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REVIEW

Peripheral Blood Mononuclear Cells in Sepsis: Immune Trajectories, Monocyte Dysfunction, and Translational Biomarkers

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Abstract: Sepsis is characterized by a dynamic and heterogeneous immune response in which hyperinflammation and immunosuppression often coexist and change over time. Peripheral blood mononuclear cells (PBMCs), including monocytes and lymphocyte subsets, provide an accessible window into this evolving immune trajectory and can be repeatedly assessed during disease progression. In this narrative review, we synthesize recent evidence from single-cell and spatial omics, mechanistic studies, and PBMC-based biomarker research, with a focus on three connected themes: time-dependent PBMC remodeling, monocyte/macrophage dysfunction, and translational immune biomarkers. Current evidence indicates that PBMC remodeling in sepsis is marked by monocyte state transitions, HLA-DR downregulation, lymphocyte apoptosis and exhaustion, regulated cell death, and immunometabolic reprogramming. These changes help explain why some patients recover after the acute inflammatory phase, whereas others progress toward persistent immunoparalysis, secondary infection, prolonged critical illness, or poor outcomes. PBMC-derived biomarkers, including transcriptomic signatures, monocyte phenotypes, lymphocyte exhaustion markers, metabolic indicators, and functional immune assays, may improve immune phenotyping and risk stratification. However, clinical translation remains limited by cohort heterogeneity, age-related differences, timing-dependent immune states, assay standardization, and insufficient prospective validation. Future studies should prioritize longitudinal, age-stratified, and biomarker-guided designs to determine whether PBMC-based immune monitoring can support individualized immunomodulatory strategies in sepsis.

Keywords: sepsis, peripheral blood mononuclear cells, PBMCs, immunopathogenesis, biomarkers, single-cell omics

Introduction

Sepsis is a life-threatening syndrome caused by a dysregulated host response to infection, leading to organ dysfunction and substantial mortality despite advances in antimicrobial and supportive care.[1] Its immune pathophysiology is not a simple linear transition from cytokine storm to immunosuppression. Instead, hyperinflammation and immune paralysis often coexist within the same patient and change over time, influencing tissue injury, pathogen clearance, secondary infection risk, and long-term outcomes.[2,3] Although clinical tools such as SOFA scoring, lactate, and procalcitonin remain useful for diagnosis and risk assessment, they do not directly capture the patient's evolving immune state.[4–6] This limitation has increased interest in immune-cell-based approaches that can reflect the biological heterogeneity of sepsis more directly.

Peripheral blood mononuclear cells (PBMCs)—including monocytes, T cells, B cells, natural killer cells, and related subsets—are well suited for this purpose. They are accessible through minimally invasive blood sampling and can be repeatedly assessed during disease progression, making them a practical window into systemic immune dynamics.[7,8] Among PBMCs, the monocyte-macrophage lineage is particularly important because it connects pathogen sensing, inflammatory mediator production, antigen presentation, metabolic adaptation, and later immune dysfunction. Key features such as reduced monocyte HLA-DR expression, altered monocyte subsets, lymphocyte exhaustion, and metabolic rewiring provide a framework for understanding why some patients recover after the acute phase whereas others

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develop persistent immunoparalysis, secondary infections, or chronic critical illness.[2,3] Although neutrophils and platelets also contribute to sepsis pathogenesis, comprehensive discussion of these cell types is beyond the scope of this review; they are considered here only where they interact with PBMC-centered immune mechanisms.[9–13] This review focuses on PBMC-centered immune remodeling in sepsis, with particular emphasis on monocyte/macrophage dysfunction, time-dependent immune trajectories, and translational biomarkers. We integrate evidence from single-cell and spatial omics, mechanistic studies of inflammatory and immunometabolic regulation, and clinical biomarker investigations. Rather than providing a broad overview of all sepsis-related immune pathways, we aim to clarify how PBMC analysis may improve understanding of sepsis immunopathogenesis, support immune phenotyping, and inform future strategies for diagnosis, risk stratification, and individualized immunomodulatory therapy.

Literature Search Strategy

Given the broad scope of sepsis immunology and the narrative nature of this review, we employed a hybrid search strategy combining systematic keyword search with purposive citation tracking.

Phase 1 - Core Identification: We conducted a PubMed search (2020–2025) using high-specificity keywords: ("sepsis"[MeSH]) AND ("PBMC" OR "single-cell RNA-seq" OR "immunometabolism" OR "HLA-DR"), restricted to high-impact (IF > 5) journals (eg, *Nature Medicine, Immunity, Intensive Care Medicine, Critical Care*). This yielded 84 highly relevant records.

Phase 2 - Snowballing: From seminal 2024–2025 publications identified in Phase 1 (eg, Scicluna et al's consensus transcriptomic framework; Hua et al's CD38high monocyte study; Monneret et al's 20-year cohort), we performed forward and backward citation tracking to capture mechanistic foundations (eg, Döcke et al, 1997) and latest derivatives.

Phase 3 - Targeted Updates: We conducted targeted searches for specific emerging concepts (eg, "TRAM sepsis", "ZIP8 ferroptosis", "4-OI immunometabolism") to ensure inclusion of cutting-edge mechanisms discussed in this review.

Phase 4 – Eligibility refinement and age-related evidence check. To address age-related differences, we performed targeted searches combining "sepsis" and "PBMC" with age-related terms including "neonate," "newborn," "preterm," "pediatric," "children," "older adults," "elderly," and "immunosenescence," together with "HLA-DR" and "immunoparalysis." Candidate records were then refined according to relevance to PBMC-centered mechanisms, support for the revised article scope, evidence type, and contribution to the central narrative. Studies focused mainly on non-PBMC mechanisms or broad sepsis management without direct relevance to the review focus were excluded or used only for contextual discussion.

Overall, Phase 1 identified 84 records and Phases 2–3 identified 78 additional records, yielding 162 candidate records. After Phase 4 screening, deduplication, and focus-based refinement, 127 references were retained in the final article. The final cited literature included original clinical, mechanistic, translational, biomarker, and interventional studies, with selected reviews, meta-analyses, and consensus papers used for background and synthesis.

The composition of the final cited literature is summarized in Supplementary Table S2 by article type, evidence type, and age-related focus. Because some studies combined clinical, translational, mechanistic, biomarker, or interventional components, categories were not mutually exclusive. The age-related evidence check showed that most PBMC-related evidence came from adult or mixed ICU cohorts or from studies without explicit age stratification, whereas neonatal, pediatric, and older-adult evidence remained limited. These findings informed our discussion of age-related generalizability and evidence gaps.

PBMC-Centered Immune Trajectories in Sepsis

Sepsis is often described as a transition from early hyperinflammation to later immunosuppression. However, these states are not strictly sequential or mutually exclusive. In many patients, inflammatory activation and immune paralysis coexist from the early phase and change in relative dominance over time.[2,3,14,15] This dynamic coexistence is central to understanding PBMC remodeling in sepsis. Rather than reflecting a single immune phenotype, PBMCs capture a moving spectrum of immune states that includes inflammatory monocyte activation, impaired antigen presentation, lymphocyte depletion, cellular exhaustion, and metabolic dysfunction.

Within PBMCs, the monocyte/macrophage lineage represents a major axis of sepsis-associated immune dysregulation. During the early response to infection, monocytes and macrophages contribute to pathogen recognition and inflammatory mediator production through NF-κB-dependent and related innate immune pathways.[16,17] As sepsis progresses, the same lineage may undergo functional reprogramming characterized by sustained HLA-DR downregulation, impaired antigen presentation, reduced cytokine-production capacity, and diminished antimicrobial competence.[2,14] Monneret et al demonstrated in a large cohort of patients with septic shock that decreased monocyte HLA-DR expression is a robust marker of immunoparalysis and is associated with secondary infections and mortality.[14] These findings support the view that monocyte dysfunction is not a peripheral phenomenon, but a central PBMC feature linking acute immune activation to later immune failure.

Adaptive immune dysfunction develops in parallel with myeloid reprogramming. Sepsis induces extensive lymphocyte apoptosis, and surviving effector T cells may acquire exhaustion phenotypes marked by checkpoint receptors such as PD-1 and TIGIT.[18–21] Preclinical studies suggest that blockade of exhaustion-associated pathways, including TIGIT, can restore aspects of T-cell function in polymicrobial sepsis models.[22] At the same time, immunosuppressive populations such as regulatory T cells and myeloid-derived suppressor cell-like populations may accumulate and further suppress lymphocyte proliferation and effector responses.[23–25] Together, these changes create a PBMC environment in which impaired antigen presentation, lymphocyte loss, and suppressive cellular states reinforce one another.

This PBMC-centered trajectory may help explain why some patients recover after the acute phase whereas others progress to prolonged immunoparalysis, secondary infection, or chronic critical illness. In patients with uncomplicated recovery, early immune suppression may be transient and resolve as pathogen burden and inflammatory stress decline. In contrast, patients with prolonged hospitalization may experience sustained antigenic stimulation, persistent tissue injury, metabolic exhaustion, lymphocyte depletion, and impaired monocyte antigen presentation. These overlapping processes can prevent restoration of immune homeostasis and contribute to persistent inflammation, immunosuppression, and catabolism syndrome. Thus, the clinically important question is not only whether inflammation or immunosuppression is present, but when each state dominates and whether PBMC function is recovering or deteriorating.

Pathogen type can further modify PBMC immune signatures, but it should be interpreted within this PBMC-centered framework rather than as a separate topic. Viral infections tend to induce interferon-stimulated gene programs through RIG-I-like receptors and endosomal Toll-like receptors, whereas bacterial sepsis more often shows prominent myeloid activation and inflammatory cytokine signaling through pathways such as TLR4–MyD88–NF-κB.[26–29] Single-cell and transcriptomic studies indicate that these pathogen-specific responses can generate distinguishable PBMC transcriptional patterns.[28] However, mixed infections and treatment exposure may blur these distinctions. Therefore, pathogen class should be considered as an important modifier of PBMC biomarkers and immune phenotypes, rather than as an independent organizing axis for this review.

