Active cytomegalovirus infection in mechanically ventilated patients with sepsis

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Abstract

Background Active cytomegalovirus (CMV) infection is associated with poor prognosis in septic patients with critical illness. Patients of septic category are highly likely to benefit from prophylactic antiviral therapy. Nevertheless, the clinical characteristics for CMV reactivation are lacking among septic patients requiring mechanical ventilation. The aim of this study was to investigate the incidence, risk factors, and clinical outcomes regarding active CMV infection in mechanically ventilated patients with sepsis.

Methods A single-center, retrospective cohort study conducted from January 2021 to December 2023 that included septic patients on mechanical ventilation at the intensive care unit (ICU) of a national hospital. Study participants were divided into active and non-active CMV infection groups based on CMV DNAemia within a 28-day hospitalization period in ICU. Clinical features, laboratory findings, treatment measures, and clinical outcomes were compared between the two groups.

Results Among 118 septic patients, 21 (17.8%) exhibited active CMV infection within 28-day ICU admission. Hemoglobin served as an independent risk factor and predictor for active CMV infection ($P < 0.05$). Moreover, the duration of mechanical ventilation and ICU stay in active CMV infection patients were significantly higher than in the comparison group ($P < 0.05$).

Conclusions Active CMV infection is common and associated with adverse clinical outcomes in mechanically ventilated patients with sepsis. A low level of hemoglobin is an independent risk factor for active CMV infection. Further prospective studies are warranted to assess the efficacy of initiating prophylactic and preemptive antiviral therapies among patients with sepsis disorders.

Keywords Active cytomegalovirus infection, Sepsis, Immunocompetent, Mechanical ventilation, Clinical characteristics

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Background

Cytomegalovirus (CMV) is a ubiquitous latent viral infection prevalent throughout the general population [1]. CMV possesses the potential for reactivation under specific conditions, and the perilous impact is well-documented, particularly in immunocompetent patients with critical illness [2]. Among those patients, our previous study found the incidence of CMV reactivation could reach more than 30%, and were associated with prolonged duration of mechanical ventilation (MV), increased length of hospital stay, and elevated mortality [2–5].

Our recent research showed that when non-immunosuppressed critically ill patients admitted for sepsis (and/or septic shock), the incidence of CMV reactivation could be significantly increased, and similar results were found in other studies [4–7]. Moreover, sepsis is acknowledged as a significant risk factor for CMV reactivation, as the hyperinflammation can prompt the transition of CMV from latency to activation [2–7]. Patients of septic category are highly likely to benefit from prophylactic antiviral therapy [8]. However, research on active CMV infection in mechanically ventilated patients with sepsis remains scarce.

Therefore, this study aimed at investigating the incidence, risk factors, and clinical outcomes of active CMV infection among mechanically ventilated patients with sepsis. These results serve as an early warning for the identification of high-risk patients, thereby ameliorating the adverse clinical outcomes and providing guidance for antiviral therapy.

Methods

Study design and ethics

A single-center, retrospective cohort study included septic patients on mechanical ventilation at the respiratory intensive care unit (ICU) of a national hospital. The Ethics Committee of the First Affiliated Hospital of Guangzhou Medical University approved the study protocol (No. ES-2024-K084-01). Informed consent was not required due to the retrospective nature of the study. The reporting of this study adheres to the *STROBE* Statement guidelines for observational research [9].

Participants and definitions

The research team conducted a comprehensive retrospective analysis of septic patients requiring MV admitted to the respiratory ICU at the First Affiliated Hospital of Guangzhou Medical University, China, from January 2021 to December 2023. Active CMV infection was ascertained through quantitative polymerase chain reaction (qPCR), utilizing blood plasma samples. Participants were classified into two groups based on CMV

DNAemia levels during their 28-day ICU stay: active infection group (CMV DNAemia ≥ 500 copies/mL) and the non-active infection group (CMV DNAemia < 500 copies/mL). It should be noted that all participants in this study underwent CMV testing, and those with a CMV viral load of 0 copies/mL were not excluded. Active CMV infection was defined as viral load greater than or equal to 500 copies/mL in plasma [10–12]. The screening of the CMV viral load in the plasma was part of the routine clinical practice in the hospital (at least once per week).

