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Cytomegalovirus end-organ disease in immunocompromised critically ill patients: key concerns demanding attention

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We delved into the clinical research conducted by Sara Fernández et al. [1] with great interest. This study is a multicenter, international research initiative spanning over a decade, primarily focusing on cytomegalovirus end-organ disease (CMV-EOD) among immunosuppressed patients with critical illness. The study revealed distinctive clinical features, risk factors, and adverse clinical outcomes in immunocompromised critically ill patients with CMV-EOD, marking it as a seminal work in the field. However, there is scope for enhancing the comprehensiveness of this study with further refinements.

First, within the specific population of immunocompromised critically ill patients, certain subjects (such as those with sepsis, trauma, and other prolonged illnesses) have been overlooked and excluded. Sepsis, a significant global health concern characterized by severe response to infection that causes organ failure, leads to over 5.3 million deaths yearly, with a mortality rate of around 30% [2–4]. Sepsis is currently understood to induce an imbalance in the immune system (innate and adaptive), leading to phenomenon known as "immune paralysis" [5–7]. The early stages (characterized by overwhelming inflammation) and the later stages (characterized by refractory inflammation, immunosuppression, and risk of secondary infections) of sepsis are both conducive to CMV reactivation [5–8]. The incidence of CMV reactivation in septic patients seems to be similar to other common immunosuppressed patients [8]. Our team's research indicates the incidence of CMV reactivation in critically ill patients with concurrent sepsis increases by at least 30%, and sepsis is an independent risk factor for CMV reactivation [9, 10]. This aligns with other mainstream research findings, where the underlying mechanism is associated with sepsis-induced immunosuppression, promoting CMV replication [11]. Therefore, definition of immunosuppressed population in CMV-EOD research should be broadened, and more effective immune function assessment indicators are required to clearly define "immunocompromised", moving beyond reliance on clinical disease types for judgment.

Second, assessing the impact of CMV load levels on clinical characteristics and outcomes in CMV-EOD population is essential. Additionally, it is necessary to evaluate CMV seropositivity, both qualitatively and quantitatively, as recent studies indicate a close relationship between CMV seropositivity and poor prognosis [12]. A combined assessment of CMV load and IgG in blood may enable earlier identification of high-risk patients, allowing for antiviral treatment to improve adverse outcomes. Third, the antiviral medications used for the subjects

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with CMV-EOD in this study may exert a negative influence on prognosis, primarily due to bone marrow suppression leading to a decrease in immune cell levels [13]. The use of the latest anti-CMV drugs Letermovir and Maribavir may mitigate these adverse effects [14]. Finally, CMV should be recognized as a systemic infectious virus, not confined to a specific organ but widely infecting various cell types, including epithelial, endothelial, fibroblast cells, and so on [15]. Notably, CMV resides in the body as a latent infection and can reactivate under immunosuppressed conditions, leading to multi-system organ damage, particularly affecting the respiratory and digestive systems in patients with CMV-EOD. However, whether CMV is a pathogen or a bystander remains a significant and unresolved question. The prevailing view is that CMV reflects immune status and has pathogenicity, especially as reactivation is more likely with lower immune function, and the pathogenicity increases with viral load. In addition, the impact of other co-infections on prognosis needs to be clarified.

In conclusion, the study by Sara Fernández et al. describes the clinical characteristics and outcomes of immunocompromised critically ill patients with CMV-EOD, thus contributing positively to the advancement of the field. A nuanced investigation into the aforementioned matters is essential to fully elucidate the intricate interplay between CMV-EOD and poor prognosis in immunocompromised critically ill patients. Further research should delve deeper into these complexities to enhance our understanding and potentially inform more effective therapeutic strategies.

Abbreviations

CMV	Cytomegalovirus
CMV-EOD	Cytomegalovirus End-Organ Disease

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ZHZ wrote the manuscript; ZHZ, JLS, XSL, and RZ revised the manuscript; XQL and YML reviewed the manuscript. XQL and YML contributed equally to the study. All authors read and approved the final manuscript.

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Declarations

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