Age is another major modifier of PBMC responses in sepsis. Preterm neonates may exhibit immature monocyte function and reduced HLA-DR expression, whereas pediatric patients can show rapid progression toward immunoparalysis with lymphocyte apoptosis and T-cell exhaustion.[30–32] Adult patients display substantial heterogeneity because of differences in comorbidities, infection source, and treatment exposure.[33] Older adults may have immunosenescence, thymic involution, reduced naive T-cell reserves, and baseline low-grade inflammation, all of which can alter the balance between inflammation and immune suppression.[34,35] These differences suggest that key PBMC features such as HLA-DR downregulation, lymphocyte exhaustion, metabolic rewiring, and immunoparalysis should not be assumed to occur uniformly across age groups.

Overall, PBMCs provide a practical and biologically informative window into the evolving immune trajectory of sepsis. The central issue is not whether individual inflammatory or suppressive pathways are present, but how PBMC states shift over time and across patient groups. The following section therefore examines the mechanisms that generate these PBMC immune-state transitions, including single-cell remodeling, upstream signaling circuits, regulated cell death, and immunometabolic reprogramming.

PBMC Immune-State Transitions and Mechanistic Reprogramming

The central mechanistic question is not simply which inflammatory pathways are activated during sepsis, but how these pathways reshape PBMC states over time. PBMCs, especially the monocyte/macrophage lineage, undergo dynamic transitions from early inflammatory activation to impaired antigen presentation, metabolic dysfunction, immune exhaustion, and late immunosuppression. Therefore, this section organizes mechanistic evidence around a temporal and functional sequence rather than a list of isolated pathways. We first summarize single-cell evidence for PBMC heterogeneity and immune-state transitions, then discuss upstream signaling circuits, downstream immune failure and cell death, and immunometabolic reprogramming as interconnected mechanisms that define PBMC-centered sepsis progression.

Single-Cell Evidence for Dynamic PBMC Remodeling

Single-cell RNA sequencing has substantially changed the understanding of sepsis-associated PBMC remodeling. Rather than representing a homogeneous immune compartment, PBMCs in sepsis contain shifting populations of inflammatory, regulatory, exhausted, and metabolically altered cells. Zhou et al used scRNA-seq to profile PBMCs from septic patients and healthy controls and identified seven major immune cell types and twelve monocyte subpopulations, including two sepsis-associated monocyte subsets that were markedly expanded in septic patients.[17,36] These findings support the view that sepsis is not defined by a single immune-cell abnormality, but by redistribution and functional remodeling of multiple PBMC subsets.

Among the newly identified myeloid populations, CD38high monocytes are particularly relevant because they link cellular phenotype with metabolic dysfunction. This subset shows increased expression of CD38, an NAD+-metabolizing ectoenzyme, and expands during early sepsis.[37] Because NAD+ availability influences immune-cell bioenergetics and inflammatory function, CD38high monocytes may reflect both early myeloid activation and metabolic stress. This population also has potential translational relevance as a diagnostic marker and as a possible therapeutic target, although its causal role in sepsis progression remains to be fully established.[37]

The value of single-cell analysis extends beyond the identification of discrete subpopulations. When combined with pseudotemporal trajectory analysis, single-cell data can reconstruct immune-state transitions during sepsis. Liu et al integrated transcriptomic and epigenetic information from a large single-cell dataset and proposed an "immunological clock" model of sepsis progression.[38] In this model, monocytes begin to transition toward macrophage-like states within the first 16–24 hours, CD8+ T-cell exhaustion becomes more prominent at approximately 36–48 hours, and HLA-DRlow immunosuppressive myeloid populations expand after 72 hours.[38] The TOX-associated exhaustion program and its epigenetic features are summarized in Figure 1, bottom panel, illustrating why the timing of checkpoint-directed immunomodulation may be critical. This temporal framework suggests that PBMC dysfunction evolves through recognizable transition points rather than through a simple binary shift from hyperinflammation to immunosuppression.

This trajectory-based interpretation is important for therapeutic timing. Interventions aimed at reducing excessive inflammatory signaling may be most relevant during early hyperactivation, whereas strategies designed to restore antigen presentation or reverse T-cell exhaustion are more likely to be useful after immunosuppressive features emerge. However, these pseudotemporal findings should be interpreted with caution. Many high-dimensional datasets are derived mainly from adult or mixed ICU cohorts, and age- or sex-stratified effects are not consistently reported. Therefore, future studies should clarify whether the same PBMC trajectories apply equally to neonates, children, adults, and older adults.

Myeloid-derived suppressor cells (MDSCs) should also be interpreted within this broader continuum of myeloid dysfunction. In sepsis, MDSC-like populations expand during emergency myelopoiesis and suppress T-cell responses through arginase-1 activity, reactive oxygen species, nitric oxide, IL-10, and TGF-β.[39–41] These cells are clinically relevant because their expansion has been associated with disease severity, secondary infection risk, and mortality. However, the phenotypic boundaries between MDSCs and dysfunctional monocytes remain uncertain. Monocytic MDSCs, commonly defined as CD14+HLA-DRlow cells, overlap substantially with sepsis-associated or exhausted monocyte states identified in single-cell studies.[42–45] This overlap raises an important unresolved question: whether MDSCs in human sepsis represent a distinct suppressor lineage or a heterogeneous collection of dysfunctional myeloid states.

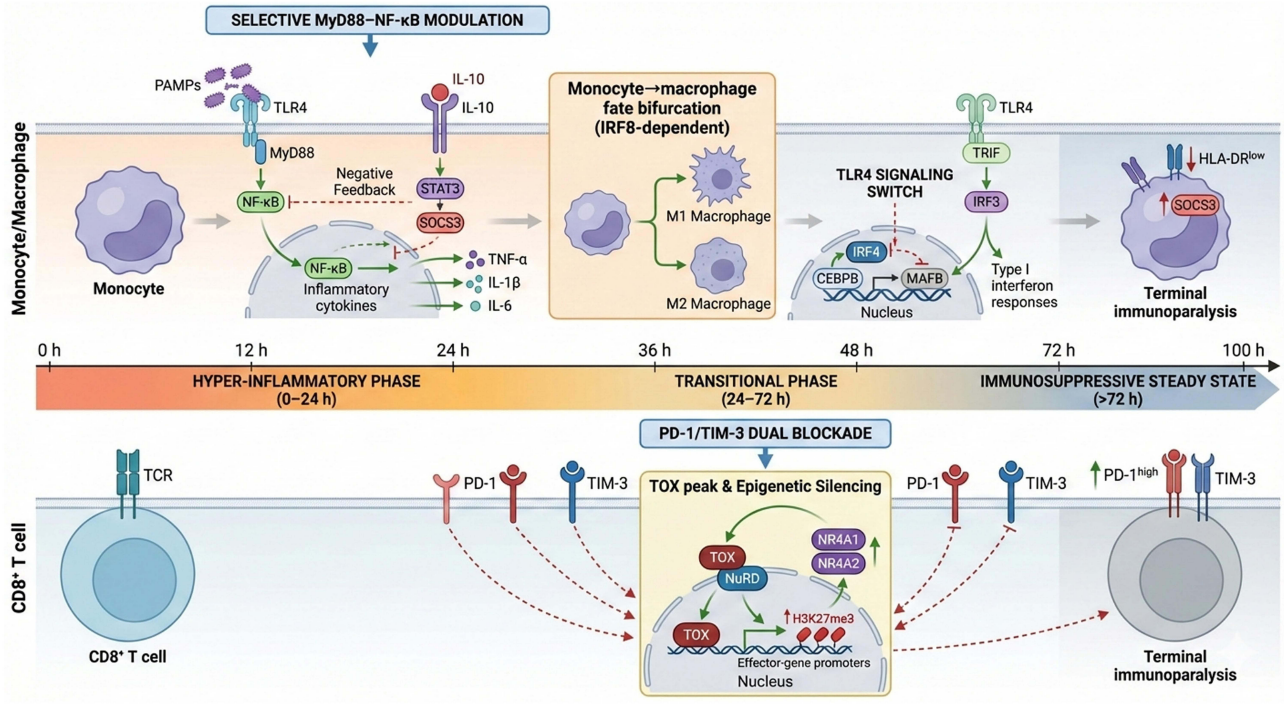

Figure 1 Time-resolved model of sepsis immune reprogramming. The timeline depicts three distinct phases: (Left) Early hyper-inflammatory phase (0–24 h): PAMPs engage TLR4, triggering MyD88-dependent NF-κB activation and cytokine production (TNF-α, IL-1β, IL-6), counterbalanced by IL-10–STAT3–SOCS3 negative feedback. (Center) Transitional phase (24–72 h): TLR4 signaling switches to TRIF-dependence, activating IRF3 and type I interferon responses; monocytes undergo IRF8-dependent fate bifurcation into M1/M2 macrophages; CD8 T cells initiate TOX-mediated epigenetic silencing (NuRD complex recruitment, H3K27me3 deposition) and upregulate PD-1/TIM-3. (Right) Late immunosuppressive steady state (>72 h): Predominance of HLA-DR SOCS3 exhausted monocytes and PD-1/TIM-3 T cells with terminal epigenetic silencing. Therapeutic interventions are phase-specific: selective MyD88–NF-κB modulation in early phase; PD-1/TIM-3 dual blockade in late phase. M2-like macrophages (anti-inflammatory) and exhausted macrophages (HLA-DR, functionally impaired) represent distinct late-phase states.