The following inclusion and exclusion criteria were as follows: (1) inclusion criteria: ①Met the diagnostic criteria for sepsis (SEPSIS-3 criteria) [13] within 24 h ICU admission; ②Required MV support. (2) exclusion criteria: ①Aged < 18 years; ②Pregnant or lactation; ③ICU stay < 5 d or survival time < 72 h; ④Duration of MV < 5 d; ⑤Lack of CMV detection (CMV testing was not conducted in both plasma and endotracheal aspirates simultaneously); ⑥Readmitted to ICU or reintubation; ⑦Prior administration of antiviral therapy (ganciclovir, valganciclovir, aciclovir, valaciclovir, or foscarnet) before ICU entry; ⑧Immunocompromised: diagnosed with solid organ or bone marrow tumor, neutropenic, systemic glucocorticoids or cytotoxic drugs were used, transplantation, connective tissue disease, and HIV; ⑨Incomplete clinical data.

Data collection and quality control

Clinical data from the electronic medical records of those enrolled patients was extracted by two independent investigators who then adjudicated the accuracy of the data, including clinical features, laboratory findings, treatment measures, complications, and clinical outcomes. In cases of disagreement, a third reviewer (critical care specialist) resolved the differences. The collected data were then entered into an electronic database to facilitate subsequent statistical analysis.

Study outcomes

The primary outcomes included the risk factors (predictive value) and clinical outcomes for active CMV infection among those participants. Moreover, the secondary outcomes included clinical features, laboratory findings, treatment measures, and complications.

Data analysis

All statistical analyses and graphical representations for data interpretation and visualization were performed using SPSS version 25.0 (SPSS Inc., Chicago, IL, USA) or GraphPad Prism 8.0 (GraphPad Software Inc., San Diego, CA, USA). Continuous variables were described as the mean $\pm$ standard deviation (SD) or as median with interquartile ranges (IQRs), and were analyzed using the

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Wilcoxon rank-sum test for comparisons. Categorical variables were summarized as frequencies and percentages and were compared using the chi-square test or Fisher's exact test, where appropriate.

Univariate logistic regression analysis was used to identify risk factors associated with active CMV infection. Variables with a *P*-value of less than 0.05 were considered potential risk factors and were included in a multivariate logistic regression model to refine the analysis. The predictive model for active CMV infection was developed by calculating regression coefficients (β), odds ratios (ORs), and the corresponding 95% confidence intervals (CIs). The predictive accuracy of the model was assessed using the receiver operating characteristic (ROC) curve, with key metrics including the area under the ROC curve (AUC), 95% CI, P-value, optimal cut-off point, sensitivity, and specificity. Lengths of 30-day MV and IMV, 28-day ventilator-free days (VFD), and duration of 30-day ICU stay rates between two groups were compared using the Kaplan–Meier (KM) survival analysis, with statistical differences assessed using the log-rank test. Correlation coefficients between CMV load in plasma and endotracheal aspirates (ETA) were calculated using the Pearson's correlation coefficient. Statistical significance was defined as a two-sided *P*-value less than 0.05.

Results

Incidence of active CMV infection

Within the 28-day ICU stay of the 118 septic patients receiving MV who were enrolled, active CMV infection was identified in 21 instances, representing 17.8% of the total (Fig. 1A, supplement files: Table E1). The percentages of the four levels of CMV DNAemia load were 23.8% (500–1000 copies/mL), 47.6% (1001–5000 copies/mL), 14.3% (5001–10000 copies/mL), and 14.3% (> 10,000 copies/mL), respectively (Fig. 1B). Out of those 21 individuals with CMV DNAemia, 19 (90.5%) tested positive upon their admission to the ICU early stage (day 0–7), and 2

cases (9.5%) showed positive results between days 15 and 21 (supplement files: Table E2). Additionally, the detection rate of CMV in lower respiratory tract specimens (ETA) was 55.9%, demonstrating a statistically significant positive correlation with CMV levels in plasma specimens (correlation coefficient, $r = 0.916$; $P < 0.001$) (supplement files: Table E2, Figure E2).

Patient clinical characteristics

Among the 118 enrolled septic patients, 94 were male (79.7%). The median age for all study participants was 67 years. The study participants median scores for APACHE II and SOFA were 23 and 9, respectively. The main cause of sepsis was severe community-acquired pneumonia (sCAP) (96.6%). The main comorbidities were hypertension ($n = 58$, 49.2%), diabetes ($n = 51$, 43.2%), and cardiovascular diseases ($n = 33$, 28.0%). Except for hypertension [28.6% vs. 53.6% (n); $P = 0.037$] and respiratory rates [22 vs. 20 (bpm, median); $P = 0.047$], differences in these clinical characteristics between the two groups were not significant (Table 1).

