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Pathophysiology-guided biomarkers and therapeutics for precision trauma medicine in polytrauma with musculoskeletal injuries

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Abstract

Polytrauma with predominant musculoskeletal (MSK) injury, resulting from blast, blunt, and crush mechanisms, remains a leading and complex challenge in both military and civilian medicine. These injuries not only disrupt tissues structurally but also trigger systemic cascades involving immune imbalance, endothelial dysfunction, mitochondrial stress, and premature cellular senescence. Such pathological processes contribute to both immediate clinical instability and long-term complications such as fibrosis, aberrant bone formation, neuroinflammation, and chronic disability. Conventional injury assessments, which rely heavily on anatomical scoring and nonspecific blood markers, fail to capture the dynamic molecular landscape underlying these conditions. To address this critical gap, we performed a comprehensive scoping review integrating evidence from basic science, translational studies, and clinical research published between January 2000 to June 2025, with particular emphasis on recent advances. The review highlights the discovery and validation of emerging blood-based and molecular biomarkers, including fatty acid-binding protein 3, syndecan-1, galectin-3, and trauma-associated microRNAs, as well as innovative diagnostic paradigms such as wearable biosensors, minimally invasive liquid biopsy platforms, and artificial intelligence (AI)-driven analytics. Unlike prior reviews, our analysis uniquely integrates findings across both military and civilian trauma contexts, providing actionable frameworks for clinical application. Building on these insights, we outline a practical roadmap: 1) deploys integrated multi-marker panels for early risk stratification, 2) expands inclusive trauma biobanking to capture diverse injury phenotypes, and 3) uses adaptive, data-driven tools for real-time triage and personalized intervention. This approach links acute systemic responses to downstream recovery and rehabilitation, offering actionable guidance for both military and civilian trauma systems.

Key words Musculoskeletal (MSK) injury, Polytrauma, Biomarkers, Endothelial dysfunction, Biosensors, Artificial intelligence (AI)

Background

Polytrauma resulting from blast, blunt, and crush mechanisms, frequently involving severe musculoskeletal (MSK) injury, represents a defining challenge of modern warfare and an enduring global health burden across civilian populations [1-6]. On the battlefield, high-energy injuries from blasts, gunfire, vehicular rollovers, and other combat exposures dominate the trauma spectrum [7], with U.S. Joint Trauma analyses demonstrating a predominance of extremity injuries in modern combat, frequently manifesting as open fractures, vascular disruption, polycompartmental muscle injury, and traumatic amputation [8]. Importantly, these patterns are not unique to military environments. Analyses from the World Health Organization, alongside reports from recent conflicts, including Ukraine and Gaza, demonstrate that urban combat, mass-casualty events, and constrained evacuation and surgical resources produce comparable high-acuity injury profiles in both combatants and civilians [9-12]. These converging trends emphasize the urgent need for adaptable, scalable trauma systems capable of responding to increasingly complex injury patterns across both military and civilian settings, where delays in evacuation and constrained rehabilitation resources amplify both acute mortality and long-term disability [13].

The term polytrauma with significant MSK injury refers to mechanism-driven traumatic injury in which MSK damage is a dominant contributor to systemic pathology, rather than the primary causal insult. In civilian contexts, such polytrauma with significant MSK injury arises from road traffic accidents,

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industrial and agricultural hazards, falls, interpersonal violence, and increasingly, natural disasters [14]. Road traffic injuries alone account for more than 1.3 million deaths and up to 50 million nonfatal injuries annually, with over 90% of fatalities occurring in low- and middle-income countries (LMICs) [15]. Large-scale disasters, such as the 2015 Nepal earthquake [15] and the 2023 Türkiye-Syria earthquake [16], have demonstrated the catastrophic orthopedic and soft-tissue trauma caused by crush injuries, further emphasizing the need for scalable and context-specific interventions.

Despite differences in biomechanics, blast, blunt, and crush injuries converge on several common systemic pathways that extend beyond structural tissue disruption [17,18]. Blast trauma generates high-pressure shockwaves and rapid acceleration-deceleration forces [19]; blunt trauma results from sudden compressive and shear loading [20]; crush trauma reflects prolonged compression with ischemia-reperfusion injury [21]. All three activate shared molecular cascades: damage-associated molecular patterns (DAMPs) such as high-mobility group box 1 (HMGB1) [22] and mitochondrial DNA (mtDNA) initiate Toll-like receptor (TLR) and NOD-like receptor (NLR) signaling [23], leading to immune dysregulation, endothelial dysfunction, mitochondrial stress, and premature cellular senescence. These systemic responses drive sepsis, multi-organ dysfunction, heterotopic ossification (HO), chronic inflammation, and impaired tissue repair [24,25]. Importantly, most existing diagnostic and classification systems, such as the Injury Severity Score or Gustilo-Anderson classification [26], remain anatomically oriented and fail to capture this evolving biology, limiting their ability to reflect evolving systemic and molecular pathophysiology. This disconnection between structural scoring and systemic pathophysiology represents a central barrier to advancing precision trauma medicine. Although leading reviews have previously detailed the systemic consequences and immunopathology of trauma [27,28], the current work uniquely integrates developments in multi-omics, molecular biomarkers, and digital diagnostics to propose a unified, evidence-driven framework for both military and civilian trauma care.

To address this gap, the present review integrates emerging evidence across three domains: 1) the shared and divergent molecular mechanisms of blast, blunt, and crush injuries; 2) the discovery and application of translational biomarkers for risk stratification and real-time monitoring; and 3) novel therapeutic frontiers spanning immunomodulators, endothelial stabilizers, regenerative interventions, and senotherapeutics. By bridging military and civilian perspectives, we outline a pathophysiology-informed framework for trauma management that links early molecular events to downstream systemic, functional, and psychosocial outcomes, thereby supporting scalable, lifespan-spanning solutions for global trauma systems.

Search strategy and review methodology

This review employed a structured narrative methodology with scoping elements to synthesize current evidence on the pathophysiological mechanisms, diagnostic innovations, and biomarker frontiers relevant to polytrauma with significant MSK injury across both military and civilian settings. While informed by principles of the preferred Reporting Items for Systematic Reviews and Meta-analyses extension for scoping reviews (PRISMA-ScR), the framework was deliberately adapted to balance systematic rigor with flexibility, enabling integration of findings from preclinical mechanistic studies, translational research, and clinical investigations [29]. Elements of the PRISMA-ScR framework were adapted to ensure transparency and reproducibility, including definition of key concepts, inclusion/exclusion criteria, and thematic categorization of studies. However, full systematic database strings, deduplication counts, and quantitative synthesis were not performed, as the objective was conceptual integration rather than exhaustive enumeration. The goal was to generate a comprehensive, thematically structured synthesis that bridges molecular pathophysiology with emerging diagnostic and therapeutic applications, reflecting the evolving shift toward precision and systems-based trauma care.

A systematic literature search was conducted across 4 major databases: PubMed, Web of Science, Scopus, and Embase, covering publications from January 2000 to June 2025. A combination of controlled vocabulary such as medical subject headings (MeSH) terms and free-text keywords were used, encompassing "MSK injury, polytrauma, blast injury, blunt trauma, crush syndrome, inflammation, endothelial dysfunction, DAMPs, cellular senescence, biomarkers, cytokine storm, heterotopic ossification, military medicine, combat injury, civilian trauma, translational medicine, proteomics, metabolomics, lipidomics, transcriptomics, single-cell RNA sequencing (scRNA-seq), spatial transcriptomics, extracellular vesicles (EVs), exosomes, circulating cell-free DNA (cfDNA), mitochondrial DNA (mtDNA), multi-omics integration, systems biology, network modeling, artificial intelligence (AI), machine learning (ML) and precision diagnostics". To maximize inclusivity and capture global perspectives, no language restrictions were applied. Reference lists of relevant reviews and eligible studies were also hand-screened to ensure important contributions not identified

in the initial search were included. Although full database strings, deduplication counts, and PRISMA flow metrics were not reported, search transparency and reproducibility were strengthened by documenting databases, time frames, and key search domains. In line with our emphasis on translational and systems-level insights, we also included seminal clinical studies that applied scRNA-seq and single-cell assay for transposase-accessible chromatin using sequencing (scATAC-seq) to circulating leukocytes in trauma patients, which defined early immune response trajectories and epigenetic reprogramming after polytrauma.

Eligibility criteria were designed to capture both breadth and depth. Studies were included if they reported original research, clinical trials, or comprehensive reviews addressing the pathophysiology, systemic immune or endothelial responses, or diagnostic innovations relevant to polytrauma with MSK injury, with specific attention to blast-, blunt-, or crush-related injuries. Preclinical and translational investigations on biomarker discovery, validation, or diagnostic technologies were prioritized. Exclusion criteria encompassed case reports, editorials, and opinion pieces lacking mechanistic or diagnostic evidence, as well as studies focused exclusively on polytrauma without major extremity injuries, such as isolated thoracic, abdominal, or neurotrauma.

Findings from eligible studies were narratively integrated across seven thematic domains: 1) epidemiology and comparative mechanisms of military versus civilian trauma; 2) systemic inflammatory and immune dysregulation; 3) endothelial dysfunction and microvascular collapse; 4) trauma-induced cellular senescence and fibrotic remodeling; 5) traditional vs. emerging biomarker strategies; 6) advances in diagnostic technologies, including multi-analyte, multi-omic, and real-time monitoring platforms; and 7) translational gaps and future priorities. These themes were selected because they represent recurring focal points across the literature and map directly onto both mechanistic pathways and clinical applications. Emphasis was placed on temporal dynamics, mechanistic insight, and clinical relevance, with results organized into conceptual frameworks and tabular summaries for clarity.

Pathophysiological and biomechanical mechanisms of polytrauma with MSK injury

Biomechanical triggers

Polytrauma with MSK injury arises when external mechanical forces disrupt tissue integrity and cellular homeostasis, the magnitude, direction, and duration of force shaping the severity and clinical manifestation of injury [30]. Although blast, blunt, and crush mechanisms differ in their physical origins and epidemiological contexts, they share downstream biological consequences that extend from localized tissue disruption to systemic inflammation and multi-organ dysfunction syndrome (MODS) [22,23,28]. Understanding their unique biomechanical triggers and convergent molecular pathways is critical for improving diagnosis, triage, and treatment in both military and civilian trauma care.

Blast trauma, the defining injury mechanism of modern warfare, is characterized by the rapid propagation of high-energy shock waves generated by explosive detonation [19,31]. The sudden overpressure exerts disproportionate stress on air- and fluid-filled structures such as the lungs, gastrointestinal tract, and auditory system, producing severe barotrauma [32]. Skeletal muscle and vascular endothelium are vulnerable to shear-related microvascular injury, which can promote ischemia and contribute to compartment physiology [33,34]. The complexity of blast trauma is amplified by its poly-mechanistic profile: secondary injuries from high-velocity fragments, tertiary injuries caused by bodily displacement and blunt impact, and quaternary effects involving burns, toxic inhalation, or radiation exposure [35,36]. This layered injury pattern underscores the systemic complexity of blast trauma, where overlapping mechanisms act synergistically to amplify tissue damage and systemic sequelae.