This distinction matters for therapy. If these cells are immature suppressor cells, differentiation-inducing strategies such as all-trans retinoic acid or vitamin D may help restore myeloid function,[46] If they instead represent terminally exhausted monocytes, differentiation therapy may be insufficient, and metabolic or epigenetic reprogramming may be required. Current uncertainty is compounded by the lack of standardized gating strategies and variable use of markers such as CD33, CD11b, and HLA-DR.[43,44,47] Single-cell multi-omics integrating transcriptomic and surface-protein information may help determine whether MDSCs are a discrete therapeutic target or part of a broader monocyte dysfunction spectrum.[48]

Taken together, single-cell and spatial omics support a trajectory-based model of PBMC remodeling in sepsis. Early inflammatory monocyte states may contribute to pathogen recognition and cytokine production, whereas persistent HLA-DRlow, metabolically impaired, or suppressive myeloid states may mark progression toward immunoparalysis, secondary infection risk, and prolonged critical illness. This interpretation provides the conceptual basis for linking cellular heterogeneity with upstream signaling, downstream immune failure, and therapeutic windows.

Upstream Sensing and Cytokine-Feedback Circuits in Monocyte Dysfunction

Monocyte dysfunction in sepsis begins with altered pathogen sensing and inflammatory signal transduction. During early infection, pathogen-associated molecular patterns and damage-associated molecular patterns activate Toll-like receptors and other pattern-recognition receptors on monocytes and macrophages. TLR engagement rapidly activates MyD88-dependent NF-κB signaling, promoting transcription of TNF-α, IL-1β, IL-6, and other inflammatory mediators[16,49] (Figure 2, upper left panel). This early NF-κB-dependent response, which is positioned within the early hyperinflammatory phase in Figure 1, top left, is necessary for pathogen containment, but excessive or sustained activation can amplify systemic inflammation, endothelial injury, and organ dysfunction.

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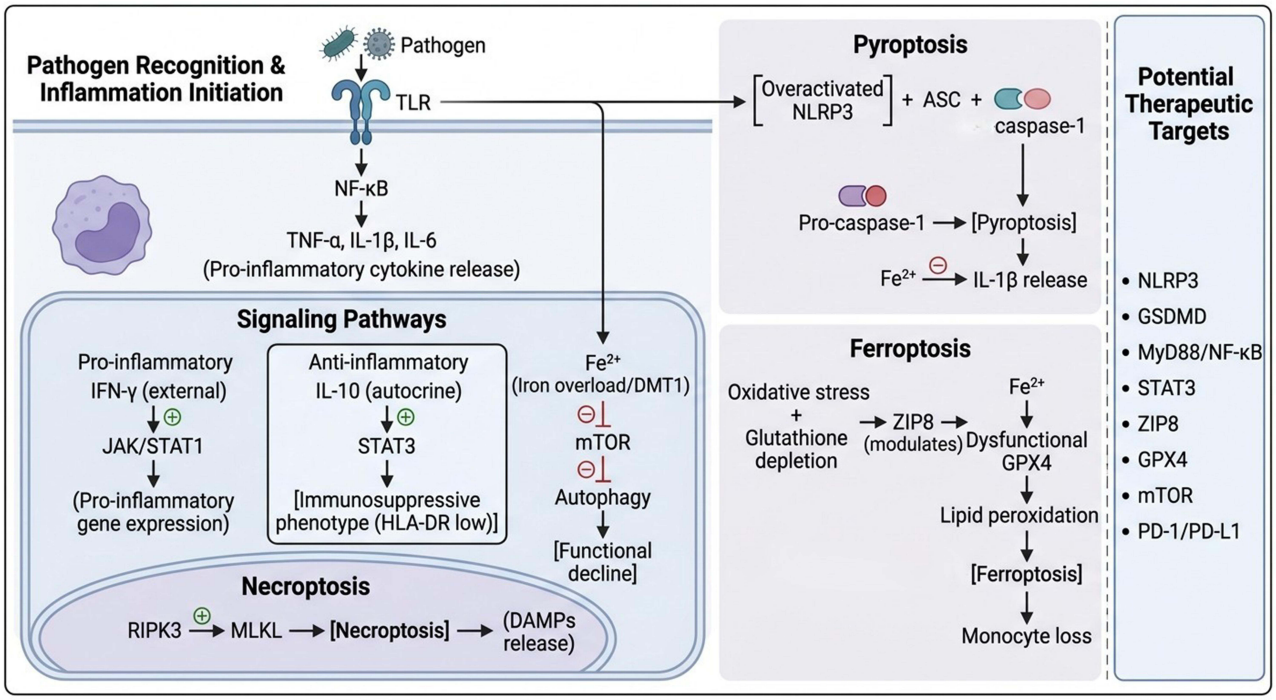

Figure 2 Key pathways driving monocyte dysfunction in sepsis. Schematic integration of pattern recognition signaling (upper left), dual JAK/STAT regulation (center), programmed cell death modalities (pyroptosis, necroptosis, ferroptosis), and metabolic perturbations (iron overload/mTOR inhibition). Right panel lists corresponding therapeutic targets discussed in the text. Upon pathogen recognition via TLRs, NF-κB is activated to produce pro-inflammatory cytokines (TNF-α, IL-1β, IL-6). Exogenous IFN-γ activates the JAK/STAT1 pathway (pro-inflammatory). In parallel, autocrine IL-10 activates STAT3 to induce an immunosuppressive phenotype characterized by low HLA-DR expression. Iron overload (Fe^{2+}) inhibits mTOR, thereby promoting autophagy and subsequent functional decline. The RIPK3-MLKL axis drives necroptosis with DAMPs release. Overactivated NLRP3 inflammasome triggers pyroptosis via caspase-1 activation (promoted by Fe^{2+}), releasing IL-1β. GPX4 dysfunction combined with lipid peroxidation induces ferroptosis, leading to monocyte loss. Potential therapeutic targets are listed.

The biological meaning of NF-κB activation depends strongly on timing. In the early phase of sepsis, excessive NF-κB activation contributes to cytokine storm and tissue injury. In later stages, however, many patients show impaired monocyte responsiveness and reduced cytokine-production capacity, indicating functional exhaustion rather than persistent activation.[50,51] Therefore, NF-κB should not be viewed simply as a harmful inflammatory pathway. Instead, it represents a phase-dependent regulatory node: excessive early activation may require restraint, whereas late immune paralysis may require restoration of monocyte responsiveness.

TLR4 adaptor specificity further shapes this transition. MyD88-dependent signaling mainly supports early NF-κB-driven inflammation, whereas TRAM-TRIF signaling links TLR4 activation to IRF3 activation and type I interferon responses. Recent studies have identified TRAM, encoded by TICAM2, as an important regulator of sepsis-associated monocyte exhaustion.[52,53] TRAM-deficient monocytes preserve HLA-DR expression, maintain cytokine-production capacity, and show improved bacterial clearance in experimental models.[52] Similarly, TICAM2 ablation facilitates post-septic monocyte recovery during the resolution phase.[53] These findings suggest that TLR adaptor usage may influence whether monocytes remain inflammatory, recover immune competence, or progress toward exhaustion.

Cytokine-feedback pathways provide another layer of regulation. JAK/STAT signaling mediates cytokine responses and exerts dichotomous effects during sepsis, as summarized in Figure 2, center panel.[21] IFN-γ-mediated STAT1 activation supports M1-like macrophage activation and enhances microbicidal function, whereas IL-10-mediated STAT3 activation promotes an immunosuppressive phenotype and is associated with reduced monocyte HLA-DR expression.[54–56] Thus, the JAK/STAT pathway functions as both an immune accelerator and an immune brake. This dual role helps explain why uniform pathway inhibition or stimulation may fail in unselected septic populations.

Negative-feedback circuits are especially relevant to the transition from acute inflammation to immunoparalysis. IL-10–STAT3–SOCS3 signaling can limit excessive inflammation, but persistent activation may impair antigen presentation, reduce inflammatory responsiveness, and promote HLA-DR downregulation.[57–59] In this context, immunosuppression is

not simply the absence of inflammation; rather, it reflects an actively regulated state shaped by cytokine feedback, adaptor signaling, and metabolic constraints. These mechanisms provide a bridge between early inflammatory activation and later monocyte dysfunction.

Downstream Consequences: Antigen-Presentation Failure, Immune Exhaustion, and Regulated Cell Death

The downstream consequence of dysregulated signaling is not only cytokine release, but progressive loss of immune competence. One of the most clinically relevant features of this process is monocyte HLA-DR downregulation. HLA-DR is required for antigen presentation to CD4+ T cells, and sustained reduction of monocyte HLA-DR reflects impaired antigen-presenting capacity. A large 20-year cohort study including 1023 patients with septic shock confirmed that reduced monocyte HLA-DR expression is a robust marker of immunoparalysis and is associated with secondary infections and mortality.[14] HLA-DRlow monocytes therefore represent a functional state that links innate immune dysfunction to impaired adaptive immune activation. IRF8, a master transcription factor for myeloid differentiation, undergoes progressive downregulation during this transitional phase. Loss of IRF8 impairs monocyte-to-dendritic cell differentiation and reduces antigen-presentation capacity, contributing to the HLA-DRlow immunosuppressive state depicted in Figure 1, transitional phase.

