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Correspondence

Correspondence to editorial on "Human cytomegalovirus reactivation in cirrhosis patients with acute decompensation"

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Keywords: Human cytomegalovirus reactivation; Acute decompensation; Pre-emptive treatment; Treatment threshold; Adverse effects

Dear Editor,

We sincerely appreciate Dr. Norihiro Imai for his interest in our recent publication, "Human cytomegalovirus reactivation in cirrhosis patients with acute decompensation"[1] and for his thoughtful editorial.[2] The editorial highlights critical issues in the management of human cytomegalovirus (HCMV) reactivation in cirrhosis patients with acute decompensation (AD) and proposed a stepwise strategy of screening and treating HCMV reactivation. We would like to take the opportunity to provide additional information based on our previous study in these important issues.

HCMV reactivation is known to associated with morbidity and mortality in transplant recipients and critically ill patients.[3] However, the role of HCMV reactivation in acutely decompensated populations is largely unexplored. In our study, we screened for HCMV reactivation using commercially available real-time qPCR and found that the incidence of HCMV reactivation was 4.8% in HCMV-seropositive cirrhosis population. HMCV reactivation was independently associated with 90-day mortality and might be a precipitating event for development of acute-on-chronic liver failure.

Among transplant recipients, there are two main strategies to prevent CMV disease: 1) Prophylaxis: daily low doses of an antiviral agent were given to all transplant recipients for a finite period; 2) Pre-emptive treatment: initiating antiviral treatments when transplant recipients were found the laboratory evidence of HCMV reactivation (over the established threshold).[4,5] In this study, some of participants with the evidence of HCMV reactivation were given pre-emptive treatment and might be benefit from antiviral treatment with ganciclovir. Due to the observational design of this study, initiating antiviral treatments was decided by the clinician, and therefore the specific viral load threshold for triggering therapy in patients with HCMV reactivation was not defined in this study. As treatment for HCMV might lead to adverse events (leukopenia, neutropenia, acute kidney injury, etc.), it is significant to determine an optimal viral load threshold for initiating pre-emptive therapy. The ideal threshold could not only avoid overtreatment in patients with lower possibility of morbidity and mortality but also ensure early treatment of patients prone to death. To

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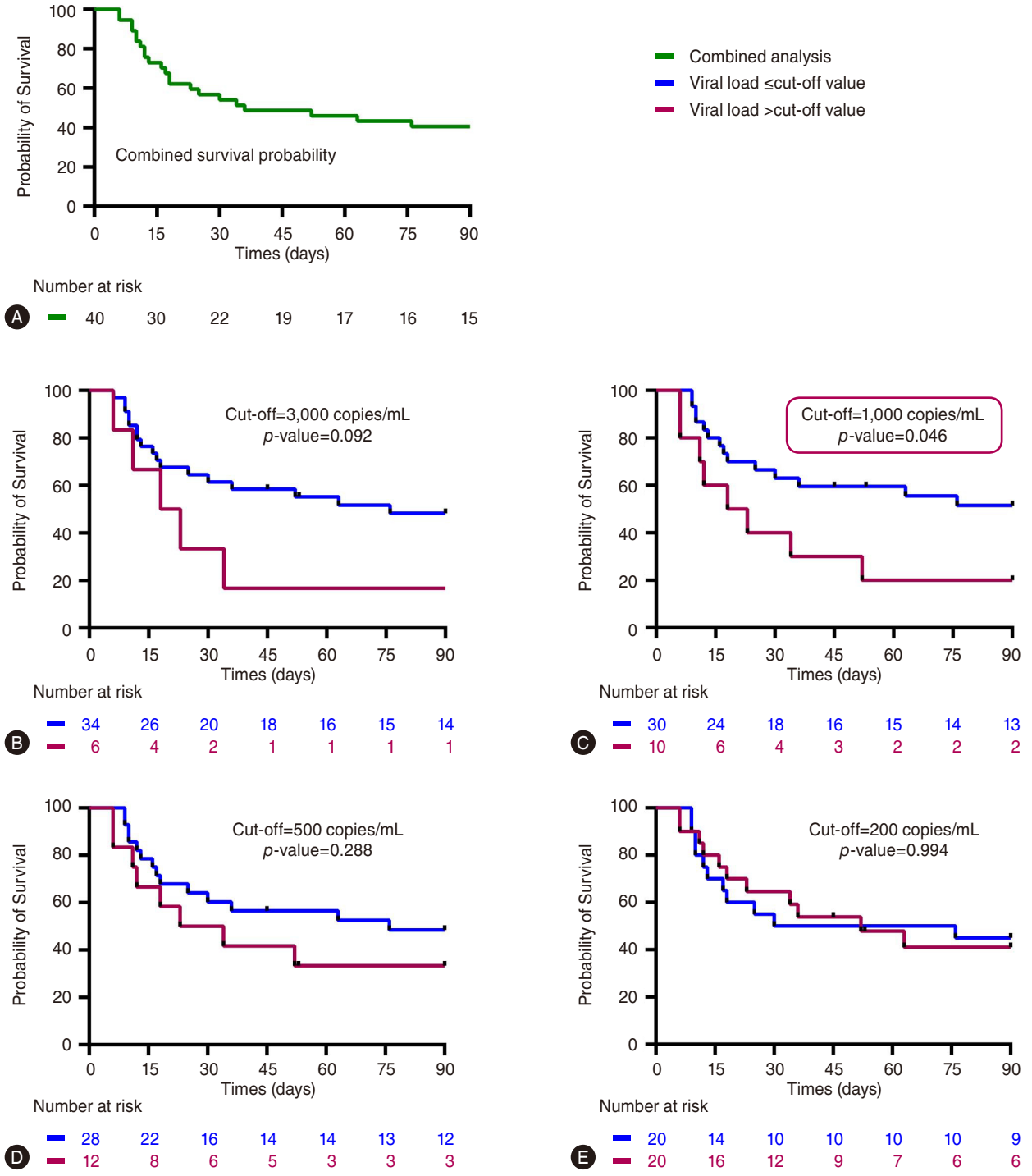