Blunt trauma, more common in civilian settings, typically results from road traffic accidents, falls, or sports-related collisions [20,37]. These injuries involve the transfer of kinetic energy over a broad surface without skin penetration, producing contusions, hematomas, and lacerations of soft tissues [38]. Acceleration-deceleration forces further contribute to shearing of neurovascular bundles, ligaments, and connective tissue, often resulting in long-bone fractures, joint dislocations, and intramuscular hematomas [39]. These injuries trigger localized ischemia, inflammatory infiltration, and progressive fibrotic remodeling, processes that compromise MSK integrity and prolong functional recovery [40].

Crush trauma, most often encountered during industrial accidents or natural disasters, is defined by sustained mechanical compression, frequently lasting more than 30 min [41]. Prolonged ischemia leads to muscle necrosis and rhabdomyolysis [42], often progressing to compartment syndrome [43]. In addition, sustained compression induces biomechanical and structural damage to peripheral nerves, resulting in long-term sensory and motor dysfunction [44]. The release of compression initiates ischemia-reperfusion injury, in which the sudden restoration of blood flow generates reactive oxygen species (ROS) that overwhelm endogenous

antioxidant defenses [45]. Reperfusion disseminates intracellular contents, including potassium, myoglobin, and DAMPs, into the systemic circulation, precipitating electrolyte imbalances, arrhythmias, acute kidney injury (AKI), and the life-threatening syndrome of crush shock [17,46].

Despite these distinct physical triggers, blast, blunt, and crush trauma converge on a set of shared downstream pathways: cellular necrosis, DAMP release, endothelial disruption, microvascular collapse, and amplification of sterile inflammation [22]. This convergence highlights a unifying biological framework in which diverse injury patterns trigger common systemic responses, driving complications such as sepsis, MODS, and impaired regeneration [47,48]. Recognizing these intersecting pathways not only enhances triage and acute care but also provides predictive insight into long-term outcomes, offering a foundation for precision approaches to trauma management across both military and civilian populations. At the molecular level, all three injury modalities initiate sterile inflammatory cascades driven by DAMPs, including mtDNA, HMGB1, and heat-shock proteins, which propagate endothelial dysfunction and immune dysregulation across organ systems [22,49,50]. Blast injury uniquely couples these molecular signals with shear- and pressure-mediated endothelial rupture [18], whereas blunt trauma preferentially promotes inflammatory infiltration and fibrotic remodeling within MSK tissues [40]. Crush injury further amplifies systemic toxicity through ischemia-reperfusion-driven ROS generation and electrolyte release, contributing to AKI and cardiac instability [41,46]. A comparative summary of these biomechanical triggers and downstream pathophysiological features is presented in Table 1 [18,23,28,31,33,36-41,43,44,46,51], highlighting their distinct mechanical origins and overlapping systemic biology. Although these shared downstream pathways explain much of the acute inflammatory and vascular pathology seen across trauma types, blast injury in particular imposes an additional layer of systemic disruption that extends beyond MSK structures. Blast-induced polytrauma with significant MSK injury manifests not only as complex fractures and extensive soft-tissue damage but also as profound neuroimmune and endocrine dysregulation that shapes the trajectory of tissue regeneration and long-term functional recovery. These chronic sequelae align with established frameworks describing blast-related neurotrauma as a driver of persistent disability, neuropsychiatric comorbidity, and systemic dysfunction, particularly in military populations [51]. Incorporating mechanisms such as neural inflammation [52], hypothalamic-pituitary-adrenal (HPA) axis perturbation [53], and injury-induced cellular senescence [54] into the patho-physiological framework provides a more integrated understanding of how blast exposure drives persistent, multisystem dysfunction, thereby reinforcing the need for precision trauma care.

Molecular alarm

At the cellular level, polytrauma with MSK injury, whether

Table 1 Comparative pathophysiological features of blast, blunt, and crush injuries

Feature	Blast trauma	Blunt trauma	Crush trauma	Shared/Convergent pathways	References
Primary mechanical trigger	High-energy shock waves, rapid over-pressure	Rapid deceleration, broad-surface impact	Sustained mechanical compression (>30 min)	All disrupt tissue integrity, trigger systemic stress responses	[18,37,46]
Tissue vulnerability	Air/fluid-filled organs (lung, gut, ear), muscle, and endothelium	Soft tissue, long bones, joints, and neurovascular bundles	Skeletal muscle, kidneys, and peripheral nerves	Microvascular rupture, ischemia, compartment syndrome	[33,40,44]
Unique sequelae	Poly-mechanistic (fragmentation, displacement, burns, inhalation injury)	Hematomas, ligament injury, joint dislocation	Rhabdomyolysis, crush shock, ischemia-reperfusion injury	Overlapping systemic inflammation, oxidative stress	[36,39,41]
Molecular triggers	Shear-induced DAMP release, endothelial rupture	Inflammatory infiltration, fibrotic remodeling	ROS burst, potassium/myoglobin release	mtDNA as unifying DAMP, extracellular HMGB1, heat-shock proteins	[23,38,43]
Systemic consequences	Barotrauma, vascular leak, multi-organ dysfunction	Hemorrhage, fibrosis, prolonged recovery	Electrolyte imbalance, arrhythmias, AKI	Sterile inflammation, immune dysregulation, and endothelial dysfunction	[18,28,40,41]
Long-term outcomes	HO, PTSD, chronic disability	Joint degeneration, fibrosis, chronic pain	Chronic kidney disease, neuropathy, and muscle weakness	Fibrosis, senescence, impaired regeneration	[28,31,40,41,51]

DAMPs. Damage-associated molecular patterns; HMGB1. High-mobility group box 1; ROS. Reactive oxygen species; mtDNA. Mitochondrial DNA; AKI. Acute kidney injury; HO. Heterotopic ossification; PTSD. Post-traumatic stress disorder

from blunt force, blast exposure, or crush injury, disrupts tissue integrity and homeostasis, activating a conserved danger-sensing cascade often termed the molecular alarm [55]. This response begins when intracellular contents released from necrotic or stressed cells act as DAMPs [47]. Once in the extracellular space, DAMPs engage pattern recognition receptors (PRRs) on immune and stromal cells, initiating sterile inflammation that facilitates debris clearance, immune recruitment, and tissue repair [47,55,56]. While essential for survival, uncontrolled activation in severe or systemic trauma amplifies inflammation, destabilizes endothelial and metabolic networks, and accelerates progression toward MODS.

As shown in Fig. 1, mtDNA represents a unifying alarmin across blast, blunt, and crush trauma, underscoring its centrality in propagating sterile inflammation [23,57]. However, mtDNA operates within a broader repertoire of DAMPs released following tissue disruption key mediators include HMGB1, which activates TLR2, TLR4, and the receptor for advanced glycation end products (RAGE) to sustain inflammatory signaling [50]; extracellular adenosine triphosphate (ATP), which reflects bacterial ancestry and potently stimulates innate immune activation; and neutrophil-derived S100A8/A9 (calprotectin), which amplifies TLR4-dependent pathways [58]. Additional alarmins, such as uric acid, heat shock proteins (HSPs), and fragmented extracellular matrix (ECM) components, reinforce these sterile inflammatory loops and highlight the redundancy built into trauma-induced signaling networks [59]. Experimental and clinical studies implicate mtDNA-driven PRR activation as a key amplifier of sterile inflammation after trauma, with associations to organ dysfunction [57].

Recognition of these trauma-associated DAMP signals occurs primarily through TLRs (particularly TLR2, TLR4, and TLR9), NLRs [particularly NOD-like receptor family pyrin domain-containing 3 (NLRP3)], and RAGE [60]. TLR engagement activates nuclear factor κB (NF-κB) and

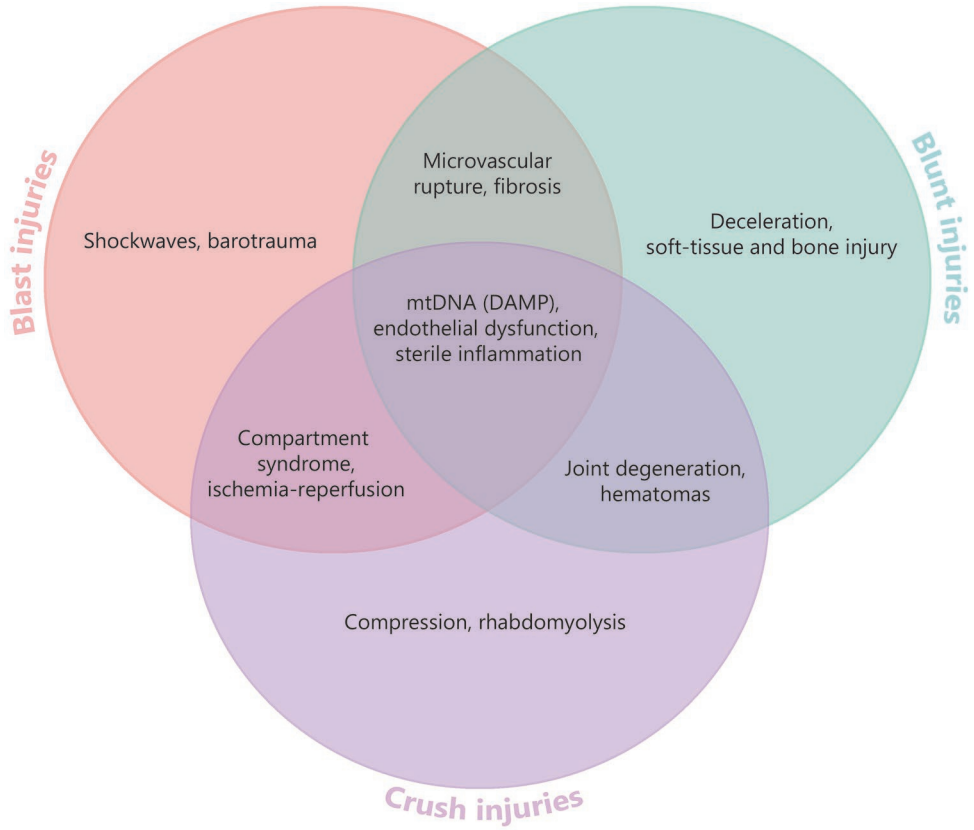

Fig. 1 Systems-level convergence of blast, blunt, and crush-induced polytrauma with musculoskeletal injury.
This Venn diagram illustrates shared and distinct pathophysiological mechanisms across trauma modalities. Blast injuries are marked by shockwaves and barotrauma; blunt injuries by deceleration, soft-tissue and bone injury; and crush injuries by compression and rhabdomyolysis. Overlapping regions highlight common pathways such as compartment syndrome/ischemia-reperfusion (blast+crush), joint degeneration/hematomas (blunt+crush), and microvascular rupture/fibrosis (blast+blunt). At the center, mtDNA release as a DAMP, together with endothelial dysfunction and sterile inflammation, represents a unifying mechanism. mtDNA is positioned centrally because it integrates mechanical, metabolic, and inflammatory stress responses, acting as a pivotal driver of systemic injury propagation and chronic sequelae. mtDNA. Mitochondrial DNA; DAMP. Damage-associated molecular pattern

mitogen-activated protein kinase (MAPK) cascades via myeloid differentiation primary response protein 88 and TIR-domain-containing adapter-inducing interferon-β adaptors, driving cytokine and chemokine release [61]. In parallel, NLRP3 inflammasomes mediate caspase-1-dependent maturation of interleukin (IL)-1β and IL-18, while RAGE promotes chronic inflammatory and fibrotic remodeling [62-64]. These mechanisms generate a broad inflammatory network in which neutrophils, macrophages, dendritic cells, endothelial cells, and even parenchymal populations contribute to amplification. Moreover, blast-related polytrauma with significant MSK injury is compounded by neuroinflammatory cascades and accelerated cellular senescence within the nervous system [54], which exacerbates systemic immune dysregulation and impairs neuromuscular recovery. Upregulation of multiple TLRs [52,65] and degeneration of neuronal cytoskeletal elements [66] identified in blast models highlight the shared molecular pathways linking central neural injury to peripheral MSK dysfunction. This interplay between neural and MSK damage highlights the multisystem complexity of blast polytrauma.