Moreover, the active CMV infection group exhibited lower hemoglobin (Hb) [71 vs. 98 (g/L, median); $P = 0.001$], higher aspartate aminotransferase (AST) [49.2 vs. 35.9 (U/L, median); $P = 0.046$], and higher serum urea nitrogen (BUN) [13.2 vs. 10.0 (mmol/L, median); $P = 0.047$] levels. However, there were no significant differences for other laboratory findings between the two groups (Table 2).

Treatment measures and complications

Most of the patients with active CMV infection received antiviral therapy [85.7% vs. 28.9% (n); $P < 0.001$] after ICU admission. Furthermore, compared to the group without active CMV infection, blood transfusion [81.0% vs. 48.5% (n); $P = 0.007$] and gamma globulin infusions [66.7% vs. 29.9% (n); $P = 0.002$] were found to have been highly administered in the group with active CMV infection
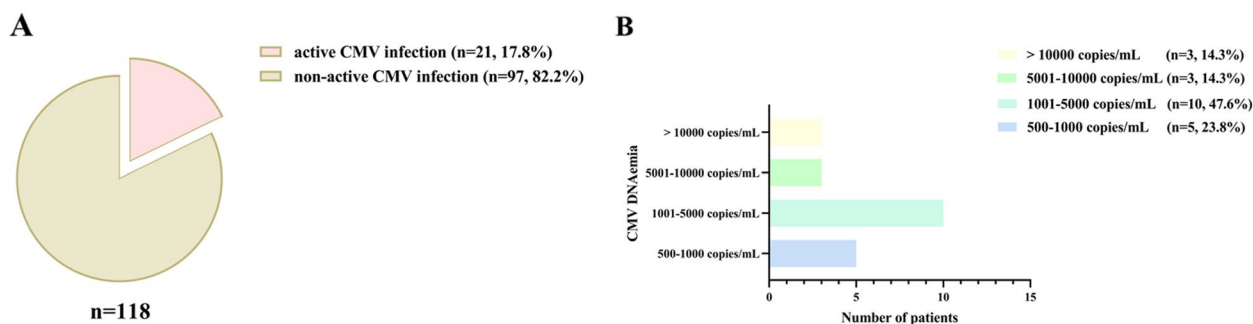

Fig. 1 Incidence of Active CMV Infection and Level of CMV DNAemia Load. **A** Incidence of active cytomegalovirus (CMV) infection within 28-day intensive care unit (ICU) admission; **B** CMV DNAemia load within 28-day ICU admission

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Table 1 Patients clinical features at ICU admission

	Total n = 118	CMV DNAemia		P
		Yes (n = 21, 17.8%)	No (n = 97, 82.2%)	
Age (yrs)	67 (58–75)	64 (58–74)	68 (59–75)	0.394
Sex, n (%)	-	-	-	> 0.999
Male	94 (79.7)	17 (81.0)	77 (79.4)	-
Female	24 (20.3)	4 (19.0)	20 (20.6)	-
Weight (kg)	59.1 ± 14.0	56.2 ± 13.8	59.8 ± 14.0	0.295
BMI (kg/m²)	21.4 ± 4.5	20.8 ± 4.5	21.6 ± 4.4	0.482
Score of disease severity				
APACHE II	23 (18–29)	23 (20–29)	23 (18–28)	0.921
SOFA	9 (7–12)	8 (6–13)	9 (7–12)	0.924
Causes of sepsis, n (%)	-	-	-	> 0.999
sCAP	114 (96.6)	21 (100.0)	93 (95.9)	-
Other	4 (3.4)	0 (0.0)	4 (4.1)	-
Vital signs				
Average blood pressure (mmHg)	85 ± 20	80 ± 18	86 ± 20	0.214
Heart rate (bpm)	100 (81–117)	110 (85–120)	98 (81–112)	0.198
Respiratory rate (bpm)	**20 (18–25)**	**22 (20–26)**	**20 (18–23)**	**0.047#**
Temperature (℃)	36.8 (36.5–37.5)	37.0 (36.5–37.8)	36.8 (36.5–37.5)	0.136
Comorbidities, n (%)				
Hypertension	**58 (49.2)**	**6 (28.6)**	**52 (53.6)**	**0.037#**
Diabetes	51 (43.2)	10 (47.6)	41 (42.3)	0.654
Cardiovascular diseases	33 (28.0)	7 (33.3)	26 (26.8)	0.546
COPD	33 (28.0)	3 (14.3)	30 (30.9)	0.123
CVA	23 (19.5)	5 (23.8)	18 (18.6)	0.805
CKD	17 (14.4)	5 (23.8)	12 (12.4)	0.312
ILD	12 (10.2)	3 (14.3)	9 (9.3)	0.772

