Although there have been advancements in supportive treatment, the lack of reliable early detection indicators often affects the timely intervention of severe cases. Understanding the occurrence mechanism of immune storm and finding effective detection indicators can assess the risk of patients, enable early treatment, and reduce the mortality rate of severe dengue fever.

2 Pathological Process and Immune Response of Severe Dengue Fever

2.1 Basic characteristics of viruses

Dengue virus belongs to the Flaviviridae family of single-stranded RNA viruses and is divided into four serotypes from DENV-1 to DENV-4. There is a certain association between the genetic differences and the clinical severity (Khanam et al., 2022; Sinha et al., 2024). After the virus enters the human body through the bites of Aedes aegypti and Aedes albopictus, it first infects local immune cells in the skin and then spreads to lymph nodes and blood circulation to form viremia (Tejo et al., 2023; Cloherty et al., 2024). During the replication process within host cells, viral RNA mediates the synthesis of various proteins, among which the non-structural protein NS1 is closely related to immune evasion and vascular injury processes.

The replication and pathogenicity of the virus are simultaneously influenced by the characteristics of the virus itself and the genetic factors of the host. For example, types such as DENV-2 have stronger replication ability and more obvious immune interference, and may be more likely to cause severe illness (Samune et al., 2024). During the infection process, the interaction between the virus and the host protein can also change the infection process (Cloherty et al., 2024; Sinha et al., 2024). Furthermore, when reinfected with different serotypes, antibody-dependent enhancement (ADE) may occur, significantly increasing the risk of severe illness, which is an important mechanism for disease aggravation (Puc et al., 2021; Khanam et al., 2022).

2.2 Main differences in immune responses between mild and severe patients

The immune response is a key link in eliminating the dengue virus. When the immune regulatory function is out of balance, immune pathological changes characterized by tissue damage in the human body may occur. Patients with milder symptoms usually exhibit an effective combination of innate immunity and adaptive immunity, thereby inhibiting viral reproduction and maintaining tissue damage at a low level (Dash et al., 2024). Abnormal immune regulation is more common in critically ill patients, especially those who are reinfected with different serotypes of viruses. The excessive release of pro-inflammatory factors can trigger a cytokine storm, causing the condition to worsen rapidly (Jiravejchakul et al., 2025).

Severe patients often have significantly elevated inflammatory factors such as IL-6 and IL-8, and their immune cells remain in a highly active state. Antibody-dependent enhancement enables some non-neutralizing antibodies to assist the virus in entering more target cells, thereby expanding and exacerbating the uncontrolled inflammatory response (Khanam et al., 2022; Dash et al., 2024; Jiravejchakul et al., 2025). When the immune regulatory capacity is insufficient, inflammation is difficult to subside, and there may also be an increase in vascular permeability. The risk of organ damage will also rise accordingly. The dynamic balance between pro-inflammatory and anti-inflammatory responses is closely related to the development process of the disease and the recovery effect.

2.3 The overall framework of increased vascular permeability, coagulation imbalance, fibrinolysis and organ damage

A sudden increase in vascular permeability is one of the main characteristics of severe dengue fever. In severe cases, it can cause plasma extravasation, blood concentration and even shock (Nanaware et al., 2021). This situation is related to both the direct destruction by the virus and immune damage: Dengue virus can affect the function of vascular endothelial cells, and NS1 protein can also damage the vascular barrier and cause inflammation (Puc et al., 2021), while pro-inflammatory factors such as TNF-α will further increase vascular permeability (Tejo et al., 2023; Dash et al., 2024).

Patients with severe dengue fever often have abnormal coagulation function, specifically manifested as reduced platelet count and weakened coagulation ability, which greatly increases the possibility of bleeding (Tejo et al.,