The downstream effects include robust cytokines, including IL-1β and IL-6 and tumor necrosis factor-α (TNF-α) secretion, chemokine-driven immune recruitment (C-X-C motif chemokine ligand 8, monocyte chemoattractant protein-1), and matrix metalloproteinase (MMP)-mediated tissue remodeling [67,68]. Locally, these cascades clear necrotic debris and prime progenitor cells for regeneration [69]. However, systemic spillover, particularly in polytrauma, delayed evacuation, or resource-limited combat environments, transforms this protective program into pathology [30]. Dysregulated activation fuels systemic inflammatory response syndrome (SIRS), endothelial leakage, and progression to MODS, while overcompensatory suppression drives compensatory anti-inflammatory response syndrome (CARS), predisposing patients to sepsis [70-72].

The dual nature of the molecular alarm highlights both its evolutionary necessity and clinical risks [73]. For trauma care, particularly in austere or battlefield environments where systemic complications are often fatal, this pathway represents an attractive therapeutic frontier. Strategies under investigation include HMGB1 release inhibitors, PRR antagonists, inflammasome-targeted therapies, and selective cytokine blockade [74]. The therapeutic goal is not to extinguish this primordial defense but to recalibrate its amplitude and duration, preserving repair functions while preventing maladaptive systemic consequences. Such precision modulation may improve survival and recovery trajectories across both military and civilian trauma populations [75].

Systemic consequences

A systems biology perspective is increasingly essential for understanding polytrauma with MSK injury. Rather than viewing it solely as an anatomical disruption requiring surgical repair, it should be conceptualized as a multi-level cascade that begins with molecular danger signaling and can progress to systemic dysfunction. Early events such as the release of DAMPs, mitochondrial dysfunction, and endothelial barrier disruption initiate downstream immune dysregulation, neuroendocrine imbalance, and premature cellular senescence [23,76]. Mapping these molecular signatures provides a foundation for rationally designed therapies that move beyond supportive care, enabling targeted immunomodulation, endothelial stabilization, senotherapeutics, and regenerative interventions. This framework emphasizes the need to link molecular pathways with clinical outcomes if trauma care is to evolve into a precision medicine discipline. In this context, severe polytrauma with extensive MSK injury exerts profound systemic consequences that extend well beyond the site of injury, disrupting immune, vascular, and metabolic homeostasis in ways that directly influence survival and recovery [77]. Rather than unfolding as isolated events, these responses represent dynamically interacting processes that form a pathophysiological trajectory from early hyperinflammation to long-term dysfunction [59], together shaping clinical outcomes in both military and civilian trauma care.

A central feature of this systemic response is immune dysregulation, which typically evolves along a biphasic but overlapping spectrum. The early phase is dominated by hyperinflammation, manifested clinically as SIRS [68]. Necrotic tissues release DAMPs that engage PRRs such as TLRs and NLRs, unleashing a systemic cytokine surge of TNF-α, IL-1β, IL-6, and interferon-γ (IFN-γ) [22]. This "cytokine storm" activates endothelium, promotes leukocyte adhesion, disrupts vascular barriers, and drives neutrophil recruitment, with the release of proteases, ROS, and neutrophil extracellular traps [78]. Clinically, these cascades present as fever, tachycardia, hypotension, hypermetabolism, and coagulopathy, and unchecked progression may culminate in MODS even in the absence of infection [71]. In parallel, the host mounts a CARS, intended to protect tissues but often overshooting into profound immunosuppression. This state is characterized by lymphocyte apoptosis, expansion of myeloid-derived suppressor cells (MDSCs), reduced monocyte expression of human leukocyte antigen-DR isotype (HLA-DR), and upregulation of immune checkpoint molecules such as programmed cell death protein 1 and cytotoxic T-lymphocyte-associated protein 4, accompanied by elevated IL-10 and

transforming growth factor (TGF)-β [79,80]. The consequence is a heightened susceptibility to secondary infections, delayed healing, and poor vaccine responses.

Recent cellular-resolution studies have further clarified these systemic immune alterations. Early scRNA-seq by Chen *et al*. [81,82] applied high-dimensional scRNA-seq and scATAC-seq to circulating leukocytes from trauma patients, demonstrating distinct transcriptional and chromatin accessibility programs that stratified patients into immunologic endotypes and independently predicted outcome across heterogeneous critical illness etiologies. Building on these foundational observations, scRNA-seq by Maniar *et al*. [83] identified the expansion of systemic immunosuppressive myeloid cells and context-dependent macrophage phenotypes as key regulators of post-traumatic immune dysregulation, while complementary findings from Cheng *et al*. [84] demonstrated that early systemic immune biomarkers, including monocyte and lymphocyte subsets, predict bone regeneration outcomes after trauma. These insights highlight how cellular dysfunction interacts with molecular signaling networks to shape both immune resolution and tissue repair, complementing the molecular framework discussed above. Importantly, hyperinflammation and immunosuppression frequently coexist in a mixed antagonist response syndrome, producing unpredictable clinical trajectories. Increasingly, biomarker-guided strategies are being investigated to tailor immunotherapies, ranging from cytokine adsorption in hyperinflammation to checkpoint inhibition or immune cell transfer in states of immunosuppression [85].

In addition, trauma inflicts profound injury on the vascular endothelium, a phenomenon often described as "endothelial collapse" [86]. The endothelial glycocalyx, a protective gel-like layer regulating vascular permeability and cell-cell interactions, is rapidly degraded by heparanase and metalloproteinases following trauma, ischemia-reperfusion, and oxidative stress [87,88]. Circulating fragments such as syndecan-1 and hyaluronic acid serve as biomarkers of this injury and correlate with poor outcomes [89,90]. Loss of glycocalyx integrity exposes endothelial surfaces, destabilizes tight junction proteins such as claudin-5 and adherens junction proteins like vascular endothelial cadherin (VE-cadherin) and CD144, eventually leading to vascular leak, tissue edema, and hypoperfusion [88]. At the same time, upregulation of adhesion molecules fosters leukocyte plugging of the microvasculature, compounding tissue ischemia [86]. Endothelial barrier failure also drives trauma-induced coagulopathy (TIC), in which dysregulated hemostasis manifests as either fibrinolytic shut down or hyperfibrinolysis, leading to a paradoxical coexistence of bleeding, thrombosis, and microvascular occlusion [91]. This complexity challenges conventional resuscitation strategies. Translationally, therapies that preserve endothelial function, including plasma-based resuscitation, albumin supplementation, and experimental glycocalyx stabilizers such as sulodexide and angiopoietin mimetics [92], represent promising strategies to mitigate early vascular failure in combat and civilian settings.

Trauma also disrupts systemic cellular and metabolic functions, particularly through mitochondrial injury, premature senescence, and neuroendocrine reprogramming. Sustained immune activation and endothelial injury create a hypoperfused, pro-oxidative microenvironment that impairs tissue regeneration. Persistent vascular leakage and loss of endothelial integrity limit oxygen and nutrient delivery to the injury site, while unresolved inflammation disrupts the balance between pro-repair macrophages and progenitor cell activation [93]. In addition, mitochondrial dysfunction restricts ATP availability and redox homeostasis, further constraining myogenic and osteogenic repair processes [94]. These intertwined disturbances explain why systemic inflammation and metabolic collapse translate into delayed functional recovery and poor structural outcomes after polytrauma [95].

Mitochondria, central to energy metabolism and redox balance, are impaired by ischemia-reperfusion and inflammatory cytokines, leading to oxidative phosphorylation failure, ATP depletion, ROS overproduction, and activation of permeability transition pores [96]. These changes drive apoptotic and necrotic cell death in skeletal muscle, liver, and immune cells, manifesting clinically as muscle weakness, acidosis, immune dysfunction, and delayed healing [97]. Concurrently, trauma accelerates stress-induced premature senescence in fibroblasts, endothelial cells, and progenitors, resulting in growth arrest mediated by p16INK4a/p21CIP1 pathways [98]. Senescent cells secrete a proinflammatory and proteolytic senescence-associated secretory phenotype (SASP) that disrupts regenerative niches and fosters chronic inflammation, fibrosis, and fracture non-union [99]. These dysfunctions are especially detrimental in aging or metabolically compromised patients [100].

At the neuroendocrine level, sustained activation of the HPA axis and sympathetic nervous system drives hypercortisolism, hyperglycemia, insulin resistance, and protein catabolism, while suppression of anabolic hormones such as insulin-like growth factor 1 (IGF-1), growth hormone, and testosterone impairs tissue repair [101]. Blast-induced polytrauma with significant MSK injuries frequently co-occurs with systemic neuroendocrine alterations that exacerbate

catabolic metabolism and impair tissue repair. Experimental models demonstrate that repeated blast exposures dysregulate the HPA axis [53], altering cortisol secretion and affecting metabolic hormones such as adiponectin and leptin [102], which critically modulate muscle and systemic metabolic homeostasis. These endocrine perturbations represent a key mechanism by which blast associated polytrauma extends its impact beyond local MSK tissue damage to influence whole-body recovery trajectories, reinforcing the importance of considering systemic network dysfunction in trauma care. These changes converge into persistent inflammation, immunosuppression, and catabolism (PICS), a syndrome increasingly recognized as a major barrier to rehabilitation after severe injury [103]. Emerging therapies, including mitochondrial protectants such as mitochondria-targeted coenzyme Q10 analogue (MitoQ), elamipretide peptide (SS-31) [104], senolytics such as dasatinib and quercetin [105], and metabolic modulators such as β-blockers, insulin sensitizers, aim to interrupt these vicious cycles [106].

The systemic consequences of polytrauma with MSK injury are best understood as the product of tightly interconnected networks rather than isolated cascades. Immune dysregulation fuels endothelial collapse, endothelial injury amplifies immune activation through the release of additional DAMPs, and both processes converge on mitochondrial dysfunction, cellular senescence, and maladaptive neuroendocrine stress responses. This reciprocal interplay transforms trauma into a disease of systemic network dyscoupled four-node cascade encompassing 1) immune activation via DAMP-, TLR-, and NLR-driven cytokine surges; 2) endothelial injury marked by glycocalyx shedding, increased permeability, and microvascular stasis; 3) mitochondrial dysfunction characterized by oxidative stress, impaired ATP generation, and metabolic collapse; and 4) premature cellular senescence with amplification of the SASP. Each node reinforces the others, cytokines accelerate glycocalyx degradation, vascular leak fosters tissue hypoxia and mitochondrial failure, mitochondrial DAMPs propagate innate immune activation, and SASP perpetuates chronic inflammation and fibrosis. This interlocked loop forms the mechanistic substrate linking acute instability to chronic sequelae.