Adaptive immune exhaustion develops in parallel with myeloid dysfunction. During sepsis, extensive lymphocyte apoptosis reduces the pool of functional T and B cells, while surviving effector T cells often express exhaustion-associated checkpoint receptors such as PD-1 and TIGIT.[18–21] Experimental studies suggest that TIGIT blockade can restore CD4+ T-cell function in polymicrobial sepsis models.[22] However, the reversibility of T-cell exhaustion likely depends on timing. Once exhaustion-associated transcriptional and epigenetic programs become established, checkpoint blockade may be less effective. At the chromatin level, this involves NuRD complex recruitment to immune-activation gene loci and concurrent H3K27me3 deposition, which establish a repressive epigenetic state that constrains T-cell responsiveness (Figure 1, transitional phase). This epigenetic constraint helps explain why checkpoint blockade may be insufficient once exhaustion programs are fully consolidated. This reinforces the need to interpret lymphocyte exhaustion as a time-dependent immune state rather than a static therapeutic target.

Regulated cell death pathways contribute to both inflammatory injury and immune-cell loss. NLRP3 inflammasome activation promotes caspase-1-mediated GSDMD cleavage, pore formation, pyroptosis, and release of IL-1β and IL-18[60–62] (Figure 2, upper right panel). During early infection, this pathway can support pathogen clearance and amplify innate immune activation. When excessive, however, NLRP3-driven pyroptosis contributes to cytokine release, monocyte/macrophage loss, and tissue injury. Preclinical studies show that inhibition of NLRP3 or its downstream effector GSDMD can attenuate inflammatory responses and improve survival in sepsis models.[61,63–66] These findings support the NLRP3–pyroptosis axis as a potential therapeutic target, but its phase-dependent role must be considered.

Other forms of regulated cell death also shape PBMC dysfunction. Apoptosis contributes to lymphocyte depletion and adaptive immunosuppression, whereas necroptosis, mediated by RIPK3–MLKL signaling, promotes DAMP release and inflammatory tissue injury.[67,68] PANoptosis integrates pyroptotic, apoptotic, and necroptotic programs and may provide a broader framework for understanding inflammatory cell death during severe infection.[67] These overlapping death pathways suggest that immune-cell loss in sepsis is not caused by a single mechanism, but by convergent inflammatory, metabolic, and death-signaling stress.

Ferroptosis has recently emerged as another relevant mechanism, particularly in monocytes and macrophages. Sepsis-associated oxidative stress, glutathione depletion, and GPX4 dysfunction can increase lipid peroxidation and promote ferroptotic cell death.[67,69] ZIP8 has been identified as an upstream regulator of monocytic ferroptosis, and ZIP8 overexpression may exacerbate iron influx, lipid peroxidation, monocyte loss, and organ injury.[65] In experimental models, ZIP8 suppression or ferroptosis inhibition using reduced glutathione or ferrostatin-1 can attenuate monocyte loss and improve survival.[65] Beyond ferroptosis, elevated intracellular Fe^{2+} may also promote caspase-1 activation, linking iron dysregulation to pyroptotic cell death, and has been proposed to inhibit mTOR signaling, contributing to autophagy dysregulation in septic monocytes (Figure 2).[65]

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Despite these promising findings, ferroptosis-targeted therapy requires caution. Ferroptosis-related iron restriction may contribute to host defense against intracellular pathogens, and systemic ferroptosis suppression could theoretically create an iron-replete environment that favors microbial persistence.[70] In addition, ferroptosis may have cell type–specific effects: monocyte preservation may be beneficial, whereas endothelial ferroptosis can contribute to capillary leak and organ dysfunction.[71] Therefore, regulated cell death should be understood as a downstream consequence of dysregulated inflammation and metabolic stress, not as a set of isolated targets. Effective therapeutic modulation will likely require phase-specific and cell type–specific strategies.

Immunometabolic Reprogramming in Sepsis

Metabolic rewiring provides a mechanistic bridge between early inflammation and later immunoparalysis. During acute sepsis, monocytes and macrophages shift from oxidative phosphorylation toward aerobic glycolysis to rapidly generate ATP and biosynthetic intermediates needed for inflammatory activation[57,72] (Figure 3, early phase). This Warburg-like response supports cytokine production and antimicrobial activity. PKM2 (pyruvate kinase M2) is a central driver of this metabolic shift: its nuclear translocation promotes HIF-1α-dependent transcription of glycolytic enzymes and pro-inflammatory mediators including HMGB1, directly coupling metabolic reprogramming to inflammatory gene expression (Figure 3, early phase).[57,72] Metabolites such as lactate and succinate can further shape inflammatory transcriptional programs; succinate, for example, stabilizes HIF-1α and sustains inflammatory gene expression.[58]

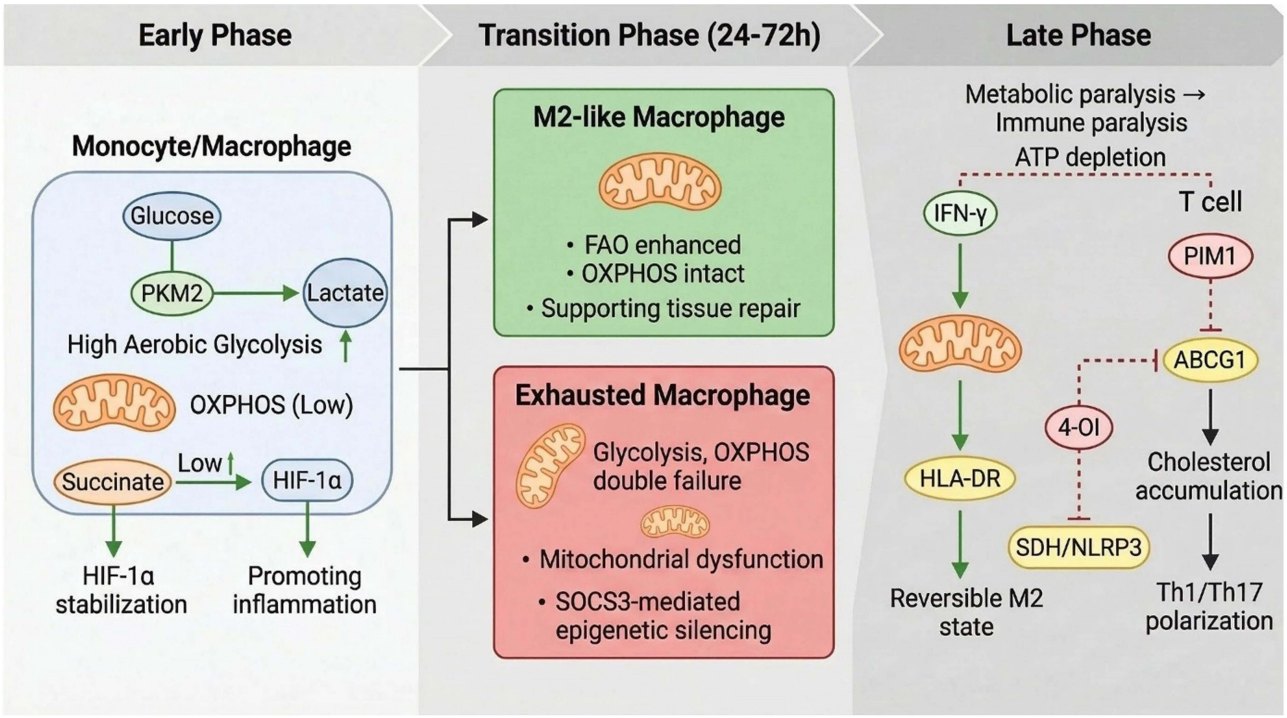

Figure 3 Temporal dynamics of immunometabolic remodeling in sepsis progression. Schematic illustration of metabolic reprogramming and functional transitions in immune cells across three distinct phases of sepsis. (Left) Early Phase (0–24h): Innate immune cells (monocytes/macrophages) undergo a Warburg-like metabolic switch characterized by PKM2-driven aerobic glycolysis, resulting in lactate accumulation and inflammatory gene expression. Mitochondrial succinate accumulates (despite low oxygen tension), stabilizing HIF-1α and promoting pro-inflammatory responses. Concurrently, $CD4^+$ T cells exhibit PIM1 overexpression and ABCG1 downregulation, leading to intracellular cholesterol accumulation that favors Th1/Th17 polarization over regulatory T cell (Treg) differentiation. Itaconate (and its derivative 4-OI) provides negative feedback by inhibiting SDH and the NLRP3 inflammasome. (Middle) Transition Phase (24–72h): Bifurcation of macrophage fates occurs. (Upper track) Repair-oriented M2-like macrophages maintain intact OXPHOS and enhanced fatty acid oxidation (FAO), supporting tissue repair. (Lower track) Exhausted macrophages exhibit "double failure" of both glycolysis and OXPHOS, accompanied by mitochondrial dysfunction and SOCS3-mediated epigenetic silencing, marking the onset of metabolic paralysis. (Right) Late Phase (Immunoparalysis): Profound ATP depletion and ROS accumulation drive metabolic and immune paralysis. Innate immune cells display downregulated HLA-DR expression (a clinical marker of immunosuppression) and disrupted membrane lipid rafts due to cholesterol depletion, impairing TLR signaling efficiency. Adaptive immune cells enter an exhausted state with altered metabolic dependencies. Dashed arrows indicate therapeutic intervention points or functional consequences; blunt-ended red lines indicate inhibitory actions.

However, prolonged inflammatory stress can drive immune cells from metabolic activation into metabolic paralysis. In this state, both glycolysis and oxidative phosphorylation become impaired, mitochondrial function declines, ATP production falls, and monocytes lose the bioenergetic capacity required for phagocytosis, cytokine production, and antigen presentation.[2,59,72,73] This process helps explain why some patients progress from early inflammatory activation to persistent immunoparalysis, secondary infection risk, and chronic critical illness. Metabolic failure is therefore not merely a consequence of severe sepsis; it is a central mechanism linking PBMC dysfunction with clinical deterioration.

