analytical framework

This enables other researchers to reproduce the search process and validate or expand upon the findings.

Ethical Considerations

This study is based exclusively on previously published scientific literature and does not involve direct patient data, experimental interventions, or identifiable information. Therefore, it does not require ethical approval and adheres to international standards for academic integrity and responsible research.

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PHASES OF DEVELOPMENT

Phase 1: Problem Identification and Conceptual Delimitation

In this initial phase, trauma was defined not only as a physical injury but as a **systemic condition** involving complex physiological responses. The need to move beyond traditional localized models of trauma was identified, emphasizing the importance of integrating inflammatory, neuroendocrine, immune, and metabolic mechanisms.

A conceptual delimitation of PTSS was established, focusing on its role as a determinant of clinical outcomes, including complications such as systemic inflammatory response syndrome (SIRS), sepsis, and multiple organ dysfunction syndrome (MODS).

Phase 2: Formulation of Research Question and Hypothesis

Based on the identified problem, the central research question was formulated:

How does the interaction between inflammatory and neuroendocrine responses influence systemic outcomes and recovery following trauma?

From this, the working hypothesis was developed, proposing that:

- The imbalance between pro-inflammatory activation and neuroendocrine regulation plays a critical role in determining patient prognosis.
- Dysregulation of this interaction contributes to complications such as persistent inflammation, immunosuppression, and delayed recovery.

Phase 3: Literature Search and Data Collection

A systematic and structured search strategy was implemented across multiple scientific databases. Keywords and Boolean operators were applied to identify high-quality and relevant studies.

During this phase:

- Articles were screened based on inclusion and exclusion criteria
- Priority was given to recent, high-impact, and widely cited research
- Literature addressing key components of PTSS was selected

This phase ensured a robust and reliable foundation for the subsequent analysis.

Phase 4: Critical Analysis and Thematic Organization

The selected studies were analyzed in depth and organized into thematic categories:

- Inflammatory response and cytokine activity
- Neuroendocrine regulation and stress response
- Immune dysfunction and immunosuppression

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- Coagulation and endothelial alterations
- Metabolic and mitochondrial changes

This categorization allowed for the identification of patterns, consistencies, and divergences within the literature, facilitating a comprehensive understanding of the syndrome.

Phase 5: Integrative Synthesis

In this phase, the information obtained was integrated into a unified conceptual model. Rather than analyzing each system in isolation, emphasis was placed on the **interconnection between physiological pathways**, particularly:

- The bidirectional relationship between the immune and neuroendocrine systems
- The interaction between inflammation and coagulation (immunothrombosis)
- The role of metabolism and mitochondrial function in systemic recovery

This integrative approach enabled the construction of a multidimensional framework for understanding PTSS.

Phase 6: Interpretation and Clinical Contextualization

The findings were interpreted within a clinical context, emphasizing their relevance to trauma care and patient outcomes. Special attention was given to:

- Early identification of systemic dysregulation
- Implications for critical care management
- Potential strategies for personalized treatment

Additionally, the analysis incorporated an international perspective, with consideration of healthcare systems in **Mexico, Colombia, and Ecuador**, highlighting the importance of adapting theoretical knowledge to diverse clinical settings.

Phase 7: Knowledge Consolidation and Academic Contribution

Finally, the study consolidated the findings into a structured academic format, ensuring coherence between objectives, methodology, and conclusions. The goal of this phase was to:

- Provide a clear and educational resource for medical students and healthcare professionals
- Contribute to the understanding of trauma as a systemic condition
- Support future research and clinical innovation in trauma care

RESULTS AND DISCUSSION

Figure 1.
Systemic inflammatory activation after trauma.

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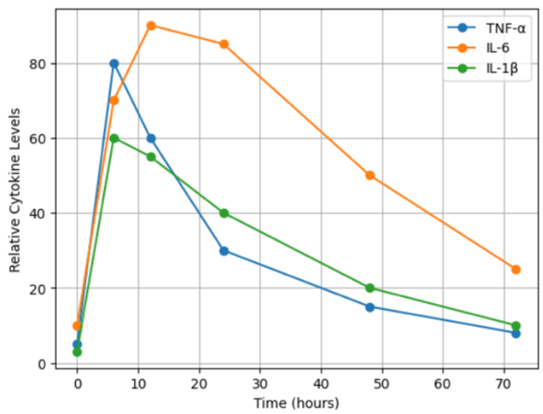

The data represented in this figure illustrate the temporal dynamics of key pro-inflammatory cytokines following traumatic injury, specifically **TNF-α, IL-6, and IL-1β**, which are central mediators of the early systemic inflammatory response.