Therapeutics

Therapeutic approaches for polytrauma with MSK injuries are rapidly evolving toward a precision, system-based paradigm that integrates immunomodulation, endothelial stabilization, regenerative medicine, metabolic support, and neuropsychiatric care. By targeting the interconnected biological and psychosocial pathways underlying trauma pathophysiology, these strategies aim to enhance survival, accelerate recovery, and reduce long-term disability in both military and civilian populations. Emerging interventions, including cytokine blockade, senolytics, mitochondrial rescue, and other targeted approaches, reflect a shift from generalized resuscitation toward mechanism-specific [107], precision-guided therapeutics that address not only acute injury responses but also the prevention of chronic complications and lifelong functional impairment (Table 2) [104,108-173]. While polytrauma with MSK injury is driven by a core four-node pathobiological cascade, therapeutic strategies exploit multiple interventional entry points within and between these nodes, including neuroendocrine and membrane-stabilizing interfaces that modulate system-level feedback rather than constituting independent pathological axes.

Immunomodulation

Immunomodulatory therapies target the immune activation node, where dysregulated cytokine signaling drives systemic inflammation and immune paralysis [174]. Early cytokine-targeted therapies have received dominant attention, with agents such as Anakinra, an IL-1 receptor antagonist, showing

Table 2 Emerging therapeutic targets and agents in polytrauma with MSK injury

Target	Agent	Mechanism of action	Translational development status	References
IL-1 pathway	Anakinra	Blocks IL-1 receptor, reduces SIRS and tissue damage	Clinical evidence in sepsis with MAS-like hyperinflammation; Trauma/MSK polytrauma evidence limited/indirect; Investigational/repurposing in trauma	[108,109]
IL-6 pathway	Tocilizumab	Inhibits IL-6 receptor; Limits cytokine storm amplification	Approved for RA, COVID-19; Trauma clinical trials ongoing	[110-112]
Extracorporeal immunomodulation	HA330 hemoperfusion	Resin-based extracorporeal adsorption of circulating cytokines reduces systemic inflammatory burden	Early clinical use in critical illness and sepsis; Limited trauma data	[113,114]
Alarmin pathways	Glycyrrhizin/anti-HMGB1 antibody	Inhibit HMGB1-TLR4/RAGE binding; Suppress NF-κB activation and downstream cytokine amplification	Preclinical trauma and hemorrhagic shock models; No clinical trials yet	[115-119]

(Continued)

Target	Agent	Mechanism of action	Translational development status	References
TLR4 signaling	TAK-242 (Resatorvid)	Inhibits downstream TLR4 signaling; Limits cytokine induction	Preclinical and early clinical studies outside trauma; Trauma applications are investigational	[120]
TLR4 signaling	Eritoran	Blocks TLR4-MD2 binding; Suppresses NF-κB activation	Phase 3 severe sepsis trial (ACCESS) showed no reduction in 28-day mortality; Trauma-specific efficacy not established	[121]
MDSC modulation	MDSC-enhancing therapies	Enhance immune regulation and reduce excessive inflammation; Preserve antimicrobial capacity	Preclinical trauma models	[122]
Alarmin S100A8/A9	S100A8/A9-targeted nanoparticles	Nanoparticle-based sequestration or neutralization of S100A8/A9 reduces neutrophil recruitment, cytokine amplification, and microvascular injury	Preclinical trauma and systemic inflammation models	[123]
Endothelium/glycocalyx	Sulodexide	Stabilizes glycocalyx, enhances barrier integrity	Ongoing trials in endothelial dysfunction; Trauma applications under evaluation	[124,125]
Endothelium	FX06	Improves vascular reactivity	Case series in COVID-19 ARDS; phase II trials registered; Trauma-specific efficacy not established	[126-130]
Endothelium	Atorvastatin	Reduces endothelial activation	Atorvastatin approved	[131-133]
Glycocalyx preservation	Doxycycline	Inhibits MMPs, reduces glycocalyx degradation and endothelial barrier disruption	Preclinical trauma and acute lung injury models; Endothelial-protective effects under investigation	[134]
Glycocalyx mimetic	Dekaparin	Synthetic glycosaminoglycan mimetic that inhibits heparanase activity, preserves glycocalyx structure, and reduces endothelial permeability and TIC	Early translational development; Preclinical and pilot-model evidence	[135]
Resuscitation	Fibrinogen-enriched plasma resuscitation	Restores fibrinogen deficits; Improves endothelial barrier stability and oncotic pressure; Enhances microvascular perfusion; Reduces TIC and vascular permeability	Phase II trauma trials: improving coagulation and endothelial function	[136]
Plasma membrane	Poloxamer 188 (P188)	Amphiphilic triblock copolymer that selectively inserts into disrupted lipid bilayers, reseals damaged sarcolemmal regions, limits Ca^{2+} overload, and reduces secondary necrosis	Preclinical skeletal muscle, ischemia-reperfusion, and mechanical injury models; Early translational exploration	[137-144]
Fibrosis pathway	Pirfenidone	Inhibits TGF-β signaling, fibroblast proliferation, and collagen synthesis	Approved for idiopathic pulmonary fibrosis	[145,146]
Fibrosis pathway	Nintedanib	Inhibits PDGF, VEGF, and FGF receptor pathways; Prevents myofibroblast activation	Approved for pulmonary fibrosis; Studied in systemic fibrosis	[147]
Senescent cells	Dasatinib plus quercetin	Induces apoptosis of senescent cells; Reduces SASP-driven inflammation	Preclinical to phase II trials mainly in fibrosis/aging contexts	[148]
Senescent cells	Navitoclax (ABT-263)	BCL-2 family inhibitor (notably BCL-xL/BCL-2); Senolytic via apoptosis induction in senescent cells	Preclinical senolytic evidence; Limited early-phase oncology trials; Translation constrained by thrombocytopenia	[149,150]
Senomorphic	Rapamycin	Inhibits mTOR signaling; Attenuates SASP production and modulates the senescent phenotype without inducing senescent cell death, thereby preserving regenerative capacity	Preclinical and early clinical studies in aging and fibrotic diseases; Trauma-specific data are lacking	[151]
Regenerative	Mesenchymal stem cells (MSCs)	Provide paracrine, angiogenic, and immunomodulatory signals; Enhance myogenesis and osteogenesis; Reduce fibrosis and inflammation	Robust preclinical evidence in volumetric muscle loss and fracture non-union models; Early-phase clinical studies reporting improved structural and functional outcomes	[152,153]

(Continued)

Target	Agent	Mechanism of action	Translational development status	References
Biomaterials	ECM-derived scaffolds and silk-based biomaterials	Bioactive matrices that provide structural support, enhance angiogenesis, and deliver growth factors for tissue integration	Preclinical and early translational studies in MSK defect and repair models	[154]
Mitochondria	MitoQ	Mitochondria-targeted antioxidant; Prevents apoptosis	Preclinical and early trauma models	[104]
Mitochondria	Elamipretide (SS-31)	Stabilizes cardiolipin; Preserves mitochondrial function	Investigational, early clinical use	[155]
Oxidative stress/redox imbalance	N-acetylcysteine	Replenishes intracellular glutathione; Reduces ROS-mediated injury; Supports mitochondrial function and cellular viability	Preclinical evidence in trauma/TBI-related models and critical care repurposing; Trauma-specific clinical evidence is limited	[156]
Metabolic	Metformin	AMPK activation, NF-κB suppression; Reduces hypercatabolism; Improves survival	Retrospective ICU/ARF, sepsis, perioperative cohorts; Trauma-specific data limited	[157-161]
Metabolic	Propranolol (β-blockade)	Reduces catecholamine-driven catabolism; Preserves lean mass; Stabilizes metabolic state	Trauma studies, pediatric and geriatric burn cohorts	[162]
Neuroinflammation	Minocycline	Reduces microglial activation; Inhibits HMGB1 release; Stabilizes the BBB; Anti-apoptotic effects	Repurposed from neurodegeneration; Trauma studies are emerging	[163-165]
Neuroinflammation	Ibudilast	PDE inhibitor; Suppresses glial cytokine production; Enhances neuroprotection	Phase II in neuroinflammation and neuropathic pain	[166-168]
Psychiatric	SSRIs	Inhibit serotonin reuptake, enhance serotonergic neurotransmission, and reduce depressive and anxiety symptoms after trauma and PTSD	Established first-line pharmacotherapy for PTSD and depression; Not trauma-mechanism-specific	[169-171]
Psychiatric	Adrenergic antagonists	Block central and peripheral adrenergic receptors, attenuating noradrenergic hyperarousal, autonomic overactivation, and trauma-related nightmares	Widely used in PTSD and trauma-related hyperarousal; Mixed evidence in trauma-prevention and chronic outcome modification	[170,171]
Non-pharmacologic	Cognitive behavioral therapy and trauma-focused psychotherapies	Structured psychotherapies that restructure maladaptive cognitions, use graded exposure to extinguish fear circuits, and enhance coping and adherence	Guideline-recommended first-line treatment for PTSD and trauma-related disorders; Robust clinical trial evidence	[172]
Neuromodulation	Transcranial magnetic stimulation	Non-invasive neuromodulation of prefrontal and network-level activity modulates cortical excitability and connectivity to reduce depressive and PTSD symptoms	Approved for treatment-resistant depression; Emerging evidence and early clinical studies in PTSD and post-traumatic syndromes	[173]

IL. Interleukin; SIRS. Systemic inflammatory response syndrome; MAS. Macrophage activation syndrome; RA. Rheumatoid arthritis; SASP. Senescence-associated secretory phenotype; BCL-2. B-cell lymphoma 2; FX06. Fibrin-derived peptide 06; MitoQ. Mitochondria-targeted coenzyme Q10 analogue; SS-31. Elamipretide peptide; DAMPs. Damage-associated molecular patterns; TLR. Toll-like receptor; TLR4. Toll-like receptor 4; MD2. Myeloid differentiation factor 2; NF-κB. Nuclear factor κB; PDE. Phosphodiesterase; TGF-β. Transforming growth factor-β; PDGF. Platelet-derived growth factor; VEGF. Vascular endothelial growth factor; FGF. Fibroblast growth factor; MSK. Musculoskeletal; RAGE. Receptor for advanced glycation end products; MDSC. Myeloid-derived suppressor cell; ECM. Extracellular matrix; AMPK. AMP-activated protein kinase; HPA. Hypothalamic-pituitary-adrenal; BBB. Blood-brain barrier; mTOR. Mechanistic target of rapamycin; MMPs. Matrix metalloproteinases; TIC. Trauma-induced coagulopathy; Ca^{2+}. Calcium ion; ICU. Intensive care unit; ARF. Acute respiratory failure; SSRI. Selective serotonin reuptake inhibitor; PTSD. Post-traumatic stress disorder; ARDS. Acute respiratory distress syndrome; ROS. Reactive oxygen species

survival benefit in sepsis patients with hyperinflammatory, macrophage activation-like phenotypes, and its use in trauma-associated acute respiratory distress syndrome (ARDS) is currently extrapolated from these sepsis and critical illness data rather than supported by trauma-specific trials [108,109]. Precision immunotherapy approaches have further supported phenotype-targeted use of IL-1 blockade in macrophage activation-like syndrome to improve organ dysfunction in

sepsis, highlighting the importance of biomarker-guided strategies despite the absence of trauma-specific trials [175].