Mitochondrial dysfunction is particularly important in this transition. Damaged mitochondria impair ATP-dependent immune functions and increase reactive oxygen species production.[74] In monocytes, mitochondrial dysfunction may contribute directly to HLA-DR downregulation and defective antigen presentation.[35] It may also affect the surrounding immune environment by altering metabolite availability and limiting the ability of effector T cells to sustain activation.[75] Thus, PBMC mitochondrial dysfunction can suppress immunity through both cell-intrinsic and cell-extrinsic mechanisms.

It is useful to distinguish repair-oriented M2-like macrophage states from terminally exhausted macrophage states. M2-like macrophages rely more on fatty acid oxidation and retain oxidative phosphorylation capacity, supporting tissue repair and resolution of inflammation.[76] In contrast, exhausted macrophages show simultaneous glycolytic and mitochondrial failure, ATP depletion, reduced HLA-DR expression, and impaired functional recovery.[59,73] This distinction has therapeutic implications. M2-like macrophages may retain enough metabolic plasticity to be repolarized by immunostimulatory signals such as IFN-γ, whereas terminally exhausted macrophages may require deeper metabolic or epigenetic reprogramming.[77,78] This metabolic bifurcation between repair-oriented M2-like macrophages and metabolically exhausted macrophages is summarized in Figure 3, transition phase.

mTOR and autophagy also regulate PBMC metabolic fitness. mTOR integrates nutrient availability, growth signals, and immune activation, while autophagy helps remove damaged organelles and maintain cellular homeostasis.[79,80] In sepsis, excessive mTOR activity can suppress autophagy and contribute to immune-cell dysfunction. This mechanism may be particularly relevant in older patients, in whom defective autophagy–lysosomal function and mTOR hyperactivation in CD4+ T cells have been linked to impaired immunity and poor outcomes.[81] Therefore, mTOR-autophagy balance may influence whether PBMCs recover function or remain metabolically impaired.

Lipid metabolism further modifies immune-cell function. Hypocholesterolemia is common in sepsis and has been associated with poor prognosis.[82,83] At the cellular level, cholesterol affects membrane architecture, lipid raft formation, and TLR signaling. Both cholesterol depletion and overload can disrupt immune signaling, indicating that cholesterol homeostasis is required for balanced monocyte activation.[83] In T cells, the PIM1–ABCG1 axis regulates cholesterol efflux and influences Th1/Th17 and regulatory T-cell balance[19] (Figure 3, late phase). These findings suggest that lipid metabolism may shape both innate and adaptive PBMC responses during sepsis.

Amino-acid metabolism also contributes to PBMC dysfunction and biomarker development. Glutamine supports immune-cell proliferation and biosynthesis, and altered glutamine metabolism has been linked to sepsis susceptibility and immunoparalysis-associated gene signatures, including SRSF7, RAB13, E2F2, and S100A8.[84–86] Arginine metabolism regulates nitric oxide production, vascular tone, and antimicrobial function; dysregulated arginase activity in monocytes and macrophages may contribute to impaired pathogen clearance and immunosuppression.[87,88]

Tryptophan metabolism, including kynurenine-related pathways and CYP1B1 activity, may further influence monocyte inflammation and migration.[85]

Finally, metabolites can act as direct immunoregulatory signals. Succinate promotes HIF-1α-mediated inflammation, whereas itaconate provides negative feedback by limiting inflammatory activation. The itaconate derivative 4-octyl itaconate inhibits succinate dehydrogenase, suppresses NLRP3 activation, and improves survival in experimental sepsis models[89] (Figure 3, late phase). These findings support the concept that metabolic interventions may modulate immune function without globally suppressing host defense. However, clinical translation will require careful patient selection, timing, and validation of immune-state biomarkers.

Mechanistic Synthesis: PBMC States Define Therapeutic Windows

The mechanisms discussed above converge on a trajectory-based model of PBMC dysfunction in sepsis. Early monocyte activation is driven by pathogen sensing, TLR–NF-κB signaling, cytokine production, and glycolytic reprogramming. As

inflammation persists, cytokine-feedback pathways, TRAM-TRIF signaling, mitochondrial dysfunction, impaired autophagy, and metabolic exhaustion contribute to HLA-DR downregulation and antigen-presentation failure. In parallel, lymphocyte apoptosis, checkpoint-associated T-cell exhaustion, and regulated cell death pathways further weaken host immune competence.

This model has two important implications. First, PBMC mechanisms must be interpreted temporally. The same pathway may be protective in one phase but harmful in another. Early NF-κB or NLRP3 activation may support pathogen clearance, whereas sustained activation may contribute to tissue injury and immune-cell loss. Conversely, immune stimulation may be harmful during uncontrolled hyperinflammation but beneficial when immunoparalysis dominates. Second, PBMC-based biomarkers should be viewed not as isolated diagnostic markers, but as readouts of immune-state transitions. HLA-DR expression, monocyte subsets, exhaustion markers, metabolic signatures, and functional immune assays may help identify where a patient lies along the sepsis immune trajectory.

This mechanistic framework provides the rationale for the following translational section. If PBMC states define disease phase and immune competence, then clinically useful biomarkers should be evaluated according to their timing, target population, biological meaning, and ability to guide immunomodulatory therapy.

PBMC-Based Biomarkers, Therapeutic Windows, and Clinical Translation

PBMC-based biomarkers provide the translational link between mechanistic immune trajectories and clinical decision-making. Because sepsis immune states change over time, PBMC-derived biomarkers should not be evaluated only as static diagnostic indicators. Instead, they should be interpreted according to three clinically relevant questions: what immune state they reflect, when they are measured, and whether they can guide treatment decisions. In this section, we organize PBMC-derived biomarkers by clinical purpose—early diagnosis, prognostic stratification, functional immune assessment, and therapeutic guidance—rather than by molecular platform alone. This organization links the mechanistic transitions described in PBMC Immune-State Transitions and Mechanistic Reprogramming to clinically usable immune phenotypes.

Conventional screening tools such as SOFA, qSOFA, NEWS, lactate, C-reactive protein, and procalcitonin remain useful for early recognition and risk assessment, but they do not directly define the patient's immune state.[4–6,90] PBMC-based biomarkers may fill this gap by capturing dynamic changes in monocyte activation, antigen-presentation capacity, lymphocyte exhaustion, metabolic stress, and functional immune responsiveness. These biomarkers are summarized in Table 1 according to their biological meaning, clinical use, sampling window, study population, predictive performance, and major limitations.

Table 1 Overview of PBMC-Related Biomarkers in Sepsis

Clinical Application Tier	Biomarker Category	Representative Biomarker (as Described)	Key Findings/Thresholds (as Described)	Translational Maturity*
Diagnosis/early identification	Cellular phenotype/ subset	$CD38^{high}$ monocyte subset[37]	Markedly expanded early after onset; increased proportion may serve as an early cytologic biomarker.[37]	Exploratory
Diagnosis/early identification	Hematology parameter	MDW (monocyte distribution width) ↑[11,79]	Significantly elevated early; retains screening utility across different immune backgrounds (eg, sepsis with HIV co-infection); reported AUC > 0.8.[11,79]	Validated
Diagnosis/early identification	Gene-expression signature	Glutamine-metabolism–related gene set: SRSF7 ↓, RAB13/E2F2/S100A8 ↑[7]	Aberrantly expressed in PBMC; proposed as a multi-gene RT-qPCR panel for assisted diagnosis/risk stratification.[7]	Validated (RT-qPCR confirmed)

(*Continued*)

Table 1 (Continued).

Clinical Application Tier	Biomarker Category	Representative Biomarker (as Described)	Key Findings/Thresholds (as Described)	Translational Maturity*
Prognosis/risk stratification	Gene-expression signature	8-gene lactylation-related model (eg, CD160, ING4, PPP1R15A)[4]	Predicts 7-, 14-, and 28-day survival (AUC ≈ 0.80); effectiveness validated in a prospective clinical cohort.[4]	Prospective
Prognosis/risk stratification	Cellular phenotype/ routine monitoring	Low monocyte HLA-DR expression (eg, < 8000 AB/C)[3,14]	Persistent low expression indicates immunoparalysis; in a 1023-patient cohort, ICU-entry HLA-DR < 8000 AB/C was associated with higher 28-/90-day mortality and more ICU-acquired infections.[14]	Validated (large cohort)/partial clinical use
Prognosis/risk stratification	Lymphocyte subsets	Reduced early memory B cells[50]	Associated with poor outcomes; prospective study suggests independent prediction of 28-day mortality.[50]	Prospective
Prognosis/risk stratification	Exhaustion phenotype	PD-1^{+} NK-cell proportion ↑[10]	Higher proportion associated with increased 28-day mortality, indicating prognostic relevance of NK-cell exhaustion.[10]	Validated (associative study)
Prognosis/risk stratification	Simple ratio index	NLR (neutrophil-to-lymphocyte ratio) ↑[51]	Meta-analysis of 36 studies: elevated NLR is significantly associated with mortality risk and may serve as an independent prognostic factor.[51]	Validated (meta-analysis)
Prognosis/risk stratification	Non-coding RNA	miR-146b-5p[52]	Correlates with T- and B-cell counts; lower levels associated with higher mortality; provides some predictive value for 28-day survival.[52]	Exploratory/ validated (single clinical association study)
Prognosis/risk stratification	Metabolic/ biochemical	Persistently high lactate/poor lactate clearance[56]	Persistent hyperlactatemia suggests adverse metabolic status and may coincide with immunosuppression; poor lactate clearance often corresponds to sustained immunoparalysis.[56]	Clinical use (routine marker; immune interpretation is suggestive)
Prognosis/risk stratification	Metabolic/ biochemical	Low cholesterol ↓ (may be interpreted with ABCG1/PIM1)[19]	Repeatedly reported as an adverse prognostic factor; combining ABCG1/PIM1 testing may help distinguish causes of hypocholesterolemia and better reflect immunometabolic status.[19]	Validated (prognostic association)
Prognosis/risk stratification	Metabolic/ biochemical	Glutamine depletion/related metabolites[7]	Glutamine depletion suggests reduced biosynthetic capacity of immune cells and may indicate host immunonutritional deficiency.[7]	Exploratory/ validated
Prognosis/risk stratification	Non-coding RNA (mentioned as supplementary)	lncRNA HOTAIR[57,58]	Upregulated in models and promotes cytokine release; high expression is hypothesized to be associated with poor prognosis.[57,58]	Exploratory
Treatment-response prediction/immune-intervention decision support	Cellular phenotype/ enrichment	Low monocyte HLA-DR expression[3,14]	Used to guide patient selection for immunostimulatory therapy (enrichment for immunosuppressed patients).[14]	Partial clinical use

(*Continued*)

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Table 1 (Continued).