Figure 1. Identification of optimal threshold in pre-emptive therapy. (A) Combined survival probability among untreated patients with HCMV reactivation in Cohort 1 and Cohort 2. (B–E) Kaplan-Meier survival curves grouped in "high-level viral load (>cut-off value)" and "low-level viral load (≤cut-off value)" among untreated patients with HCMV reactivation in Cohort 1 and Cohort 2. HCMV, human cytomegalovirus.

Abbreviations:

AD, acute decompensation; HCMV, human cytomegalovirus

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test four viral load threshold, survival analyses were performed among untreated patients with HCMV reactivation (Fig. 1). The thresholds used in the analysis started from 200 copies/mL and raised to exceed 3,000 copies/mL. HCMV viral loads of 1,000 copies/mL showed clear separation in survival probability, suggesting that 1,000 copies/mL might serve as an actionable threshold for initiating antiviral treatment for HCMV reactivation among acutely decompensated patients. Notably, this viral load threshold was based on analysis of baseline viral loads, dynamic changes of viral load might provide more information about the optimal treatment threshold. Randomized trials with dynamic surveillance of viral load in the future were necessary to define effect of pre-emptive treatment and the corresponding optimal treatment threshold.

Intravenous ganciclovir and oral valganciclovir have all been studied for pre-emptive treatment and are currently the most used drug for it in organ transplant recipients.[6] Hematologic toxicity is the principal cause of adverse effects, most commonly leukopenia and neutropenia, and these adverse effects are reversible after discontinuation of drugs.[6] Nine patients with HCMV reactivation in our study received ganciclovir. Of these, five received treatment for more than two weeks, three for 10–12 days, and one died of gastrointestinal bleeding after receiving only two days of treatment. During antiviral treatment, none of patients in treated group had leukopenia (count of <3,500/μL[7]) and neutropenia (count of <1,000/μL[7]). In terms of renal toxicity, acute kidney injury occurred in 2 (22.2%) patients in the ganciclovir group versus 13 (32.5%) patients in the untreated group (P=0.702). And none of treated patients were discontinued treatment for adverse effects. The recent study on liver transplant recipients shows the incidence of severe neutropenia (count of <500/μL) is 12% (12/100) in the pre-emptive treatment with duration of 100-day treatment.[7]

And this come to the next question: when should clinicians withdraw the antiviral treatments? In this study, two patients discontinued therapy before achieving undetectable HCMV DNA due to personal reason or worsened condition during antiviral therapy. Of the remaining seven patients: 5 discontinued antiviral therapy with at least one undetectable HCMV DNA via routine quantitative PCR or by metagenomic next-generation sequencing. However, the small sample size of treated group and lack of recurrent viremia surveillance in this study make it difficult to address this issue with current data.

We appreciate that the editorial conducts comprehensive analysis of our work and sheds light on the critical issues which future studies need to address. It highlights the need for targeted research identifying optimal thresholds and duration of antiviral treatment to initiate antiviral therapy promptly and minimize the incidence of adverse effects from it. Our study suggests that patients with HCMV reactivation exhibit a significantly higher incidence of respiratory failure, indicating that the lungs may be one of most vulnerable organs for the virus. By understanding the immunological and virological mechanisms underlying viral pathogenesis in the lungs, organ-specific biomarkers and monitoring viral load in bronchoalveolar lavage fluid enable earlier identification of high-risk individuals and timely initiation of therapy. We hope that our research contributes to a broader discussion on impact of HCMV reactivation on decompensated cirrhosis population.

Authors' contribution

Data collection and analysis: H.C, C.J. Manuscript drafting and revision: H.C, C.J.

Conflicts of Interest

The authors have no conflicts to disclose.

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