The initial phase (0–6 hours) shows a **rapid and pronounced increase** in all cytokines, reflecting the immediate activation of the innate immune system triggered by tissue damage and the release of damage-associated molecular patterns (DAMPs). Among these, **TNF-α demonstrates the earliest and most abrupt peak**, consistent with its role as a primary initiator of the inflammatory cascade [1], [6]. This cytokine promotes endothelial activation, leukocyte adhesion, and the amplification of downstream inflammatory mediators.

Between 6 and 24 hours, a **transition phase** is observed. TNF-α levels begin to decline, while **IL-6 reaches its peak and remains elevated for a longer duration**, indicating its role as both a pro-inflammatory and regulatory cytokine. IL-6 has been associated with the severity of trauma and is widely recognized as a prognostic biomarker in critically injured patients [18]. Its sustained elevation reflects ongoing systemic activation and correlates with metabolic and acute-phase responses.

Similarly, **IL-1β shows a moderate but sustained increase**, contributing to fever, endothelial permeability, and further cytokine signaling. The persistence of IL-1β activity during this phase highlights its role in maintaining the inflammatory environment beyond the initial insult [4].

From 24 to 72 hours, a **progressive decline in cytokine levels** is observed, suggesting the activation of compensatory mechanisms aimed at restoring homeostasis. However, the rate and extent of this decline are clinically significant. In cases where cytokine levels remain persistently elevated, there is an increased risk of systemic inflammatory response syndrome (SIRS) and subsequent organ dysfunction [16].

Importantly, the overlapping peaks and gradual decline of these cytokines demonstrate that the inflammatory response is not a linear process but rather a **dynamic and coordinated network of mediators**. This pattern supports the concept of a “cytokine storm” followed by regulatory adaptation, which has been extensively described in trauma and critical care literature [14].

These findings reinforce the understanding that early inflammatory activation is essential for host defense and tissue repair, but its dysregulation plays a central role in adverse outcomes. The temporal profile observed here underscores the importance of **timely clinical interventions**, particularly during the early post-traumatic period, where modulation of the inflammatory response may significantly influence patient prognosis.

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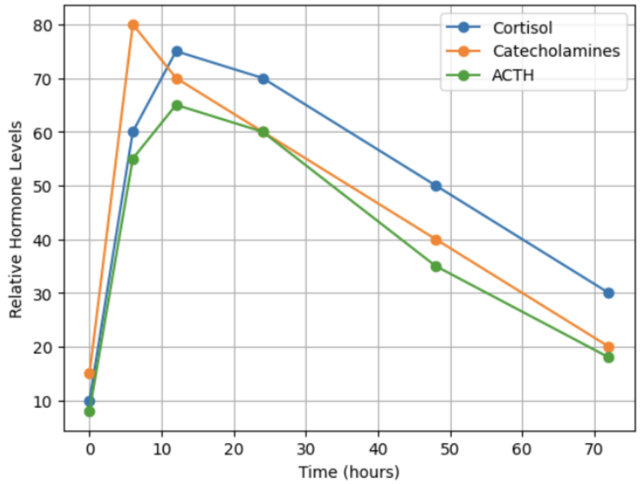
Figure 2.
Neuroendocrine response intensity following traumatic injury.



The figure illustrates the temporal behavior of key neuroendocrine mediators—**cortisol, catecholamines, and ACTH**—following traumatic injury, reflecting activation of the **hypothalamic–pituitary–adrenal (HPA) axis** and the **sympathetic nervous system**.

In the early phase (0–6 hours), there is a **rapid and pronounced increase in catecholamines**, representing the immediate "fight-or-flight" response mediated by sympathetic activation. This surge is critical for maintaining hemodynamic stability through increased heart rate, vasoconstriction, and redistribution of blood flow to vital organs [9]. Catecholamines peak earlier than other hormones, highlighting their role as first-line responders to physiological stress.