Clinical Application Tier	Biomarker Category	Representative Biomarker (as Described)	Key Findings/Thresholds (as Described)	Translational Maturity*
Treatment-response prediction/immune-intervention decision support	Immune functional assay	Whole-blood LPS stimulation → monocyte TNF-α production capacity[80]	Quantifies the degree of immunoparalysis and correlates with risk of secondary infection.[80]	Validated (functional readout)
Treatment-response prediction/immune-intervention decision support	Immune functional assay	NLRP3 inflammasome activation/subgroup with insufficient IL-1β production[67,81]	Patients whose monocytes are difficult to activate ex vivo to produce IL-1β show substantially increased risk of severe reinfection after discharge; proposed for discharge assessment to identify low responders.[67,81]	Validated → translational recommendation
Treatment-response prediction/immune-intervention decision support	Composite score/multi-marker	Surface functional molecules (PD-1, HLA-DR, integrins, etc.) and integrated immune functional scores[68,69]	Integrating multiple functional assays better discriminates high-risk subgroups and supports immune-intervention decision-making.[68,69]	Exploratory/ validated (scoring system)

Notes: Translational maturity: Exploratory = preliminary association/mechanistic signal; Validated = large cohorts/meta-analyses or replicated validation; Prospective = explicitly validated in prospective cohorts; Clinical use = explicitly described as used for clinical monitoring or therapeutic decision-making.

From PBMC Immune Trajectories to Biomarker Categories

The biomarker value of PBMCs arises from their ability to reflect different stages of the sepsis immune trajectory. Early in sepsis, markers of myeloid activation and cellular heterogeneity may support diagnosis and early risk stratification. During the transition phase, markers of HLA-DR downregulation, lymphocyte exhaustion, and metabolic dysfunction may identify patients at risk of persistent immunoparalysis. In later or clinically stable phases, functional assays may be more informative because they directly test whether immune cells can respond to stimulation.

This temporal logic is important because the same biomarker may have different meanings depending on when it is measured. For example, early monocyte activation may indicate an appropriate antimicrobial response, whereas persistent HLA-DR downregulation at 48–72 hours may indicate impaired antigen presentation and increased risk of secondary infection. Similarly, metabolic indicators such as lactate, glutamine-related signatures, or cholesterol disturbance should be interpreted in relation to the immunometabolic transitions summarized in Figure 3, rather than as isolated biochemical abnormalities. Therefore, PBMC-based biomarker translation requires integration of biological mechanism, sampling time, and clinical context.

Multi-omics technologies have expanded the range of candidate PBMC biomarkers. Transcriptomics captures dynamic gene-expression programs and is useful for mechanistic discovery and prognostic stratification.[91–94] Proteomics provides information closer to functional protein abundance and druggable pathways.[95,96] Metabolomics offers immediate functional readouts of immune-cell metabolic status and may support subphenotyping when combined with machine learning.[97,98] However, each platform has limitations in turnaround time, cost, analytical complexity, and reproducibility. For near-term clinical use, the most promising approach may combine a small number of robust cellular, molecular, metabolic, and functional indicators rather than rely on a single high-dimensional assay.

Diagnostic Biomarkers of Early PBMC Activation

Diagnostic PBMC biomarkers are most useful when they identify early immune activation before clinical deterioration becomes irreversible or before treatment obscures immune signatures. Among cellular biomarkers, CD38high monocytes are particularly relevant because they connect early myeloid activation with NAD+-linked metabolic stress. Hua et al reported that this subset expands rapidly during early sepsis, with samples collected within 0–24 hours after onset and before empirical antibiotic administration.[37] The diagnostic performance of CD38high monocytes was stronger than that

of conventional inflammatory markers in this cohort, suggesting that monocyte-state markers may improve early discrimination between sepsis and non-septic inflammation.[37] This early activation state is consistent with the temporal PBMC trajectory summarized in Figure 1.

Monocyte distribution width (MDW) represents another clinically attractive diagnostic marker because it can be derived from routine complete blood count analysis. MDW reflects heterogeneity in monocyte cell volume, which may increase during early inflammatory activation. Studies have shown that MDW is elevated in early sepsis compared with non-septic infection and healthy controls.[99] Sun et al further validated MDW in HIV-infected patients with sepsis co-infection, reporting favorable diagnostic performance when samples were obtained immediately upon emergency department admission.[100] Because MDW is inexpensive, rapid, and widely available, it may be useful as a first-line screening biomarker, particularly when combined with more specific PBMC phenotyping.

Transcriptomic signatures also show diagnostic and prognostic potential. High-throughput transcriptomics combined with machine learning has identified gene-expression models that stratify sepsis risk and outcome. For example, Li et al developed a prognostic model based on lactylation-related genes, including CD160, ING4, and PPP1R15A, using whole-blood RNA samples obtained within 6 hours of ICU admission.[75] This model showed good discrimination for 14-day and 28-day mortality and illustrates how metabolic dysregulation can be translated into RNA-based risk stratification.[75] Similarly, glutamine metabolism–associated genes, including SRSF7, RAB13, E2F2, and S100A8, have been identified in septic PBMCs and may be developed into targeted qPCR panels for diagnostic or prognostic use.[86]

Despite their promise, early diagnostic biomarkers face several limitations. First, early sepsis is biologically heterogeneous, and diagnostic signatures may differ by infection source, pathogen class, age group, comorbidity, and treatment exposure. Second, many transcriptomic assays remain too slow or technically demanding for urgent bedside decisions. Third, most biomarkers require prospective validation in diverse cohorts before they can be incorporated into clinical workflows. Therefore, early diagnostic PBMC biomarkers should be viewed as complementary tools that refine, rather than replace, clinical assessment and conventional sepsis screening.

Prognostic Biomarkers of Immunoparalysis and Adverse Outcomes

Prognostic PBMC biomarkers are most valuable when they identify persistent or worsening immune dysfunction rather than a single inflammatory snapshot. Monocyte HLA-DR remains the most established marker in this category. Because HLA-DR is required for antigen presentation, sustained reduction of monocyte HLA-DR reflects impaired antigen-presenting capacity and is commonly interpreted as a marker of immunoparalysis. A large cohort study by Monneret et al including 1023 patients with septic shock showed that low monocyte HLA-DR expression was associated with mortality and ICU-acquired infections.[14] This supports the use of HLA-DR as both a prognostic biomarker and an enrichment marker for immunostimulatory strategies.

The timing of HLA-DR measurement is critical. A single early low value may reflect transient immune suppression during acute stress, whereas persistent reduction at 48–72 hours or beyond may identify patients at higher risk of secondary infection and prolonged critical illness. This distinction helps explain why PBMC monitoring should be dynamic. Repeated HLA-DR assessment may better capture whether a patient is recovering immune competence or progressing toward persistent immunoparalysis.

Lymphocyte-based biomarkers provide complementary prognostic information. Sepsis is associated with lymphocyte apoptosis, T-cell exhaustion, and altered B-cell and NK-cell compartments. Sun et al reported that reduced memory B-cell proportions on ICU day 1 were associated with increased 28-day mortality.[101] Tang et al showed that elevated PD-1+ NK-cell proportions at 48–72 hours predicted 28-day mortality, supporting the relevance of NK-cell exhaustion as a prognostic indicator.[102] These markers suggest that adverse outcomes are not driven solely by myeloid dysfunction, but also by impaired adaptive and innate lymphocyte responses.

Simple blood-count-derived indices may also contribute to prognostic stratification. The neutrophil-to-lymphocyte ratio (NLR) is not PBMC-specific, but it reflects the balance between innate inflammatory activation and lymphocyte depletion. A recent meta-analysis showed that elevated NLR within 48 hours of admission was associated with mortality, and dynamic increases in NLR improved predictive performance compared with single-point measurement.[103] Because

NLR is inexpensive and widely available, it may be useful as a low-cost screening marker when interpreted alongside PBMC-specific indicators such as HLA-DR and lymphocyte exhaustion markers.

Non-coding RNAs may further refine prognostic assessment. miR-146b-5p has been associated with lymphocyte subset counts and 28-day mortality in sepsis.[104] Mechanistically, the miR-146 family is involved in negative feedback regulation of TLR/NF-κB signaling, suggesting that circulating miRNA levels may reflect the balance between inflammatory activation and immune regulation.[105] Long non-coding RNAs such as HOTAIR have also been implicated in inflammatory regulation in experimental sepsis models.[106,107] However, non-coding RNA biomarkers remain less mature than cellular markers such as HLA-DR, and their clinical utility will require further standardization and validation.

Overall, prognostic PBMC biomarkers are strongest when interpreted as dynamic indicators of immune trajectory. Persistent HLA-DR downregulation, lymphocyte exhaustion, memory B-cell depletion, elevated PD-1+ NK-cell proportions, and worsening NLR may together identify patients who are failing to restore immune competence. These biomarkers may be particularly important for identifying patients at risk of secondary infection, prolonged ICU stay, and chronic critical illness.