IL-6 inhibition with tocilizumab remains less conclusive in trauma settings, with variable efficacy and safety concerns, although early-phase studies continue to refine its risk-benefit profile [110]. Beyond rheumatoid arthritis, IL-6 receptor has shown benefit in severe COVID-19-associated ARDS and systemic hyperinflammation, supporting its role in cytokine storm syndromes, while trauma applications remain investigational [111,112]. Device-based immunomodulation approaches, particularly extracorporeal cytokine adsorption, have emerged as adjuncts for controlling hyperinflammation. HA330 hemoperfusion cartridges selectively remove circulating cytokines through resin-based adsorption and have demonstrated reductions in IL-6, TNF-α, and other inflammatory mediators in early trauma and critical care studies [114]. However, evidence to date is largely retrospective or small-scale and is derived primarily from sepsis/critical illness cohorts; robust trauma-specific survival or organ-protection data are still needed [113,114].

Upstream targeting of alarmins, particularly HMGB1, represents an emerging immunomodulatory strategy. HMGB1-neutralizing antibodies and small-molecule inhibitors such as glycyrrhizin block HMGB1-TLR4/RAGE interactions, thereby reducing NF-κB activation, cytokine amplification, and sterile inflammatory propagation. Glycyrrhizin has been shown to attenuate traumatic brain injury via HMGB1-RAGE inhibition in preclinical models [115-118]. In addition, HMGB1 can signal via TLR5, contributing to neuroinflammation and pain hypersensitivity *in vivo* [119].

Downstream innate immune signaling has also been explored as a therapeutic target. TAK-242 (Resatorvid) inhibits intracellular TLR4 signaling and is under early clinical evaluation outside trauma, including phase II trials in severe alcoholic hepatitis and acute-on-chronic liver failure [120]. Whereas Eritoran, a TLR4-MD2 antagonist, failed to reduce 28-day all-cause mortality in the phase III ACCESS trial in severe sepsis and remains investigational without demonstrated trauma-specific efficacy [121].

More recently, next-generation cellular and nanoparticle-based interventions have emerged to refine immune recalibration. Modulation of MDSCs has demonstrated the capacity to dampen excessive inflammation while preserving antimicrobial function in experimental trauma models [122]. In addition, nanoparticle formulations targeting the alarmins S100A8/A9 have been engineered to sequester or neutralize these damage-associated proteins, thereby reducing neutrophil recruitment, cytokine amplification, and microvascular injury in preclinical models of systemic inflammation and trauma [123].

Endothelial protection

Endothelial-stabilizing therapies target the vascular injury node, aiming to preserve the glycocalyx, maintain microvascular integrity, and prevent TIC and organ failure [176]. Syndecan-1, a biomarker of glycocalyx degradation, shows a strong correlation with the severity of endothelial injury, increased vascular permeability, coagulopathy, MODS, and mortality in trauma and critical illness [124]. Among pharmacologic approaches, sulodexide has emerged as an endothelium-stabilizing agent. Supported by preclinical balloon-injury models and sepsis endothelial dysfunction studies, glycocalyx reconstruction and barrier integrity restoration [125]. Ongoing clinical trials focus on endothelial dysfunction, while trauma-specific applications remain under evaluation [124,125]. Fibrin-derived peptide B β15-42 [fibrin-derived peptide 06 (FX06)] has been evaluated in early phase II trauma and critical illness studies, where it demonstrated potential to reduce vascular leakage and TIC [126-130]. Statins, particularly atorvastatin, provide pleiotropic endothelial and anti-inflammatory benefits, demonstrated in endothelial radioprotection and improved endothelium-dependent vasodilation outside trauma contexts [131-133]. Adjunctive strategies, targeting glycocalyx preservation, include doxycycline, an MMP inhibitor that reduces glycocalyx shedding and attenuates endothelial barrier disruption in preclinical trauma and acute lung injury models [134]. Moreover, synthetic glycosaminoglycan mimetics such as dekaparin replicate key structural domains of the endothelial glycocalyx to inhibit heparanase-mediated degradation, reduce vascular permeability, and attenuate TIC in early translational models [135]. At the resuscitation level, fibrinogen-enriched plasma resuscitation has gained attention as an endothelium-centered strategy. By restoring fibrinogen deficits, improving oncotic pressure, and stabilizing endothelial barrier function, this approach mitigates TIC and vascular permeability. Phase II trauma studies report improvements in coagulation parameters and endothelial integrity [136].

Restoration of plasma membrane integrity

Plasma membrane-repair strategies target the cellular barrier-integrity sub-node of the mitochondrial-endothelial injury axis, where mechanical disruption of the lipid bilayer initiates pathological calcium influx, bioenergetic collapse, and secondary necrotic cell death [137,177]. Preservation and restoration of plasma membrane integrity are therefore critical prerequisites for effective recovery following blast

and crush injuries, in which high-energy mechanical forces frequently overwhelm endogenous repair mechanisms [177]. Under physiological conditions, acute membrane disruptions are rapidly repaired through intrinsic mechanisms [178]. These include calcium-triggered annexin recruitment to the wound edge, where they promote membrane curvature, vesicle aggregation, and resealing [179]. Dysferlin plays an essential role in sarcolemmal repair by orchestrating vesicle fusion and patch formation at injury sites [180]. Stress-inducible chaperones such as HSP70 and HSP27 stabilize cytoskeletal-membrane interfaces and facilitate membrane resealing [181]. Preconditioning paradigms that upregulate these proteins can enhance intrinsic repair capacity and confer partial resistance to subsequent mechanical insults [182]. However, in the context of high-energy polytrauma, the magnitude and repetition of membrane disruption often overwhelm endogenous repair capacity. Sustained calcium influx, oxidative stress, and necrotic cell death result in amplifying both local and systemic inflammation [138,183]. In this setting, exogenous membrane-stabilizing agents function as critical adjuncts to intrinsic repair mechanisms. Among these, amphiphilic triblock copolymers, particularly poloxamer 188 (P188), have emerged as leading membrane-sealants. P188 selectively inserts into disrupted lipid bilayers, stabilizes sarcolemmal defects, limits Ca^{2+} overload, and improves cell survival across multiple experimental injury models [139]. Foundational biophysical studies demonstrated polymer-mediated sealing of structurally damaged membranes [138], while early studies showed potent neuroprotection through amphiphilic triblock copolymers [140]. In skeletal muscle injury models, P188 reduced contraction-induced force decline in dystrophic mdx mice [141] and conferred marked protection *in vivo* [142]. Additional studies confirmed its ability to stabilize sarcolemmal integrity and limit calcium overload across ischemia-reperfusion and mechanical injury models [137,143], and reperfusion injury [144].

Regenerative and anti-senescent therapies

Regenerative and anti-senescent therapies target the senescence-mitochondrial node, where early onset of cellular senescence and bioenergetic failure impair tissue repair and promote maladaptive fibrosis [184]. Rather than providing an exhaustive overview of regenerative modalities, this discussion emphasizes their relevance within the interconnected framework of immune dysregulation, endothelial dysfunction, and mitochondrial impairment. By restoring cellular energy homeostasis, modulating inflammation, and re-establishing vascular integrity, these approaches link early systemic disturbances to improved long-term regenerative outcomes, with measurable endpoints including enhanced tissue regeneration, reduced fibrosis, and improved functional recovery [185]. Among pharmacologic strategies, fibrosis-targeting small molecules such as pirfenidone and nintedanib, approved for pulmonary fibrotic diseases, are increasingly recognized as mechanistically relevant to trauma-induced tissue remodeling [145]. Pirfenidone reduces TGF-β-mediated fibroblast activation and collagen deposition [145,146], whereas nintedanib inhibits platelet-derived growth factor, vascular endothelial growth factor, and fibroblast growth factor receptor signalling pathways, thereby limiting myofibroblast activation and fibrosis progression [147]. Beyond fibrosis control, senolytics aim to eliminate senescent cells that accumulate early after trauma and drive chronic inflammation through the SASP. Combinatorial dasatinib plus quercetin has demonstrated senolytic efficacy across aging and fibrotic disease models, reducing SASP-mediated inflammation and improving tissue function [148]. Navitoclax (ABT-263), a BCL-2 family inhibitor targeting BCL-xL and BCL-2, induces apoptosis in senescent cells and has shown senolytic activity in vascular, neurovascular, and cutaneous wound-healing models; however, translational application is constrained by dose-limiting thrombocytopenia observed in early-phase oncology studies [149,150]. In contrast to senolytics, senomorphic agents modulate the senescent phenotype without inducing cell death. Rapamycin, through inhibition of mechanistic target of rapamycin signaling, suppresses SASP production and preserves regenerative capacity while limiting inflammatory amplification [151]. This approach may offer advantages in trauma settings where excessive clearance of senescent cells could impair early reparative processes. Although the majority of supporting evidence for these interventions originates from studies in aging and fibrotic disorders, their relevance to trauma is increasingly recognized. In the context of polytrauma, where early onset of cellular senescence contributes to sustained inflammation, impaired repair, and delayed recovery, regenerative and anti-senescent therapies remain hypothesis-generating translational prospects. Given the absence of trauma-specific clinical trials, focused preclinical and translational studies are required to define optimal timing, dosing, and safety profiles before clinical adoption [186].

Mesenchymal stem cells

MSC-based therapies provide paracrine, angiogenic, and immunomodulatory signals that enhance myogenesis and osteogenesis, reduce fibrosis, and restore tissue integrity after trauma. Robust preclinical evidence supports MSCs in

volumetric muscle loss and fracture non-union models, with early-phase clinical studies reporting improvements in both structural repair and functional outcomes [152,153]. Beyond cell-based therapies alone, biomaterial platforms play a critical role in optimizing MSC delivery and function. ECM-derived scaffolds and silk-based biomaterials serve as bioactive matrices that provide structural support while delivering growth factors and regenerative cues, thereby enhancing tissue integration and repair. In translational models, sequential delivery of TGF-β3 via silk fibroin/cartilage ECM scaffolds has been shown to promote chondrogenic differentiation of adipose-derived stem cells, underscoring the synergistic potential of combining MSCs with advanced biomaterial systems [154].