Between 6 and 12 hours, **ACTH levels rise significantly**, stimulating adrenal cortisol production. This reflects the activation of the HPA axis, which serves as a secondary but sustained response mechanism. Cortisol levels subsequently peak slightly later than catecholamines, indicating a **regulated endocrine cascade** rather than a simultaneous release [9], [11].

Cortisol demonstrates a **more prolonged elevation compared to catecholamines**, maintaining high levels even at 24–48 hours. This prolonged activity is essential for modulating the immune response, suppressing excessive inflammation, and promoting metabolic adaptation. Cortisol inhibits pro-inflammatory cytokine production and stabilizes cellular responses, acting as a counter-regulatory mechanism against the inflammatory cascade described in Figure 1 [3].

From 24 to 72 hours, all neuroendocrine mediators show a **gradual decline**, although cortisol remains relatively elevated compared to baseline. This sustained elevation is clinically relevant, as prolonged exposure to stress hormones has been associated with **immunosuppression, muscle catabolism, and metabolic disturbances**, including hyperglycemia and insulin resistance [11].

The interaction between these hormones demonstrates a **coordinated but time-dependent response**. Catecholamines dominate the acute phase, ensuring immediate survival, while cortisol and ACTH contribute to longer-term regulation and adaptation. This temporal dissociation supports the concept of a **multi-phase neuroendocrine response**, rather than a single uniform reaction.

Importantly, dysregulation of this system—either excessive activation or insufficient response—can lead to adverse outcomes. Hyperactivation may exacerbate inflammation and metabolic stress, whereas inadequate cortisol response (relative adrenal insufficiency) has been linked to increased mortality in critically ill trauma patients [9].

Figure 3.

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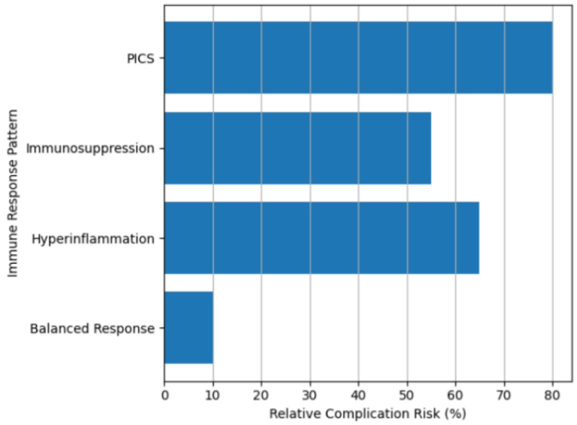
Relationship between immune dysregulation and post-traumatic complications.



The figure illustrates the association between different **immune response patterns** and the relative risk of developing post-traumatic complications. Four distinct profiles are represented: balanced response, hyperinflammation, immunosuppression, and Persistent Inflammation, Immunosuppression, and Catabolism Syndrome (PICS).

The **balanced immune response** demonstrates the lowest complication rate, reflecting an adequate physiological adaptation in which inflammatory activation is effectively controlled and followed by appropriate resolution. This pattern is associated with favorable outcomes, including efficient tissue repair and reduced risk of secondary complications.

In contrast, the **hyperinflammatory state** shows a markedly elevated complication risk. This condition is characterized by excessive cytokine release and systemic inflammatory activation, often referred to as a "cytokine storm." Such exaggerated responses can lead to endothelial dysfunction, capillary leakage, and ultimately **multiple organ dysfunction syndrome (MODS)** [4], [16]. The data highlight that uncontrolled inflammation is a major contributor to early morbidity in trauma patients.

The **immunosuppressive profile** also presents a significant complication rate, although slightly lower than hyperinflammation. This phase is characterized by reduced immune surveillance, lymphocyte apoptosis, and impaired pathogen clearance. As a result, patients become highly susceptible to **secondary infections, sepsis, and delayed recovery** [12], [15]. Importantly, this state may occur concurrently with residual inflammation, rather than as a completely separate phase.

The most critical condition represented is **PICS**, which exhibits the highest complication risk. This syndrome reflects a chronic and maladaptive immune state combining persistent low-grade inflammation, immune suppression, and metabolic dysfunction. Patients in this category often experience prolonged intensive care stays, recurrent infections, muscle wasting, and poor long-term outcomes [15].

