The NS1 protein can increase the release of inflammatory factors through the TLR4 pathway and reduce vascular barrier function (Fernandez-Santos and Azeredo, 2022). Some autoantibodies produced during infection can also bind to endothelium-related targets, further aggravating endothelial damage.

During the critical stage of illness, the complement system and the coagulation system are often overactivated. Excessive complement response can amplify inflammation and increase vascular leakage. Coagulation dysfunction is prone to cause thrombocytopenia and increase the risk of bleeding. Meanwhile, platelets interact with white blood cells, releasing more pro-inflammatory substances and continuously damaging endothelial cells. Under the superposition of multiple abnormalities, vascular stability is disrupted, which may eventually lead to plasma leakage, shock and multiple organ failure (Amin et al., 2025).

5 Research Progress of Biomarkers Related to Immune Storm

5.1 Pro-inflammatory and Anti-inflammatory cytokines

The changes in cytokine levels have important reference value in the disease assessment of severe dengue fever. The increase of pro-inflammatory factors such as IL-6 and TNF-α in critically ill patients is often associated with increased vascular permeability and increased risk of bleeding (Paul et al., 2025). Among them, a significant increase in IL-6 is considered closely related to the increased demand for intensive care and the elevated risk of death (Sivasubramanian et al., 2022; McBride et al., 2024).

Among anti-inflammatory factors, the role of IL-10 is rather complex. When the inflammatory response is too intense, IL-10 will increase, which may help "suppress" the inflammation. But if it increases too much, it will suppress the body's immune response against the virus, making it more difficult to clear the virus (Masyeni et al., 2024; Prajapati et al., 2024). The key lies not in the level of a single cytokine, but in whether the effects of pro-inflammatory factors and anti-inflammatory factors are balanced. Once out of balance, patients may present with severe symptoms (Figure 2) (Dash et al., 2024). Recent studies have pointed out that the imbalance in the combined changes of IL-6, IL-8, and IL-10 may be related to early bleeding, which indicates that the "combination of cytokines" is of great value in judging the prognosis of patients.

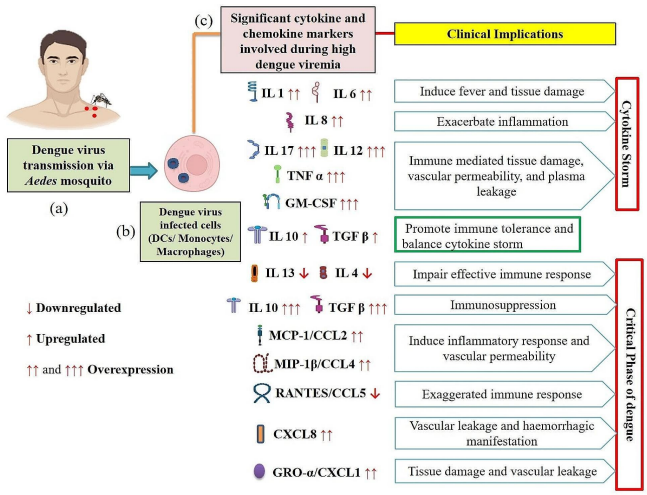

Figure 2 Mechanistic effects of complex interplay between pro-inflammatory and anti-inflammatory cytokines and chemokines during dengue virus (DENV) infection (Adopted from Dash et al., 2024)

Image caption: (a) Infection of DENV to host via Aedes mosquito during blood meal. (b) DENV infects target cells including dendritic cells, macrophages, and monocytes, initiating host immune response. (c) Infected cells release pro-inflammatory cytokines, such as IL-1, IL-6, IL-8, IL-17, IL-12, TNF-α, and GM-CSF and chemokines such as MCP-1/CCL-2, MIP-1β/CCL-4, CXCL-8, and GRO-α/CXCL-1. Proinflammatory cytokines activate other immune cells and promote the release of anti-inflammatory cytokines, such as IL-10 and TGF-β that limits the extent of immune responses. During high dengue viremia, excessive release of pro-inflammatory cytokines (IL-1, IL-6, IL-8, IL-17, IL-12, TNF-α, and GM-CSF) and chemokines (MCP-1/CCL-2, MIP-1β/CCL-4, CXCL-8, and GRO-α/CXCL-1), upregulation of anti-inflammatory cytokines (IL-10 and TGF-β), and downregulation of chemokine RANTES/CCL-5 lead to exaggerated immune response; This surge in immune response results in cytokine storm and contribute to SD manifestations (Adopted from Dash et al., 2024)