Metabolic stabilization

Metabolic stabilization therapies target the mitochondrial and neuroendocrine nodes, aiming to restore bioenergetic balance and counteract trauma-induced hypercatabolism [187]. Mitochondrial dysfunction is a central driver of post-traumatic organ failure, systemic inflammation, and delayed recovery, making metabolic resuscitation a critical component of precision trauma care [188]. Among mitochondria-targeted strategies, antioxidants such as MitoQ and SS-31 preserve oxidative phosphorylation and limit ATP depletion [189]. Evidence from Huntington's disease models supports MitoQ's ability to reduce mitochondrial toxicity and synaptic damage [104], while elamipretide stabilizes cardiolipin and improves mitochondrial function, as summarized in mechanistic reviews [155]. Beyond direct mitochondrial targeting, redox modulation represents an additional metabolic stabilization strategy. N-acetylcysteine replenishes intracellular glutathione stores and reduces oxidative stress, contributing to improved cellular viability and organ function in preclinical trauma and traumatic brain injury models [156]. Systemic metabolic regulation further involves modulation of endocrine and inflammatory signaling. Metformin, through AMP-activated protein kinase (AMPK) activation and NF-κB suppression, has demonstrated survival benefits in retrospective trauma cohorts and is under evaluation in prospective critical illness/intensive care unit (ICU) trials, including acute respiratory failure, sepsis, and perioperative populations. However, prospective trauma-specific clinical data remain limited [157-161]. Moreover, β-adrenergic blockade, most notably with propranolol, reduces catecholamine-driven hypermetabolism, preserving lean body mass and improving survival and metabolic balance, especially in pediatric and geriatric trauma and burn patients [162]. However, anabolic hormone replacement therapies have shown inconsistent benefits and safety concerns in clinical studies, limiting their routine application in trauma care [190].

Neuropsychiatric interventions

Neuropsychiatric interventions target the neuroendocrine-immune node, addressing HPA-axis dysregulation, neuroinflammation, and behavioral impairments that critically shape long-term trauma outcomes [191]. These interventions recognize that neuropsychiatric sequelae of trauma arise from tightly coupled biological and psychosocial processes rather than isolated central nervous system pathology. Among pharmacologic strategies, minocycline, a tetracycline derivative, has emerged as a leading neuroinflammation-modulating agent. Minocycline exerts neuroprotective effects through inhibition of microglial activation, suppression of HMGB1 signaling, stabilization of the blood-brain barrier, and anti-apoptotic mechanisms [163]. Preclinical and clinical studies support its capacity to reduce neuroinflammation and improve outcomes following central nervous system injury [164,165]. Notably, in traumatic brain injury, minocycline reduced chronic microglial activation as demonstrated by positron emission tomography imaging, although concomitant increases in neurofilament light levels highlight nuanced and context-dependent efficacy [165]. Additional glial-modulating approaches include ibudilast, a phosphodiesterase inhibitor that suppresses glial cytokine production and enhances neuroprotection [166]. Preclinical studies and early-phase clinical trials in post-traumatic stress disorder and neuropathic pain support its potential role in mitigating trauma-associated neuroinflammation and central sensitization [166-168]. Symptom-targeted psychiatric pharmacotherapies remain integral to trauma care despite limited mechanistic precision. Selective serotonin reuptake inhibitors enhance serotonergic neurotransmission and are widely used to reduce depressive and anxiety symptoms following trauma and PTSD [169]. Adrenergic antagonists, by blunting noradrenergic hyperarousal and autonomic overactivation, are commonly employed to address trauma-related hyperarousal and sleep disturbances. However, both classes exhibit heterogeneous efficacy, and benzodiazepines are generally discouraged due to associations with adverse outcomes and dependence risk [170,171]. Beyond pharmacologic therapies, non-pharmacological interventions play a central role in long-term neuropsychiatric recovery. Cognitive behavioral therapy and trauma-focused psychotherapies are guideline-recommended first-line treatments for PTSD and trauma-related disorders, demonstrating robust efficacy in reducing symptom burden and improving functional outcomes [172]. In addition,

transcranial magnetic stimulation provides non-invasive neuromodulation of prefrontal and network-level activity and is approved for treatment-resistant depression, with emerging evidence supporting its utility in PTSD and post-traumatic neuropsychiatric syndromes [173]. Complementing these therapeutic strategies, emerging diagnostic and monitoring tools, including digital phenotyping, electroencephalogram analytics, and AI-assisted behavioral assessment, are under early translational development. These approaches aim to integrate biological and behavioral data to enable early detection, stratification, and personalized intervention, rather than serving as stand-alone therapies [192]. Early recognition and multidisciplinary integration of neuropsychiatric interventions are critical for optimizing neurobehavioral recovery and long-term quality of life, particularly in pediatric and high-risk trauma populations.

From traditional biomarkers to emerging molecular signatures

Traditional biomarkers such as creatine kinase (CK), lactate dehydrogenase (LDH), and myoglobin have long been utilized as frontline tools for evaluating polytrauma with MSK injury [193]. These markers primarily reflect myocyte injury and necrosis, offering early signals of muscle breakdown and associated risks such as rhabdomyolysis and AKI [194]. CK, particularly the muscle-specific CK-MM isoform, is the most widely used and commonly rises substantially following blunt or crush injuries [195]. LDH is sensitive to cellular damage but lacks muscle specificity due to its broad tissue distribution [196], whereas myoglobin rises rapidly but is transient because of its fast clearance [197]. Diagnostic performance remains modest: CK generally demonstrates AUC values of 0.70–0.75, and both LDH and myoglobin are influenced by injury or dysfunction in multiple organs [194]. Additional confounders, including liver injury, hemolysis, sepsis, metabolic disorders, strenuous physical activity, and impaired renal clearance, further reduce specificity and can obscure the true extent of muscle injury. As a result, although useful for detecting overt tissue necrosis, these traditional biomarkers provide only retrospective snapshots and cannot resolve the upstream immune, endothelial, and metabolic perturbations that drive systemic trauma biology.

Advancements in trauma diagnostics have accelerated the development of next-generation biomarkers that provide improved sensitivity and mechanistic resolution beyond conventional indicators of muscle necrosis. Among these, muscle-enriched circulating microRNAs (miRNAs) such as miR-206 and miR-486 correlate strongly with the extent of muscle injury and demonstrate diagnostic sensitivity and specificity exceeding 80% in early studies [198]. Complementing these injury-burden markers, miRNAs including miR-21 and miR-223 reflect inflammatory activation, fibrosis, and maladaptive tissue remodeling, linking molecular injury signatures to downstream repair failure [199]. EVs, including exosomes and microvesicles released by stressed or injured cells, further extend this diagnostic spectrum by transporting miRNAs, proteins, and lipids that report oxidative stress, mitochondrial dysfunction, and immune activation, while also actively modulating trauma-induced inflammation [200].

Among circulating protein biomarkers, fatty acid-binding protein 3, which is predominantly expressed in skeletal muscle [201], has demonstrated strong prognostic utility, with clinical data showing an AUC of 0.82 for predicting post-traumatic AKI, outperforming CK, and associations with trauma severity and complications such as compartment syndrome [202,203]. Additional mechanistic biomarkers include galectin-3, which reflects persistent inflammation, fibrosis, and cellular senescence and has been linked to HO risk, although large-scale trauma-specific validation remains ongoing [204]. Beyond individual tissues, muscle-bone endocrine mediators, including myokines (irisin, myostatin, IL-6) and osteokines (osteocalcin, sclerostin, fibroblast growth factor-23), provide integrated readouts of metabolic crosstalk during regeneration and systemic stress [205]. Complementing these systemic markers, the collagen X degradation fragment has emerged as a real-time indicator of endochondral ossification and bone healing velocity, enabling dynamic monitoring of skeletal repair after trauma [206,207].

Despite their promise, most of these biomarkers remain in early clinical development, with validation largely limited to single-center or pilot trauma cohorts using enzyme-linked immunosorbent assay or multiplex immunoassay platforms, underscoring the need for assay standardization, regulatory qualification, and multicenter validation prior to widespread clinical adoption [208].

Integrating biomarker discovery with therapeutic innovation forms a foundational paradigm for precision trauma medicine in polytrauma with MSK injury. Syndecan-1 elevation [89] may identify patients who would benefit from glycocalyx-protective agents such as sulodexide [127,128] or FX06. Cytokine ratios, such as elevated IL-6 relative to IL-10, may guide the timing of IL-6 receptor blockade with tocilizumab [209]. Persistently high HMGB1 levels may inform the use of antagonists targeting DAMP- or TLR-driven inflammation [121]. Increased S100A8/A9 [210] may identify candidates for nanoparticle-based immunomodulation. Although these precision-guided

approaches require validation through dedicated trauma trials, they exemplify how biomarker-informed stratification can shift trauma care from generalized resuscitation toward individualized, mechanism-targeted therapy.

Assessing the translational potential of biomarkers of polytrauma with MSK injury necessitates consideration of the distinctive conditions in military and civilian trauma care settings. Military trauma care is frequently delivered in austere environments characterized by delayed evacuation, constrained surgical capacity, and high injury complexity, conditions that favor biomarkers which are stable, rapidly quantifiable, and compatible with rugged point-of-care (POC) platforms [211,212]. In these settings, biomarkers such as CK, myoglobin, fatty acid-binding protein 3 (FABP3), and select cytokines or DAMPs measurable through portable immunoassays are particularly valuable for early triage, evacuation prioritization, and prediction of complications including AKI and multi-organ dysfunction [89,203,213]

However, civilian trauma systems, which benefit from advanced imaging, comprehensive biobanking, and access to high-throughput laboratory infrastructure, are better positioned to deploy multiplex panels, circulating miRNA profiling, EV analysis, metabolic panels, and longitudinal biomarker surveillance. These capabilities allow deeper mechanistic stratification of inflammation, fibrosis, metabolic dysregulation, and impaired regeneration following MSK trauma [200,204,210]

The utility of biomarkers varies across clinical phases of trauma care, with acute, subacute, and chronic stages presenting distinct diagnostic priorities and operational constraints. In the acute phase, frontline military outposts depend heavily on rugged POC assays to enable rapid detection of hemorrhage, endotheliopathy, and muscle breakdown, whereas civilian trauma centers can deploy broader multiplex panels and advanced diagnostics within emergency department settings [214,215]. During the subacute period, biomarker monitoring shifts toward prognostication of inflammatory burden, fibrosis, and optimal rehabilitation timing, occurring along evacuation chains in military contexts or within inpatient and rehabilitation services in civilian systems. Long-term care prioritizes surveillance of veterans and civilian patients at risk of disability, frailty, and chronic complications, with sustained monitoring of regenerative, anabolic, and neurotrophic mediators, most notably IGF-1, which plays a central role in MSK regeneration and repair [216,217].

Clinical and translational studies have established phase-specific biomarker applications across military and civilian trauma environments, encompassing endothelial injury markers, immune mediators, metabolic regulators, and regenerative signals [203,204,210,211]. Increasingly, these workflows are augmented by continuous wearable biosensors and AI-enabled analytics, enhancing predictive accuracy and individualized management across the trauma trajectory. These phase-dependent biomarker strategies and enabling technologies are summarized in Table 3 [203,204,210,211,213,217], which outlines biomarker-guided approaches spanning acute, subacute, and chronic phases of trauma care.