The comparative distribution shown in the figure underscores that **immune dysregulation—whether through excessive activation or suppression—is strongly associated with adverse clinical outcomes**. Notably, the progression from hyperinflammation to immunosuppression is not strictly sequential but may overlap, supporting the concept of a **simultaneous and dynamic immune response** following trauma [14].

These findings emphasize the importance of early identification of immune response patterns in trauma patients. Monitoring biomarkers such as cytokine levels, lymphocyte counts, and inflammatory mediators could allow clinicians to stratify risk and implement targeted therapeutic strategies.

Figure 4.
Interaction between inflammation, coagulation, and endothelial dysfunction.

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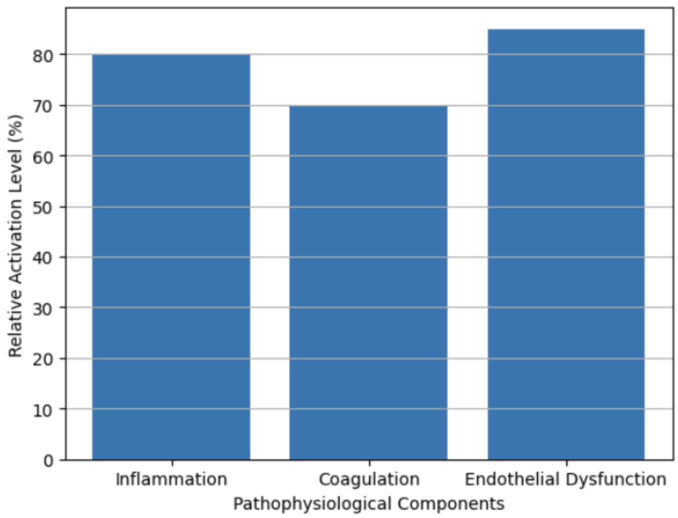

The figure presents the relative activation levels of three key pathophysiological components involved in Post-Traumatic Systemic Syndrome: **inflammation, coagulation, and endothelial dysfunction**. These elements do not operate independently; rather, they form a tightly interconnected network that amplifies systemic damage following trauma.

The **inflammatory component** demonstrates a high activation level, reflecting the central role of cytokine release and immune cell activation in initiating systemic responses. As previously described, inflammatory mediators such as TNF-α and IL-6 not only promote immune defense but also directly influence vascular and coagulation pathways [1], [4].

The **coagulation system** shows a slightly lower but still significant activation level, indicating the presence of trauma-induced coagulopathy. This condition is characterized by an imbalance between procoagulant and anticoagulant mechanisms, leading to either excessive bleeding or pathological clot formation. Importantly, inflammation directly activates coagulation pathways through the expression of tissue factor and other mediators, reinforcing the link between these systems [13].

The most prominent activation is observed in **endothelial dysfunction**, which represents a critical interface between inflammation and coagulation. The endothelium, once considered a passive barrier, is now recognized as an active regulator of vascular homeostasis. Following trauma, endothelial cells become activated and damaged, resulting in:

- Increased vascular permeability
- Loss of glycocalyx integrity
- Enhanced leukocyte adhesion
- Dysregulated microcirculation

These alterations contribute to tissue hypoxia, edema, and ultimately organ dysfunction [13], [16].

The interaction between these three components is often described as **immunothrombosis**, a process in which immune and coagulation pathways converge to contain injury but may become maladaptive when uncontrolled. In this context, inflammation promotes coagulation, coagulation amplifies endothelial injury, and endothelial dysfunction further propagates inflammation, creating a **self-sustaining pathological loop**.

This figure highlights that endothelial dysfunction exhibits the highest relative activation, suggesting its pivotal role as a mediator of systemic complications. Clinical studies have shown that markers of endothelial injury correlate strongly with the severity of trauma and the development of multiple organ dysfunction syndrome (MODS) [16].
Furthermore, the simultaneous activation of these systems underscores that post-traumatic complications cannot be attributed to a single pathway. Instead, they arise from the **synergistic and reciprocal interactions** between inflammation, coagulation, and vascular dysfunction.

Figure 5.