ICU Intensive Care Unit, *CMV* Cytomegalovirus, *DNAemia* DNA detection by quantitative polymerase chain reaction (qPCR) on peripheral blood samples, *BMI* Body Mass Index, *APACHE II* Acute Physiology and Chronic Health Evaluation II, *SOFA* Sequential Organ Failure Assessment, *sCAP* Severe Community-acquired Pneumonia, *COPD* Chronic Obstructive Pulmonary Disease, *CVA* Cerebrovascular Accident, *CKD* Chronic Kidney Disease, *ILD* Interstitial Lung Disease

# $P < 0.05$; Categorical variables were expressed as n (%), Continuous variables were expressed as Mean ± SD or Median (IQRs); Bold font indicates the difference was statistically significant

after ICU admission. Other therapeutic measures were not significantly different between the two groups (Table 3).

Acute respiratory failure (ARF) with a prevalence of 88.1% was found to be a major complication in septic patients undergoing MV. Comparison of complications between the two groups revealed no statistically significant differences (Table 3).

Clinical outcomes

In-hospital duration of MV [34 vs. 20 (d, median); $P = 0.047$], IMV [32 vs. 17 (d, median); $P = 0.042$], and ICU stay [35 vs. 21 (d, median); $P = 0.013$] in the active CMV infection group were significantly higher than in the non-active CMV infection group (Table 3). Lengths of 30-day MV and IMV, and duration of 30-day ICU stay rates were high in the group with active CMV infection

using the KM survival analysis (Log-rank $P < 0.05$) (Fig. 2). Other clinical outcomes between the two groups showed no statistically significant differences (Table 3).

Risk factors and predictive value

In the multivariate regression model, lower Hb level was associated with patients with active CMV infection ($P < 0.05$). Based on the regression coefficient (β), Hb [β: -0.03] was a protective factor (supplement files: Table E3). ROC curve was plotted for Hb level to assess the predictive value of active CMV infection, and found the AUC of Hb level was 0.73 (specificity: 66.7%, sensitivity: 82.5%; $P = 0.001$). Furthermore, we used the cut-off method to obtain 76 g/L as the threshold for predicting active CMV infection (Fig. 3, supplement files: Table E4).

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Table 2 Laboratory findings at ICU admission

	Total $n = 118$	CMV DNAemia		P
		Yes ($n = 21$, 17.8%)	No ($n = 97$, 82.2%)	
PaO$_2$/FiO$_2$	210 (144–286)	119 (134–270)	211 (146–287)	0.439
White blood cells (10^9/L)	11.6 (8.1–15.8)	9.9 (6.9–13.0)	12.1 (8.2–16.2)	0.098
Neutrophils (10^9/L)	9.9 (7.0–13.8)	8.7 (5.4–12.1)	10.3 (7.0–14.1)	0.109
Lymphocytes (10^9/L)	0.5 (0.4–0.8)	0.6 (0.3–0.8)	0.5 (0.4–0.8)	0.855
Monocytes (10^9/L)	0.5 (0.3–0.9)	0.3 (0.2–0.8)	0.5 (0.3–0.9)	0.130
Hemoglobin (g/L)	**92 (74–112)**	**71 (69–91)**	**98 (79–112)**	**0.001#**
Platelet (10^9/L)	179 (126–265)	159 (81–265)	186 (127–262)	0.536
Procalcitonin (ng/mL)	1.33 (0.25–8.04)	1.59 (0.64–17.22)	1.04 (0.25–6.00)	0.209
Blood lactate (mmol/L)	1.6 (1.3–2.7)	1.8 (1.3–2.7)	1.6 (1.3–2.6)	0.744
PT (s)	15.2 (14.3–16.4)	15.9 (14.6–16.6)	15.2 (14.2–16.3)	0.373
APTT (s)	43.3 (37.6–51.7)	44.3 (36.1–56.6)	43.3 (37.8–51.4)	0.933
Cardiac troponins (ng/ml)	41.6 (14.7–215.0)	54.7 (26.4–218.4)	39.3 (13.7–198.4)	0.275
NT-proBNP (pg/mL)	1357 (445–5454)	2518 (1256–11,358)	1080 (412–4518)	0.061
AST (U/L)	**38.9 (21.9–77.7)**	**49.2 (38.7–119.0)**	**35.9 (20.6–74.0)**	**0.046#**
Albumin (g/L)	31.5 ± 5.2	31.4 ± 5.5	31.5 ± 5.1	0.921
T-BIL (µmol/L)	13.7 (9.8–20.2)	13.7 (10.5–20.2)	13.5 (9.8–18.9)	0.615
Scr (µmol/L)	90.5 (63.2–169.7)	120.1 (71.0–213.7)	89.2 (63.3–147.1)	0.097
BUN (mmol/L)	**10.3 (6.7–17.2)**	**13.2 (10.2–19.7)**	**10.0 (6.3–15.7)**	**0.047#**