Multi-analyte panels, real-time monitoring, and liquid biopsy approaches

The precision medicine era is redefining diagnostics for blast-, blunt-, and crush-related polytrauma with major MSK injury, shifting away from reliance on single biomarkers toward integrated, multidimensional platforms that capture the evolving biology of injury. This transition is particularly critical in complex polytrauma scenarios, such as battlefield

Table 3 Biomarker-guided phases of trauma management across military and civilian contexts

Phase	Military context	Civilian context	Key biomarkers/ Technologies	Clinical utility	Evidence highlights	References
Acute (0–72 h)	Forward bases with limited labs, reliance on rugged POC devices	Advanced diagnostics in emergency departments	Syndecan-1, FABP, lactate, miRNAs, calprotectin (S100A8/A9), wearables	Rapid triage, early detection of hemorrhage/ endotheliopathy, prediction of MODS	Syndecan-1 (AUC=0.80), FABP3	[203,210,211,213]
Subacute (days-weeks)	Evacuation chain, transport prioritization	Inpatient and rehabilitation monitoring	Galectin-3, IL-6, HMGB1, mitochondrial DNA, EVs, metabolomics panels	Prognosis of inflammation, fibrosis, and optimized rehab timing	Galectin-3 correlated with HO risk	[204]
Chronic (weeks-years)	Long-term veteran follow-up	Disability care, aging-related management	IGF-1, BDNF, osteocalcin, CTX-II, DHEA-S, CRP, TNF-α	Tracking regeneration, systemic adaptation, and mental health	IGF-1 role in MSK repair	[217]

POC. Point of care; FABP. Fatty acid-binding protein; FABP3. Heart-type fatty acid-binding protein 3; miRNAs. MicroRNAs; EVs. Extracellular vesicles; IL-6. Interleukin-6; HO. Heterotopic ossification; IGF-1. Insulin-like growth factor-1; BDNF. Brain-derived neurotrophic factor; CTX-II. C-terminal crosslinked telopeptide of type II collagen; DHEA-S. Dehydroepiandrosterone sulfate; CRP. C-reactive protein; TNF-α. Tumor necrosis factor-α; MODS. Multi-organ dysfunction syndrome; HMGB1. High-mobility group box 1; S100A8/A9. S100 calcium-binding proteins A8 and A9 calprotectin

blast exposures, urban crush injuries, and mass-casualty events, where heterogeneous damage patterns demand rapid, individualized evaluation.

High-dimensional multi-omics and systems integration

Contemporary studies combine proteomics, metabolomics, transcriptomics, including single-cell and spatial, extracellular-vesicle cargo, lipidomics, and cfDNA/mtDNA analytics to map coordinated cascades across coagulation/complement, thrombo-inflammation, endothelial injury, and metabolic reprogramming [218,219]. In particular, scRNA-seq and chromatin accessibility profiling of trauma patient leukocytes have demonstrated that immune-endotype-specific transcriptional and epigenetic programs are strongly associated with clinical phenotype and outcome, providing a prototype for multi-omic patient classification in polytrauma [81,82]. Integrated pipelines merge these layers with clinical/physiologic data to support causal inference, risk stratification, and target prioritization. In trauma cohorts, proteo-metabolomic and EV-omic signatures correlate with infection risk, endotheliopathy, and organ dysfunction, while cfDNA/mtDNA refine organ-source attribution and predict trajectories [57,59,218,220,221]. Coupled with AI-enabled digital-twin frameworks, these datasets inform adaptive triage, timing of immunomodulatory or endothelial-protective therapies, and monitoring of regeneration [222-224]. Although still in early translation, these tools provide the foundation for clinically actionable, precision-guided trauma panels [225].

Multi-analyte biomarker panels

Panels that combine classical tissue-injury markers (CK, LDH, myoglobin) with miRNAs, inflammatory cytokines (IL-6, TNF-α), DAMPs, and senescence-associated proteins provide a multidimensional view of patient status [226]. Combining acute-phase cytokines with senescence markers (p16INK4a, SASP factors) provides early insight into maladaptive healing and fibrotic risk [227]. ML models align temporal biomarker dynamics with clinical metadata to refine prognosis and guide intervention [228].

Real-time monitoring technologies

Wearable and implantable biosensors are extending diagnostics beyond the laboratory, offering continuous monitoring of physiologic and biochemical parameters [229-231]. These devices track lactate, tissue oxygen saturation (StO_2), perfusion indices, and inflammatory mediators in sweat, saliva, or interstitial fluid, potentially useful for rapid decision-making in both military and civilian trauma care [232,233]. Such systems hold promise for early detection of systemic inflammation or compartment syndrome, optimizing triage in austere and remote environments.

Liquid biopsy

Adapted from oncology, liquid biopsy approaches are emerging as minimally invasive, repeatable tools for probing systemic injury and organ-associated pathophysiological responses in trauma [234]. Circulating cfDNA, mtDNA, miRNAs, and EV cargoes represent core liquid biopsy components. These analytes reflect cellular injury, immune activation, metabolic stress, and organ dysfunction, and have demonstrated strong potential for tracking inflammation, fibrosis, and regeneration across the trauma phase [221,235-237]. Their serial measurement enables longitudinal profiling of dynamic pathophysiological responses, making them central to emerging trauma liquid biopsy platforms.

Large-scale proteomic and metabolomic profiling can be viewed as liquid-biopsy-like approaches because both approaches quantify circulating proteins, peptides, lipids, and metabolites derived from injured tissues, dysregulated immune cells, activated endothelium, and stressed mitochondria. Proteomic signatures in trauma consistently reveal alterations in coagulation, complement activation, and energy metabolism, while metabolomic profiling identifies shifts in amino-acid, lipid, and mitochondrial-related pathways that correspond to injury severity, early sepsis, and systemic metabolic stress [238,239]. By capturing these circulating molecular fingerprints through blood sampling, proteomics and metabolomics function as extensions of liquid biopsy, enabling the construction of dynamic network models for clinical risk stratification, precision monitoring, and therapeutic targeting [240-242].

Clinical convergence and translation

Integrating multi-omics, multi-analyte panels, and real-time biosensing can enable earlier identification of high-risk patients, personalized treatment selection, and responsive monitoring [243]. Portable, rugged, and cost-effective platforms tailored to trauma-specific biomarkers are key for battlefield and low-resource deployment [244].

Technological integration

Wearables and biosensors

The convergence of wearable devices and biosensors with trauma analytics has demonstrated feasibility and potential to improve early risk detection, physiologic monitoring, and triage efficiency [245]. Evidence from prehospital [246,247]

and simulated mass-casualty environments shows that these technologies can reduce time-to-triage, enhance detection of occult deterioration, and support more accurate resuscitation decisions [248,249]. Modern devices extend well beyond activity tracking. To begin with, inertial measurement units, electromyography sensors, and optical platforms quantify gait asymmetry, joint loading, and muscle activation to support early functional risk detection and personalized rehabilitation [250,251]. In addition, physiologic signals, such as heart-rate variability, perfusion indices, and skin temperature, often presage clinical deterioration and can serve as early-warning markers when integrated with continuous monitoring systems [252-255]. Next-generation biochemical biosensors now enable minimally/non-invasive sampling of sweat, saliva, interstitial fluid, or capillary blood (LDH, CK, cortisol, electrolytes) to flag metabolic imbalance, rhabdomyolysis, or hypovolemia [256,257]. Importantly, although wearable lactate sensing has been shown to shorten triage times in simulated disaster studies, these same evaluations reveal durability constraints, sensor drift, and incomplete data integration under operational stressors [244]. Adoption barriers, costs, workflow fit, and alarm fatigue remain prominent [253]. In prehospital and battlefield settings, these devices can accelerate triage and guide resuscitation decisions under constrained resources [222].

Domain-specific AI applications and validation

AI applications in trauma care are rapidly expanding, with several domain-specific use cases showing clinical promise. One major area involves the real-time prediction of hemodynamic decompensation and hemorrhage risk during field evacuation or intensive care monitoring, where algorithms trained on streaming vital signs and sensor telemetry enable early triage and timely intervention [222,258]. Similarly, AI-driven forecasting of sepsis, MODS, and related deterioration employs models based on physiologic time-series data, laboratory parameters, and, in some studies, metabolomic inputs [259-261]. Meta-analyses indicate that such early-warning systems can improve recognition of critical deterioration and guide resuscitation strategies [258]. Beyond the acute phase, ML models are increasingly applied to rehabilitation and recovery, using longitudinal biomarker and imaging data to stratify risk for delayed MSK recovery and fibrotic complications after polytrauma, with biologic surrogates such as galectin-3 (a fibrosis-associated marker) supporting model interpretability [204].

Validation efforts are evolving from single-site retrospective studies to multicenter, externally validated models and prospective trials encompassing both military and civilian trauma cohorts [262,263]. Wearable and biosensor-based AI platforms have demonstrated feasibility in simulated and operational field contexts, though practical constraints in data integration and interoperability persist [244,258]. These limitations largely reflect the technical challenges of managing high-frequency sensor data under variable environmental and operational conditions. Despite these advances, several failure modes and biases limit generalizability. Overfitting remains a key challenge, particularly given the underrepresentation of female and geriatric populations in training datasets and the predominance of combat injury data [264]. Field-deployed systems also face technical reliability issues, including signal noise, sensor dropout, and intermittent network connectivity, while human-factor barriers such as alarm fatigue, workflow burden, and limited clinician acceptance hinder operational uptake [244,253,258]. To address these challenges, emerging frameworks prioritize explainable AI, human-in-the-loop oversight, and privacy-preserving or federated learning approaches to enhance interpretability, data security, and cross-site robustness.

Military vs. civilian deployment

The deployment of AI-driven trauma diagnostics and monitoring platforms diverges significantly between military and civilian settings due to distinct operational constraints and priorities. In austere or forward military environments, devices must be portable, ruggedized, and require minimal calibration while offering rapid decision support, often within 30 min, to aid triage and evacuation under intermittent connectivity. These systems prioritize speed, robustness, and interpretable outputs suitable for non-specialist users in high-stress conditions [222,244]. In contrast, civilian hospital and rehabilitation environments benefit from stable infrastructure that supports high-plex assays, advanced imaging modalities, and integration with electronic health records (EHRs). Here, longer processing times are acceptable when offset by higher analytical depth and actionable insights, such as multiplex proteomic or EV analyses [222,229-233,256,257].

Sample handling and time-to-result differ markedly between these settings. Field diagnostics typically rely on minimally invasive sampling, capillary blood, sweat, or interstitial fluid, paired with on-device analytics to deliver short turnaround times (TAT). However, these approaches remain vulnerable to motion artifacts, temperature fluctuations, and environmental contamination [244,256,257]. Civilian hospital workflows utilize venous sampling, refrigerated logistics, and centralized analyzers, allowing longer TAT but achieving superior

analytical resolution through multi-analyte or liquid-biopsy workflows [229-233,237].

Throughput and workflow design also reflect contextual divergence. Field-deployed platforms emphasize low-plex, high-frequency monitoring with edge analytics optimized for bandwidth efficiency and data compression [222,244]. Similarly, civilian core laboratories leverage higher throughput, batchable assays, and seamless EHR-integrated decision support to deliver comprehensive, longitudinal data interpretation [222,229-233,256,257].

Context critically shapes the clinical utility and performance of these systems. At the point of injury, wearable lactate or StO_2 sensors and hemodynamic AI algorithms can substantially improve triage and evacuation prioritization despite lower analytical granularity [222,231,244,258]. In the intensive care or rehabilitation phases, multi-analyte and liquid-biopsy panels, such as those assessing cfDNA, mtDNA, or EV cargo, combined with AI-driven risk modeling, provide enhanced predictive power for sepsis, multi-organ dysfunction, and recovery trajectories, where slightly delayed turnaround is acceptable given the higher clinical impact [57,221,235-237,265].