Functional Biomarkers of Immune Competence

Functional biomarkers may be closer to clinical decision-making than static molecular measurements because they test whether PBMCs can still respond to immune stimulation. Static markers such as HLA-DR expression or gene-expression signatures infer immune status, whereas functional assays directly measure immune-cell capacity. This distinction is important because two patients with similar biomarker concentrations may differ substantially in their ability to produce cytokines, activate inflammasomes, or respond to immunostimulatory therapy.

Whole-blood lipopolysaccharide (LPS) stimulation assays are among the most widely discussed functional tests. These assays measure monocyte TNF-α release after ex vivo stimulation and are typically performed after initial hemodynamic stabilization, often around ICU days 3–5.[108] Reduced TNF-α production suggests impaired monocyte responsiveness and may identify patients with clinically relevant immunoparalysis. This type of assay is particularly useful because it evaluates immune reserve rather than baseline inflammation alone.

Inflammasome function provides another functional readout. PBMC NLRP3 activation assays measure IL-1β release after ex vivo stimulation and may identify patients with impaired inflammasome responsiveness before discharge or during recovery.[109,110] Patients with low IL-1β production after stimulation have been reported to be at increased risk of reinfection and readmission.[109,110] The mechanistic basis of this assay is linked to the NLRP3–caspase-1–GSDMD pyroptosis axis summarized in Figure 2. Therefore, NLRP3 functional testing may help identify a "cryptic immunosuppression" phenotype that is not captured by conventional inflammatory biomarkers.

Other functional or semi-functional indicators include checkpoint receptor expression, integrin expression, cytokine-production capacity, and composite immune-function scores.[111,112] These multidimensional scores may outperform single biomarkers because they integrate myeloid function, lymphocyte exhaustion, and inflammatory responsiveness. However, clinical implementation remains challenging. Functional assays require standardized stimulation protocols, rapid processing, defined thresholds, and prospective evidence that assay-guided interventions improve outcomes.

A practical translational strategy may involve stepwise immune assessment. Rapid and inexpensive markers such as MDW and NLR could be used for initial screening. Flow-cytometric markers such as monocyte HLA-DR, CD38high monocytes, and exhausted lymphocyte subsets could then refine immune phenotyping. Finally, functional assays such as LPS-induced TNF-α release or NLRP3-induced IL-1β production could identify patients who may benefit from immunostimulatory or immune-restorative therapies. This layered approach may be more feasible than routine comprehensive omics for all patients.

Biomarker-Guided Therapeutic Windows and Interventional Evidence

The major clinical implication of PBMC-based immune monitoring is that immunomodulatory therapy should be matched to immune state and timing. These biomarker categories should be interpreted within the temporal immune trajectory summarized in Figure 1. Early inflammatory activation may justify selective suppression of tissue-damaging pathways, whereas

persistent HLA-DR downregulation, lymphocyte exhaustion, or impaired functional responses may support immunostimulatory approaches. This temporal principle explains why non-stratified sepsis immunotherapy has often failed.

Several failed trials illustrate the problem of treating sepsis as a uniform syndrome. Trials of recombinant human activated protein C, eritoran, and broad anti-inflammatory interventions failed to demonstrate consistent benefit in unselected sepsis populations.[113] Large phase 3 trials of anakinra in the 1990s also failed to show overall survival benefit when patients were not selected by immune phenotype.[114,115] These negative results do not necessarily invalidate immunomodulation; rather, they show that the direction and timing of immune intervention matter. A therapy designed to suppress inflammation may be harmful or ineffective in patients who are already immunoparalyzed, whereas immunostimulation may be inappropriate during uncontrolled hyperinflammation.

More recent phenotype-guided studies support a different model. Post-hoc analyses of anakinra trials suggested that IL-1 blockade may benefit patients with macrophage activation syndrome features, including marked hyperferritinemia.[115] The PROVIDE trial further supported phenotype-guided anti-inflammatory therapy by using ferritin-based enrichment to identify patients with a macrophage activation phenotype.[116] In contrast, the ImmunoSep trial used immune markers such as monocyte HLA-DR and ferritin to guide immunostimulatory therapy; recombinant IFN-γ improved organ function in patients with immunoparalysis characterized by low monocyte HLA-DR and lower ferritin levels.[117] These findings support the concept that PBMC-related biomarkers can identify not only prognosis, but also treatment direction.

IL-7 provides another example of immune-state-specific intervention. The IRIS-7 trial showed that IL-7 restored lymphocyte counts in septic patients with profound lymphopenia, inducing sustained increases in CD4+ and CD8+ T cells.[118] This approach is biologically distinct from anti-inflammatory therapy: it targets immune restoration rather than inflammatory suppression. Therefore, IL-7-like strategies should be considered only in patients with evidence of lymphocyte depletion or adaptive immune failure, not as universal sepsis therapy.

Mechanism-guided interventions emerging from PBMC biology also require biomarker-based selection. NLRP3 or GSDMD inhibition may be most relevant in patients with excessive inflammasome activation or pyroptosis, whereas IFN-γ, GM-CSF, or IL-7 may be more appropriate in patients with persistent HLA-DR downregulation, impaired cytokine production, or lymphopenia. Metabolic interventions, including approaches targeting succinate, itaconate pathways, mitochondrial dysfunction, or ferroptosis, should be aligned with immunometabolic states summarized in Figure 3. Without such stratification, pathway-targeted therapies risk reproducing the failures of earlier broad sepsis trials.

To address why most immunomodulatory trials in sepsis have failed and how immune phenotyping could improve this, we have compiled Supplementary Table S1, which systematically summarizes PBMC-relevant interventions by target, intended immune state, timing, evidence type, current status, and major limitation. The table includes both failed non-stratified approaches (eg, eritoran/TLR4 antagonism) and emerging biomarker-guided strategies (eg, IFN-γ, GM-CSF, IL-7, checkpoint modulation, NLRP3/GSDMD inhibition, metabolic and ferroptosis-related interventions), because negative studies are essential for understanding the necessity of immune phenotyping.

Future clinical trials should therefore move beyond single-marker enrollment and adopt adaptive immune-phenotyping designs. Such trials should incorporate repeated PBMC monitoring, predefined immune-state thresholds, and dynamic adjustment of therapy according to biomarker response. Platform trial structures may allow parallel testing of anti-inflammatory, immunostimulatory, and metabolic interventions across different immune endotypes. The success of adaptive trial designs in other critical-care contexts, such as REMAP-CAP during the COVID-19 pandemic, supports the feasibility of this approach.[119]

Overall, PBMC-based biomarkers are most useful when interpreted as dynamic readouts of immune-state transitions rather than isolated laboratory values. Diagnostic markers such as CD38high monocytes and MDW may identify early myeloid activation, whereas prognostic markers such as persistent HLA-DR downregulation, exhausted lymphocyte subsets, and impaired functional responses identify patients at risk of immunoparalysis and secondary infection. The major translational challenge is no longer simply biomarker discovery, but validation of time-specific, population-specific, and treatment-relevant biomarker panels. Future interventional trials should combine patient enrichment, temporal immune monitoring, and adaptive trial designs to test whether PBMC-guided therapy can improve outcomes.

Controversies, Evidence Limitations, and Future Directions

Although PBMC-based immune profiling provides a promising framework for sepsis stratification, several limitations prevent immediate clinical implementation. Current evidence remains heterogeneous with respect to patient age, infection source, comorbidity burden, sampling time, assay platform, and treatment exposure. In addition, many mechanistic findings are derived from preclinical models, in vitro systems, or single-center observational cohorts and have not been prospectively validated in broad clinical populations. Therefore, the main challenge is no longer only to identify additional PBMC biomarkers or pathways, but to determine which findings are reproducible, clinically actionable, and applicable to specific patient populations.

Population Heterogeneity and Age-Related Evidence Gaps

A major limitation of the current evidence base is population heterogeneity. Sepsis is not a single biological entity, and PBMC responses may vary according to infection source, pathogen type, baseline immune status, comorbidities, treatment exposure, and genetic background. Many PBMC transcriptomic and single-cell studies have been performed in adult or mixed ICU cohorts, whereas neonatal, pediatric, and older adult populations remain less consistently represented. This creates uncertainty about whether the same PBMC immune trajectories apply across the lifespan.

Age is particularly important because baseline immune architecture differs substantially between neonates, children, adults, and older adults. Neonates and young children may show developmental immaturity of innate and adaptive immune coordination, whereas older adults may exhibit immunosenescence, thymic involution, reduced naive T-cell pools, and chronic low-grade inflammation. These differences may alter the timing and severity of HLA-DR downregulation, lymphocyte apoptosis, metabolic rewiring, and immunoparalysis. Therefore, PBMC mechanisms identified in adult cohorts should not be assumed to apply directly to pediatric or elderly patients without age-stratified validation.

The temporal immune trajectory summarized in Figure 1 should therefore be validated separately across age groups and clinical trajectories, particularly in patients who progress from acute sepsis to prolonged critical illness. Future studies should report age distribution, sex, infection source, comorbidities, immune-modulating treatments, and sampling time in sufficient detail. Without such information, it remains difficult to determine whether observed PBMC signatures reflect universal sepsis biology or cohort-specific immune states.

Timing Dependence and Reversibility of PBMC Dysfunction

The interpretation of PBMC biomarkers and mechanisms depends strongly on sampling time. Early immune activation, transient immune suppression, and persistent immunoparalysis may produce superficially similar biomarker patterns but have different biological meanings. For example, reduced monocyte HLA-DR expression at admission may reflect acute stress and early immune dysregulation, whereas persistent HLA-DR downregulation at 48–72 hours or beyond more strongly suggests impaired antigen presentation and clinically relevant immunoparalysis. Similarly, early inflammatory monocyte activation may support pathogen clearance, whereas prolonged activation may contribute to tissue injury, metabolic exhaustion, and immune-cell loss.