ICU Intensive Care Unit, *CMV* Cytomegalovirus, *DNAemia* DNA detection by quantitative polymerase chain reaction (qPCR) on peripheral blood samples, *PT* Prothrombin Time, *APTT* Activated Partial Thromboplastin Time, *NT-proBNP* N-terminus Precursor of B-Type Natriuretic Peptide, *AST* Aspartate Aminotransferase, *T-BIL* Total Bilirubin, *Scr* Serum Creatinine, *BUN* Serum Urea Nitrogen

# $P < 0.05$; Continuous variables were expressed as Mean ± SD or Median (IQRs); Bold font indicates the difference was statistically significant

Discussion

Our study revealed incidence of active CMV infection in septic patients on mechanical ventilation, with 17.8% testing positive during the 28-day ICU stay. Hb level emerged as a significant predictor, with lower levels indicating a higher risk of active CMV infection. Patients with active CMV infection also exhibited longer durations of MV, IMV, and ICU stay. These findings highlight CMV as a crucial factor in septic patients, emphasizing the necessity for early intervention strategies.

Active CMV infection is a relatively frequent occurrence among non-immunosuppressed patients with critical illness. Our research team's systematic review and meta-analysis not only showed that the incidence of CMV reactivation in immunocompetent individuals could reach as high as 31%, but also revealed sepsis as an independent risk factor for CMV reactivation [3], consistent with other research [2]. Furthermore, our two clinical studies demonstrated that among critically ill patients complicating sepsis or septic shock, the incidence of active CMV infection significantly improved [4, 5]. This phenomenon was further confirmed in a review from the authoritative team [6]. The increased incidence of CMV reactivation in sepsis patients may be attributed to the hyperinflammatory state of sepsis, which triggers

the replication of latent CMV, leading to reactivation. This hypothesis has been validated in animal experiments showing that sepsis-associated mediators (lipopolysaccharide, IL-6, IL-1β, TNF-α) promote the occurrence and progression of CMV reactivation [14, 15].

Clinical studies focusing on immunocompetent sepsis patients as a specific research subject have a history of nearly 35 years since 1990, during which approximately eight studies have clarified the role of CMV reactivation in non-immunosuppressed patients with sepsis [7, 16–22]. The incidence of active CMV infection in this study was 17.8%, which is lower compared to 24%—41% incidence of active CMV infection observed in other studies involving patients with sepsis not caused by immunosuppression [6, 7, 16–22]. The incidence of active CMV infection in our study may differ from previous findings due to disease background of study subjects, varying criteria and detection methods. Particularly, the timing and duration of CMV testing in other research could influence the reported rates. As a retrospective study, ours might have underestimated the incidence by not capturing every time point. Concurrently, the discovery that 90.5% of study participants experienced CMV reactivation within the early stage of their ICU admission indicated that these individuals might have already had CMV

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Table 3 Treatment Measures, Complications, and Clinical Outcomes