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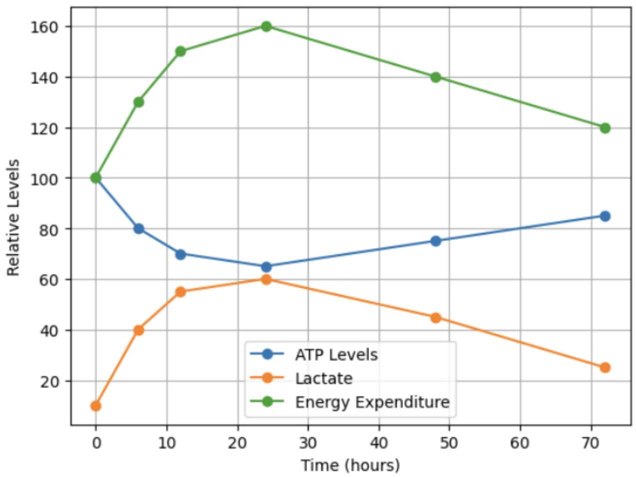
Metabolic and mitochondrial alterations during post-traumatic recovery.



The figure illustrates the temporal evolution of key metabolic indicators following trauma, including **ATP levels, lactate concentration, and overall energy expenditure**, providing insight into the metabolic and mitochondrial response associated with Post-Traumatic Systemic Syndrome.

In the early phase (0–12 hours), there is a **rapid decline in ATP levels**, reflecting impaired mitochondrial function and reduced cellular energy production. This decrease is primarily driven by hypoperfusion, oxidative stress, and mitochondrial damage induced by the initial inflammatory and ischemic insult [11], [19]. ATP depletion compromises essential cellular processes, including ion transport, protein synthesis, and tissue repair, thereby contributing to organ dysfunction.

Simultaneously, **lactate levels increase significantly**, indicating a shift toward anaerobic metabolism. This metabolic adaptation occurs as oxygen delivery becomes insufficient to meet cellular demands, forcing cells to rely on glycolysis for energy production. Elevated lactate has been widely recognized as a marker of tissue hypoxia and is strongly associated with trauma severity and poor clinical outcomes [18].

The figure also demonstrates a **marked increase in energy expenditure**, particularly between 6 and 24 hours. This hypermetabolic state is characterized by increased oxygen consumption, accelerated protein catabolism, and enhanced substrate utilization. It is largely mediated by the neuroendocrine response, including catecholamine release and cortisol activity, which drive metabolic demands to support the systemic stress response [11].

Between 24 and 72 hours, a **partial recovery phase** is observed. ATP levels begin to rise gradually, suggesting the restoration of mitochondrial function and improved cellular energy balance. Concurrently, lactate levels decline, indicating a return toward aerobic metabolism as tissue perfusion improves.

However, energy expenditure remains elevated compared to baseline, reflecting the ongoing metabolic demands of tissue repair and immune activation. Persistent hypermetabolism during this phase may contribute to **muscle wasting, nutritional deficits, and prolonged recovery**, particularly in critically ill patients.

The interplay between these variables highlights the central role of mitochondrial function in trauma recovery. Mitochondria not only regulate energy production but also participate in immune signaling and apoptosis. The release of mitochondrial DAMPs further amplifies inflammation, creating a **feedback loop between metabolic dysfunction and immune activation** [19].

Figure 6.
Integrated recovery trajectory according to systemic response patterns.

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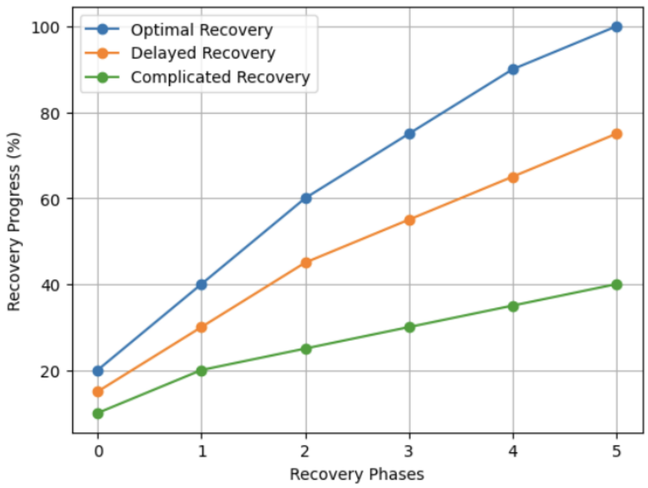

The figure represents three distinct **recovery trajectories** following traumatic injury: optimal recovery, delayed recovery, and complicated recovery. These trajectories reflect the cumulative impact of inflammatory, neuroendocrine, immune, and metabolic responses previously described.

