

2023). When the platelet count drops significantly and is accompanied by vascular endothelial injury, severe bleeding is more likely to occur. Blood leakage, direct damage of viruses to tissues, and overactivated immune responses can simultaneously affect the liver, kidneys, and central nervous system, leading to liver function problems, poor kidney function, and even multiple organ failure in some patients (Estrada-Jimenez et al., 2022; Dash et al., 2024; Teramoto, 2025).

3 Concept and Evidence of Severe Dengue Immune Storm

3.1 Definition and general characteristics of immune storm/cytokine storm

An immune storm refers to a state in which, under the stimulation of infection, cytokines increase significantly in a short period of time, triggering an uncontrolled inflammatory response. In patients with severe dengue fever, various interleukins and tumor necrosis factor- α will rapidly increase, keeping immune cells in an activated state all the time. During the critical period of the disease, a significant increase in vascular permeability and an increased risk of shock often occur simultaneously (Pal et al., 2024). The cytokines released by infected cells will continuously amplify the immune response, forming a self-reinforcing process, and thereby aggravating the damage to tissues and blood vessels (Kadi et al., 2025).

The immune storm of severe dengue fever is related to both innate immunity and adaptive immunity. It should be emphasized that although this intense inflammation is a response against the virus, it can, in turn, disrupt the normal functions of blood vessels and organs (Dash et al., 2024; Kadi et al., 2025). Compared with mild cases, the immune response of severe patients is more difficult to control in a timely manner, and thus they are more likely to lose control of their condition.

3.2 The relationship between abnormal cytokines and disease progression in critically ill patients

Patients with severe dengue fever often experience abnormal changes in the types and quantities of cytokines, and such changes are closely related to the disease's development process and clinical outcomes. The levels of inflammatory factors IL-6, TNF- α , anti-inflammatory factor IL-10 and various chemokines in critically ill patients are generally elevated, and they persist in the early stage of the disease. They are often accompanied by severe symptoms such as blood leakage and impaired organ function (Dash et al., 2024; Masyeni et al., 2024), among which the elevated levels of IL-6 and IL-8 are closely related to the increased risk of bleeding (Bhatt et al., 2024), and the abnormal changes in IL-10 levels are more obvious in disease types mainly characterized by liver injury.

The dynamic changes of cytokines in the disease course have indicative significance. The peak of some factors at a specific stage can indicate disease progression. Compared with the absolute level of a single indicator, the imbalance of pro-inflammatory and anti-inflammatory responses can better reflect the risk of severe illness (Bhatt et al., 2024). Secondary infections and individual genetic differences can change the intensity of immune responses and increase the possibility of excessive initiation of inflammatory responses (Dash et al., 2024; Masyeni et al., 2024; Pal et al., 2024).

3.3 Mechanisms of leakage, shock and organ damage caused by excessive inflammation

When a patient with severe dengue fever experiences vascular leakage and shock, it indicates a serious inflammatory state. The excessive release of cytokines such as TNF- α and IL-6 can directly damage vascular structure, aggravate abnormal vascular endothelial function, promote blood exudation, reduce the amount of effectively circulating blood, and some patients may develop shock. This process is regarded as one of the important fatal causes in disease progression (Dash et al., 2024; Kurosu et al., 2024).

Long-term uncontrolled inflammatory responses can also affect coagulation and metabolic processes, manifested as thrombocytopenia accompanied by multiple organ damage, excessive IL-10, and related to liver function impairment. Some chemokine changes are associated with renal and lung disease phenotypes. Specific cytokine intervention studies can alleviate clinical manifestations to a certain extent, supporting the key role of excessive inflammation in the progression of severe cases (Kadi et al., 2025). Early suppression of abnormal inflammatory responses helps reduce the risk of severe complications and death.