Remote monitoring and telemedicine

Secure data transmission from field and rural locations to centralized command or hospital centers enables a continuous and coordinated approach to trauma care. Rather than functioning as data-integration platforms themselves, telemedicine systems serve as clinical oversight and decision-support channels, allowing specialists to interpret incoming physiologic and biochemical information and provide real-time guidance across all stages of care, from the point of injury through transport, acute management, and rehabilitation [222]. By leveraging remote expertise, these platforms enhance situational awareness, optimize resource allocation, and ensure continuity of care across geographically dispersed military and civilian trauma networks.

Implementation risks and equity

Despite rapid technological progress, significant implementation challenges remain for integrating wearable biosensors and AI analytics into trauma workflows. Practical barriers include ensuring device ruggedness under extreme or unpredictable conditions, managing high volumes of streaming data without overwhelming providers, and maintaining robust data privacy and cybersecurity safeguards. Additional hurdles involve regulatory and reimbursement uncertainties and the need for targeted training programs to support AI-assisted clinical decision-making [266,267]. Beyond technical limitations, equity concerns persist, particularly in regions with limited connectivity, maintenance capacity, or workforce readiness [268]. To ensure sustainable adoption, deployment strategies should include provisions for reliable infrastructure, local capacity building, and culturally attuned implementation models that bridge the gap between high-resource and low-resource trauma care settings [244,253,258].

Future outlook

The global burden of polytrauma with major MSK injury emphasizes the urgent need for transformative, not merely incremental, advances in trauma care. Although major progress has been made in understanding trauma biology, identifying reliable biomarkers, and developing therapeutic interventions, a wide translational disconnect remains between preclinical discovery and clinical application. This gap is particularly evident in regions disproportionately affected by high-energy injuries linked to armed conflict, road traffic collisions, and natural disasters. Addressing these challenges demands coordinated, mechanism-driven, and technology-enabled frameworks that redefine how trauma is investigated, diagnosed, and managed across diverse health systems.

A promising path forward is the establishment of a Global Trauma Initiative modeled after successful multinational consortia such as the International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC) [269,270], active across more than 60 countries in Europe, North America, Africa, and Asia, and the International Traumatic Brain Injury Research (InTBIR) initiative. This global coalition would unite military, academic, clinical, and public health stakeholders to develop harmonized trauma registries, longitudinal biobanks, and multi-omics datasets that represent diverse injury profiles, emphasizing inclusion of LMICs. The integration of genomic, transcriptomic, proteomic, and metabolomic data with standardized clinical metadata could generate an equitable evidence base for the advancement of precision trauma medicine.

Within this global framework, the concept of a Precision Trauma Panel illustrates how mechanistic insights could translate into actionable diagnostics for polytrauma patients with significant MSK injury. By combining biomarkers such as FABP3 (muscle injury), IL-6 and IL-10 (inflammatory balance), syndecan-1 (endothelial glycocalyx degradation), and galectin-3 (fibrosis and senescence), these multi-analyte panels could enable early risk stratification and guide personalized interventions. Designed for both advanced laboratories and portable POC platforms, such tools could support triage and longitudinal monitoring across resource settings, whether in

austere combat environments or tertiary trauma centers.

AI and ML will be central to managing the complexity of multi-modal trauma data. By integrating biomarker kinetics, physiologic signals, imaging, and contextual metadata, AI-driven systems can generate individualized predictive models. The emerging concept of a Combat Trauma Digital Twin, a real-time computational representation of the injured patient, exemplifies how digital platforms may automate triage, anticipate clinical deterioration, and personalize therapy across both military and civilian contexts.

Realizing this vision requires concurrent strengthening of foundational health-system components. The Global Alliance for MSK Health (G-MUSC) blueprint provides an actionable structure for such efforts, emphasizing adaptable, country-specific implementation strategies [271,272]. Future initiatives should prioritize embedding biomarker-informed pathways within integrated service models supported by sustainable financing and workforce capacity building. Enhanced surveillance frameworks that link functional recovery metrics with molecular and clinical data will be crucial for benchmarking outcomes and ensuring equitable technology validation between high- and low-resource regions.

To operationalize this vision, priority actions over the next 5 years should include: 1) launching pilot trauma biomarker registries and multi-omics biobanks in diverse cohorts, including LMICs; 2) developing regulatory pathways and standardized qualification pipelines for multi-analyte panels; 3) funding multicenter randomized controlled trials to validate AI-enabled triage systems and digital twin frameworks across heterogeneous trauma populations; 4) establishing global collaborations for equitable biospecimen sharing, data harmonization, and open-access analytics; and 5) conducting interventional trials targeting cellular senescence and the SASP to mitigate chronic inflammation, fibrosis, and long-term disability.

While prototypes such as the Precision Trauma Panel and wearable biosensors show promise, most remain investigational and limited to early validation phases [225,273,274]. Broader implementation will depend on rigorous multicenter testing, technical standardization, ethical governance, and equitable access. Through sustained international collaboration and regulatory alignment, trauma care can evolve from reactive management toward predictive, precision-guided, and resilient systems that improve survival and long-term recovery worldwide.

Limitations

Although the review emphasized biomarkers and therapeutic pathways most directly linked to acute systemic pathophysiology, including immune dysregulation, endothelial dysfunction, mitochondrial injury, and trauma-induced senescence, this focused scope necessarily excluded several other clinically relevant biomarker domains. Important indicators of MSK remodeling and neurotrophic recovery, such as the myostatin-follistatin axis, brain-derived neurotrophic factor, troponin T, and IGF-1, as well as bone and cartilage turnover markers including osteocalcin, sclerostin, bone-specific alkaline phosphatase, and C-terminal crosslinked telopeptide of type II collagen, were not systematically evaluated. Likewise, broader endocrine and metabolic regulators (vitamin D, dehydroepiandrosterone sulfate, and cortisol), nonspecific inflammatory markers (C-reactive protein and TNF-α), and high-throughput proteomic discovery platforms were outside the scope of this analysis. The exclusion of these domains limits the review's ability to integrate acute injury biology with the longer-term processes of MSK adaptation, rehabilitation, and chronic recovery. Future reviews that bridge acute mechanistic responses with longitudinal remodeling trajectories will be essential to advancing precision trauma care.

Conclusions

Polytrauma with predominant MSK injury, whether caused by battlefield blast exposures or civilian blunt and crush injuries, extends far beyond localized tissue damage. These injuries trigger complex systemic cascades involving immune dysregulation, endothelial dysfunction, metabolic disruption, and premature cellular senescence, profoundly influencing both acute management and long-term recovery. Persistent sequelae such as chronic pain, fibrosis, HO, neuroinflammation, and disability remain prevalent, highlighting the insufficiency of conventional frameworks based on anatomical scoring and nonspecific markers such as CK and myoglobin. These limitations mandate the adoption of next-generation diagnostics that capture the dynamic and evolving molecular landscape of trauma.

Emerging biomarkers, including miRNAs, EVs, FABP3, galectin-3, and muscle- and bone-derived cytokines, are redefining the molecular understanding of trauma by revealing signatures of immune activation, vascular injury, and regenerative potential. When coupled with wearable biosensors, multiplex assays, and liquid biopsy technologies, these biomarkers enable real-time and minimally invasive profiling of injury dynamics. AI and ML further strengthen this model by transforming complex multimodal datasets into predictive, clinically actionable insights. Seminal scRNA-seq and scATAC-seq studies in trauma patients now provide high-resolution immune endotypes that can be integrated

into such analytic frameworks, enabling biology-guided patient classification and precision triage. Novel concepts such as biomarker-based trauma scoring systems and "Combat Trauma Digital Twins" exemplify the shift toward proactive and individualized care, bridging the gap between military and civilian trauma contexts.

Parallel therapeutic advances, such as senolytics, endothelial stabilizers, mitochondrial protectants, immunomodulators, glycocalyx-preserving agents, and bio-instructive scaffolds, reflect a transition from symptom control to biological recalibration. These interventions aim to restore vascular integrity, temper chronic inflammation, and accelerate functional regeneration, aligning treatment with the mechanistic roots of trauma pathology.

The future of trauma medicine lies in uniting mechanistic discovery with clinical implementation to create proactive, biology-informed models of recovery. Through sustained international collaboration, equitable access to innovation, and ethical governance of data and technology, the field stands poised to transform trauma care, improving survival, resilience, and long-term quality of life across global populations.

Abbreviations

AKI: Acute kidney injury
AI: Artificial intelligence
ARDS: Acute respiratory distress syndrome
ATP: Adenosine triphosphate
Ca^{2+}: Calcium ion
CARS: Compensatory anti-inflammatory response syndrome
cfDNA: Circulating cell-free DNA
CK: Creatine kinase
DAMPs: Damage-associated molecular patterns
ECM: Extracellular matrix
EHR: Electronic health record
EVs: Extracellular vesicles
FABP3: Fatty acid-binding protein 3
FX06: Fibrin-derived peptide 06
HLA-DR: Human leukocyte antigen DR isotype
HMGB1: High-mobility group box 1
HO: Heterotopic ossification
HPA: Hypothalamic-pituitary-adrenal
HSP: Heat shock protein
IFN-γ: Interferon-γ
IGF-1: Insulin-like growth factor 1
IL: Interleukin
LDH: Lactate dehydrogenase
LMICs: Low- and middle-income countries
MAPK: Mitogen-activated protein kinase
MDSC: Myeloid-derived suppressor cell
miRNAs: MicroRNAs
MitoQ: Mitochondria-targeted coenzyme Q10 analogue
ML: Machine learning
MMP: Matrix metalloproteinase
MODS: Multi-organ dysfunction syndrome
MSCs: Mesenchymal stem cells
mtDNA: Mitochondrial DNA
MSK: Musculoskeletal
NF-κB: Nuclear factor κB
NLR: NOD-like receptor
POC: Point-of-care
PRISMA-ScR: Preferred reporting items for systematic reviews and meta-analyses extension for scoping reviews
PRRs: Pattern recognition receptors
P188: Poloxamer 188
RAGE: Receptor for advanced glycation end products
ROS: Reactive oxygen species
SASP: Senescence-associated secretory phenotype
scATAC-seq: Single-cell assay for transposase-accessible chromatin using sequencing
scRNA-seq: Single-cell RNA sequencing
SIRS: Systemic Inflammatory Response Syndrome
SS-31: Elamipretide peptide
StO_2: Tissue oxygen saturation
TAT: Turnaround times
TGF-β: Transforming growth factor-β
TIC: Trauma-induced coagulopathy
TLR: Toll-like receptor
TNF-α: Tumor necrosis factor α

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Authors' contributions

RJRST conceptualized, conceived, and initiated the review, developed the first and final manuscript drafts, and designed the figures and tables. Formal literature analysis was conducted by RJRST and PA. MYG, CYP, and PA contributed to the drafting process, critically reviewed, and revised the manuscript. Textual contributions were made by RJRST, MYG, CYP, and PA, while visualization was managed by RJRST and PA. Writing, review, and editing responsibilities were shared by RJRST and PA. All authors read and approved the final manuscript.

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