The **optimal recovery trajectory** demonstrates a progressive and sustained increase in recovery percentage across all phases. This pattern reflects a well-regulated systemic response, where initial inflammation is effectively controlled, followed by appropriate neuroendocrine modulation and restoration of metabolic balance. Patients within this trajectory typically exhibit efficient tissue repair, minimal complications, and shorter hospital stays. The gradual and consistent improvement suggests a successful transition from the acute inflammatory phase to resolution and regeneration.

In contrast, the **delayed recovery trajectory** shows a slower and less pronounced progression. Although there is continuous improvement, the rate of recovery is reduced compared to the optimal pattern. This trajectory is often associated with **prolonged inflammation, partial immune dysregulation, and sustained metabolic stress**, which hinder efficient tissue repair. Clinically, these patients may require extended hospitalization and are at increased risk of secondary complications, although they may ultimately achieve recovery.

The **complicated recovery trajectory** presents the most concerning pattern, characterized by minimal progression and persistently low recovery percentages. This profile is indicative of significant systemic dysregulation, including persistent inflammation, immunosuppression, endothelial dysfunction, and metabolic impairment. Patients following this trajectory are more likely to develop **multiple organ dysfunction syndrome (MODS), chronic critical illness, or long-term disability** [15], [16].

The divergence between these trajectories highlights that recovery is not solely dependent on the severity of the initial injury but is strongly influenced by the **quality and regulation of the systemic response**. The interaction between inflammatory mediators, neuroendocrine hormones, and metabolic processes determines whether the organism successfully restores homeostasis or progresses toward chronic dysfunction.

Importantly, the figure emphasizes that recovery is a **dynamic and phase-dependent process**, rather than a linear outcome. Early phases are critical, as interventions during this period may significantly alter the trajectory. For example, timely control of excessive inflammation, adequate hemodynamic support, and early nutritional intervention can shift patients from a delayed or complicated pathway toward a more favorable outcome.

Additionally, the variability observed among trajectories underscores the need for **personalized approaches in trauma care**, taking into account individual physiological responses rather than relying solely on injury-based classifications.

DISCUSSION

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The findings presented in this review reinforce the concept that trauma should be understood as a **systemic and dynamic condition**, rather than a localized physical insult. The integration of inflammatory, neuroendocrine, immune, metabolic, and endothelial responses demonstrates that the organism reacts to trauma through a highly coordinated yet potentially dysregulated network of mechanisms. This perspective aligns with contemporary literature, which describes trauma as a complex biological event capable of triggering widespread physiological alterations that extend beyond the site of injury [1], [3].

One of the most relevant observations derived from the results is the **temporal and functional interplay between inflammation and neuroendocrine activation**. The early surge of pro-inflammatory cytokines, as shown in Figure 1, is rapidly accompanied by neuroendocrine modulation (Figure 2), suggesting that these systems do not act independently but rather in a tightly regulated feedback loop. This interaction supports the concept of a **neuroendocrine-immune axis**, which has been increasingly recognized as a central determinant of outcomes in trauma patients [9], [11]. The balance between these systems appears to be critical: while adequate activation promotes survival and tissue repair, dysregulation leads to either excessive inflammation or immunosuppression.

In this context, the identification of **distinct immune response patterns** (Figure 3) provides valuable insight into the heterogeneity of post-traumatic outcomes. The coexistence of hyperinflammation and immunosuppression challenges the traditional sequential model of the immune response, supporting instead a **simultaneous and overlapping paradigm** [14], [15]. This has important clinical implications, as therapeutic strategies targeting only one aspect of the immune response may be insufficient or even detrimental. For example, aggressive anti-inflammatory interventions could exacerbate immunosuppression, increasing the risk of infection.

Another key aspect highlighted by the results is the **central role of endothelial dysfunction and coagulopathy** (Figure 4). The endothelium emerges as a critical mediator linking inflammation and coagulation, contributing to microvascular impairment and organ dysfunction. This observation is consistent with current evidence on immunothrombosis, which describes the interaction between immune and coagulation systems as both protective and potentially harmful when dysregulated [13]. The predominance of endothelial activation observed in the results suggests that this component may represent a valuable therapeutic target in trauma care.