This timing dependence is especially relevant to patients who survive the acute phase but develop prolonged hospitalization, secondary infection, or persistent inflammation, immunosuppression, and catabolism syndrome. These later phenotypes may emerge because sustained antigenic stimulation, ongoing tissue injury, metabolic stress, lymphocyte depletion, and impaired antigen presentation prevent restoration of immune homeostasis. Thus, the absence of overt immunoparalysis in early survivors does not mean that the same mechanisms are irrelevant; rather, they may become clinically visible only when immune dysfunction persists beyond the early phase.

The reversibility of immune exhaustion is another unresolved issue. Checkpoint-associated T-cell exhaustion and monocyte dysfunction may be reversible during early or intermediate stages, but late-stage exhaustion may become constrained by epigenetic remodeling and terminal differentiation. Recent evidence suggests that by later time points, CD8+ T cells may acquire TOX-associated transcriptional and epigenetic programs that reduce responsiveness to checkpoint blockade.[120,121] This "point-of-no-return" concept remains debated, but it has important implications for trial design: immunostimulatory therapies may fail if they are administered after immune dysfunction has become biologically fixed.

Metabolic dysfunction shows similar timing complexity. Early sepsis is often associated with Warburg-like glycolytic activation, which supports inflammatory cytokine production. In prolonged sepsis, however, the metabolic state of PBMCs remains controversial. Some studies describe persistent glycolytic activation or a "glycolytic trap," whereas others report complete metabolic paralysis with failure of both glycolysis and oxidative phosphorylation.[122,123] The immunometabolic transitions summarized in Figure 3 should therefore be interpreted cautiously, because late sepsis may involve different metabolic states depending on cohort characteristics, sampling time, disease duration, and assay platform.

Discordance Between Single-Cell, Bulk, and Functional Immune Assays

Another limitation is the incomplete agreement between different analytical platforms. Single-cell RNA sequencing can identify rare or transient PBMC subsets, such as CD38high monocytes or HLA-DRlow myeloid states, that may be missed by bulk transcriptomic approaches. Conversely, bulk transcriptomics may better capture dominant systemic expression patterns but cannot resolve whether changes arise from altered cell composition, altered gene expression within a subset, or both. Therefore, results from single-cell and bulk studies should not be interpreted as interchangeable.

The clinical significance of rare PBMC subsets also remains uncertain. Some subsets identified by scRNA-seq may represent causal drivers of sepsis pathobiology, whereas others may be epiphenomena of severe inflammation or treatment exposure. For example, rare monocyte states may have disproportionate functional effects if they produce large amounts of cytokines or suppress T-cell responses, but this requires direct functional validation. Without paired transcriptomic, surface-protein, and stimulation-assay data, it is difficult to determine whether a transcriptionally defined subset is clinically actionable.

Functional assays add another layer of complexity. A patient may show a transcriptomic signature of inflammation but have poor ex vivo cytokine-production capacity, or may show low baseline cytokine levels but retain strong inducible responses. As summarized in Table 1, PBMC biomarkers differ substantially in sampling window, clinical purpose, platform requirements, and validation status. Future studies should therefore integrate cell-frequency data, single-cell transcriptomics, surface immunophenotyping, metabolomics, and functional stimulation assays in the same patients. Such integrated designs are needed to distinguish immune-cell abundance, immune-cell state, and immune-cell capacity.

Barriers to Clinical Implementation

Even when PBMC biomarkers show strong biological plausibility, several practical barriers limit clinical translation. High-dimensional technologies such as scRNA-seq, ATAC-seq, mass cytometry, proteomics, and untargeted metabolomics remain expensive, technically demanding, and difficult to implement within the time-sensitive decision windows of sepsis care. Turnaround time is a major limitation: many omics workflows require specialized processing and analysis that may exceed the period during which immunomodulatory decisions are most relevant.[124–127]

Preanalytical and analytical variability further complicate implementation. Blood collection method, anticoagulant, sample handling time, cell isolation procedure, storage conditions, sequencing depth, gating strategy, and batch effects can all influence PBMC measurements. This is particularly relevant for transcriptomic and metabolomic assays, which may be sensitive to processing delays and inter-laboratory variation. Even for more established markers such as monocyte HLA-DR, differences in antibody panels, calibration methods, and reporting units can limit comparability across studies.

Functional assays face similar standardization problems. LPS-induced TNF-α release, NLRP3-induced IL-1β production, and composite immune-function scores require standardized stimulation conditions, incubation times, readout methods, and clinically validated thresholds. Without harmonized protocols, it is difficult to define which patients truly have immunoparalysis, excessive inflammasome suppression, or preserved immune reserve. Therefore, assay standardization is as important as biomarker discovery.

Another barrier is the lack of prospective evidence that biomarker-guided decisions improve outcomes. Many PBMC biomarkers predict mortality, secondary infection, or immune dysfunction, but prediction alone does not establish clinical utility. To change practice, biomarkers must show that they can guide an intervention, change management, or improve patient-centered outcomes. The intervention landscape summarized in Supplementary Table S1 illustrates that treatment failure often reflects insufficient immune-state enrichment rather than the absence of biologically plausible targets. Future trials must therefore test biomarker-guided treatment algorithms rather than isolated biomarkers.

Future Directions for PBMC-Guided Sepsis Research

Future studies should prioritize longitudinal, age-stratified, and biomarker-guided designs. Longitudinal sampling is essential because PBMC states evolve rapidly during sepsis. Single time-point measurements cannot reliably distinguish transient immune activation from persistent immune paralysis. Repeated sampling at predefined windows—such as admission, 24 hours, 48–72 hours, days 5–7, and recovery or discharge—would help define when specific immune states emerge, persist, or resolve.

Age-stratified studies are also needed. Neonatal, pediatric, adult, and older adult cohorts should be analyzed separately before conclusions are generalized across the lifespan. Such studies should evaluate whether key mechanisms, including HLA-DR downregulation, T-cell exhaustion, metabolic paralysis, and functional immune suppression, follow similar trajectories across age groups. This is particularly important because therapeutic windows and safety profiles may differ between children, adults, and older adults.

Integrated immune phenotyping should become a central design principle. Rather than relying on one marker, future studies should combine cellular phenotyping, transcriptomic or targeted gene-expression signatures, metabolic indicators, and functional assays. A practical clinical panel may include monocyte HLA-DR, selected monocyte and lymphocyte subsets, one or more transcriptomic or metabolic markers, and a functional stimulation assay. Such panels should be evaluated against clinically meaningful outcomes, including secondary infection, organ dysfunction trajectory, ICU length of stay, readmission, and mortality.

Clinical trials should also use immune-state enrichment. Instead of applying uniform immunomodulatory therapy to all septic patients, future trials should allocate therapy according to immune phenotype. Patients with hyperinflammatory features may be considered for selective anti-inflammatory approaches, whereas patients with persistent HLA-DR downregulation, lymphopenia, or impaired cytokine-production capacity may be better candidates for immunostimulatory therapy. The immune-state rationale summarized in Supplementary Table S1 can serve as a framework for matching intervention type to patient biology.

Finally, PBMC-guided sepsis research should move toward adaptive and platform trial designs. Such designs can incorporate repeated immune monitoring, allow treatment allocation to change over time, and test multiple interventions across immune endotypes. This approach is better aligned with the dynamic biology of sepsis than fixed, one-size-fits-all trial designs. Only through standardized, longitudinal, and temporally informed approaches can PBMC-based immune profiling move from mechanistic discovery toward clinically useful precision immunology in sepsis.

Conclusion

PBMCs provide an accessible and clinically relevant window into the dynamic immune response of sepsis. Rather than following a simple linear progression from hyperinflammation to immunosuppression, sepsis involves overlapping and time-dependent immune states that differ across patients and disease stages. Evidence from single-cell profiling, transcriptomics, mechanistic studies, and functional immune assays indicates that PBMC remodeling—particularly monocyte/macrophage dysfunction, HLA-DR downregulation, lymphocyte exhaustion, regulated cell death, and immunometabolic reprogramming—plays a central role in this evolving immune trajectory.

This PBMC-centered perspective has important translational implications. PBMC-derived biomarkers may help move sepsis assessment beyond static inflammatory markers toward dynamic immune phenotyping. Early markers such as CD38high monocytes and monocyte distribution width may support early diagnosis, whereas persistent monocyte HLA-DR downregulation, exhausted lymphocyte subsets, metabolic signatures, and functional stimulation assays may identify patients at risk of immunoparalysis, secondary infection, and prolonged critical illness. These markers may also help define therapeutic windows, allowing anti-inflammatory, immunostimulatory, or metabolic interventions to be matched more closely to the patient's immune state.

However, PBMC-guided precision immunology in sepsis remains an emerging field. Current evidence is limited by cohort heterogeneity, age-related differences, variable sampling times, assay standardization challenges, and insufficient prospective validation. Future studies should therefore prioritize longitudinal and age-stratified immune monitoring, standardized PBMC assays, integrated biomarker panels, and biomarker-guided interventional trials. With these advances, PBMC-based immune profiling may become a practical tool for improving risk stratification and guiding individualized immunomodulatory strategies in sepsis.

Data Sharing Statement

No new datasets were generated or analyzed in this review. Further information is available from the corresponding author upon reasonable request.

Author Contributions

Zhiheng Qian: Conceptualization, Methodology, Investigation, Literature Search, Data Curation, Formal Analysis, Visualization, Writing – Original Draft, and Writing – Review & Editing. The author has read and approved the final article.

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