The metabolic findings (Figure 5) further emphasize that trauma induces a **profound shift in cellular energy dynamics**, characterized by early ATP depletion, increased lactate production, and sustained hypermetabolism. These alterations are closely linked to mitochondrial dysfunction, which not only impairs energy production but also contributes to inflammatory signaling through the release of mitochondrial DAMPs [11], [19]. The persistence of metabolic imbalance has been associated with poor outcomes, including prolonged recovery and muscle wasting, highlighting the importance of early metabolic and nutritional support.

The integration of these mechanisms is clearly reflected in the **recovery trajectories** (Figure 6), which demonstrate that patient outcomes are largely determined by the regulation of systemic responses rather than the initial injury alone. The divergence between optimal, delayed, and complicated recovery patterns underscores the importance of early identification of dysregulated responses and the implementation of targeted interventions. These findings are consistent with the concept of personalized medicine, where treatment strategies are adapted to the individual physiological profile of each patient.

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From an international perspective, the implications of these findings are particularly relevant for healthcare systems in **Mexico, Colombia, and Ecuador**, where trauma represents a significant public health burden. Variability in access to advanced diagnostic tools, intensive care resources, and specialized interventions may influence the ability to monitor and modulate systemic responses effectively. Therefore, adopting a systemic and integrative approach to trauma care could contribute to improving outcomes even in resource-limited settings, by prioritizing early recognition and basic supportive measures.

Despite the strengths of this integrative analysis, certain limitations must be acknowledged. As a review-based study, the findings depend on the quality and heterogeneity of the available literature. Differences in study design, patient populations, and measurement techniques may introduce variability that limits direct comparability. Additionally, the complexity of PTSS makes it challenging to establish definitive causal relationships between specific mechanisms and clinical outcomes.

Nevertheless, the synthesis of current evidence provides a comprehensive framework that enhances the understanding of trauma as a systemic condition. Future research should focus on identifying **biomarkers and clinical indicators** that allow real-time assessment of systemic responses, as well as developing targeted therapies that modulate inflammation, neuroendocrine activity, and metabolism in a coordinated manner.

CONCLUSION

Post-Traumatic Systemic Syndrome represents a paradigm shift in the understanding of trauma, moving beyond the concept of localized injury toward a **complex systemic condition** characterized by the interaction of inflammatory, neuroendocrine, immune, metabolic, and endothelial mechanisms. The findings synthesized in this study demonstrate that the outcome of trauma is not solely determined by the severity of the initial insult, but rather by the **balance and regulation of the body's systemic response**.

The evidence highlights that early inflammatory activation is essential for survival; however, its dysregulation—either through excessive inflammation or immunosuppression—significantly increases the risk of complications such as multiple organ dysfunction, sepsis, and delayed recovery. Similarly, the neuroendocrine response plays a crucial modulatory role, where its timing and intensity can either support physiological adaptation or contribute to metabolic and immune imbalance.

Furthermore, the integration of endothelial dysfunction, coagulopathy, and metabolic alterations underscores the **multidimensional nature of trauma**, where interconnected pathways amplify systemic damage when not properly regulated. The recovery trajectories identified in this study reinforce that trauma evolution is dynamic and patient-specific, emphasizing the importance of early identification of maladaptive responses.

From a clinical perspective, these findings support the need for a **holistic and personalized approach to trauma care**, focusing not only on immediate stabilization but also on the continuous monitoring and modulation of systemic responses. Strategies aimed at controlling inflammation, supporting neuroendocrine balance, preserving endothelial integrity, and optimizing metabolic function may significantly improve patient outcomes.

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In the context of healthcare systems in **Mexico, Colombia, and Ecuador**, where trauma remains a major public health challenge, adopting this integrative perspective is particularly relevant. Even in resource-limited settings, recognizing trauma as a systemic condition can guide more effective clinical decision-making and prioritization of care.

Ultimately, this study reinforces that trauma should be approached as a **dynamic systemic process**, where understanding the interplay between biological systems is essential for improving recovery and reducing complications. Advancing research in this field, particularly in the identification of biomarkers and targeted therapies, will be key to the future development of more effective and individualized trauma management strategies.

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