	Total n = 118	CMV DNAemia		P
		Yes (n = 21, 17.8%)	No (n = 97, 82.2%)	
Treatment measures, n (%)				
Before ICU admission				
Glucocorticoids	26 (22.0)	4 (19.1)	22 (22.7)	0.941
Blood transfusion	12 (10.2)	5 (23.8)	7 (7.2)	0.060
Gamma globulin infusions	12 (10.2)	2 (9.5)	10 (10.3)	> 0.999
After ICU admission				
Glucocorticoids	87 (73.7)	14 (66.7)	73 (75.3)	0.417
Blood transfusion	**64 (54.2)**	**17 (81.0)**	**47 (48.5)**	**0.007#**
Gamma globulin infusions	**43 (36.4)**	**14 (66.7)**	**29 (29.9)**	**0.002#**
Immunosuppressive drugs[b]	10 (8.5)	3 (14.3)	7 (7.2)	0.534
Antiviral therapy[c]	**46 (39.0)**	**18 (85.7)**	**28 (28.9)**	**< 0.001#**
IMV	110 (93.2)	19 (90.5)	91 (93.8)	0.942
CRRT	42 (35.6)	11 (52.4)	31 (32.0)	0.076
ECMO	21 (17.8)	5 (23.8)	16 (16.5)	0.631
Complications, n (%)				
ARF	104 (88.1)	18 (85.7)	86 (88.7)	0.995
MODS	55 (46.6)	12 (57.1)	43 (44.3)	0.286
Septic shock	42 (35.6)	6 (28.6)	36 (37.1)	0.459
AKI	40 (33.9)	8 (38.1)	32 (33.0)	0.654
ARDS	30 (25.4)	6 (28.6)	24 (24.7)	0.715
AECOPD	30 (25.4)	2 (9.5)	28 (28.9)	0.065
AHF	23 (19.5)	4 (19.1)	19 (19.6)	> 0.999
DIC	12 (10.2)	1 (4.8)	11 (11.3)	0.613
Clinical outcomes				
Length of MV[a] (d)	**20 (11–35)**	**34 (17–39)**	**20 (11–29)**	**0.047#**
Length of IMV[a] (d)	**18 (10–32)**	**32 (12–39)**	**17 (10–28)**	**0.042#**
28-day VFD[a] (d)	0 (0–3)	0 (0–0)	0 (0–4)	0.087
Duration of ICU stay (d)	**21 (14–41)**	**35 (22–52)**	**21 (13–36)**	**0.013#**
Duration of hospital stay (d)	35 (20–48)	39 (23–53)	33 (19–46)	0.125
28-day all-cause mortality, n (%)	10 (8.5)	1 (4.8)	9 (9.3)	0.809
In-hospital all-cause mortality, n (%)	17 (14.4)	4 (19.1)	13 (13.4)	0.745

ICU Intensive Care Unit, *CMV* Cytomegalovirus, *DNAemia* DNA detection by quantitative polymerase chain reaction (qPCR) on peripheral blood samples, *IMV* Invasive Mechanical Ventilation, *CRRT* Continuous Renal Replacement Therapy, *ECMO* Extracorporeal Membrane Oxygenation, *ARF* Acute Respiratory Failure, *MODS* Multiple Organ Dysfunction Syndrome, *AKI* Acute Kidney Failure, *ARDS* Acute Respiratory Distress Syndrome, *AECOPD* Acute Exacerbation of Chronic Obstructive Pulmonary Disease, *AHF* Acute Heart Failure, *DIC* Disseminated Intravascular Coagulation, *VFD* Ventilator-Free Days

# $P < 0.05$; Categorical variables were expressed as n (%), Continuous variables were expressed as Mean ± SD or Median (IQRs); Bold font indicates the difference was statistically significant

[a] In-hospital period

[b] Included Cyclophosphamide, Methotrexate, and Mycophenolate Mofetil

[c] Included Ganciclovir, Valganciclovir, or Sodium Phosphate

reactivation prior to their ICU admission. Therefore, CMV detection should be conducted throughout the entire hospitalization cycle, not just upon admission to the ICU. Early recognition of CMV reactivation, coupled with timely interventional therapy, will improve poor prognosis in mechanically ventilated patients with sepsis. In addition, among acute respiratory distress syndrome (ARDS) patients with sepsis, those patients who received

MV for more than 4 days had a 27% cumulative risk of CMV reactivation [21]. CMV reactivation in mechanically ventilated patients is a matter of concern, especially since the causal relationship between the two needs to be further verified by basic research.

Consistent with our findings, prior research has established a link between active CMV infection and certain clinical parameters, including low Hb levels, elevated
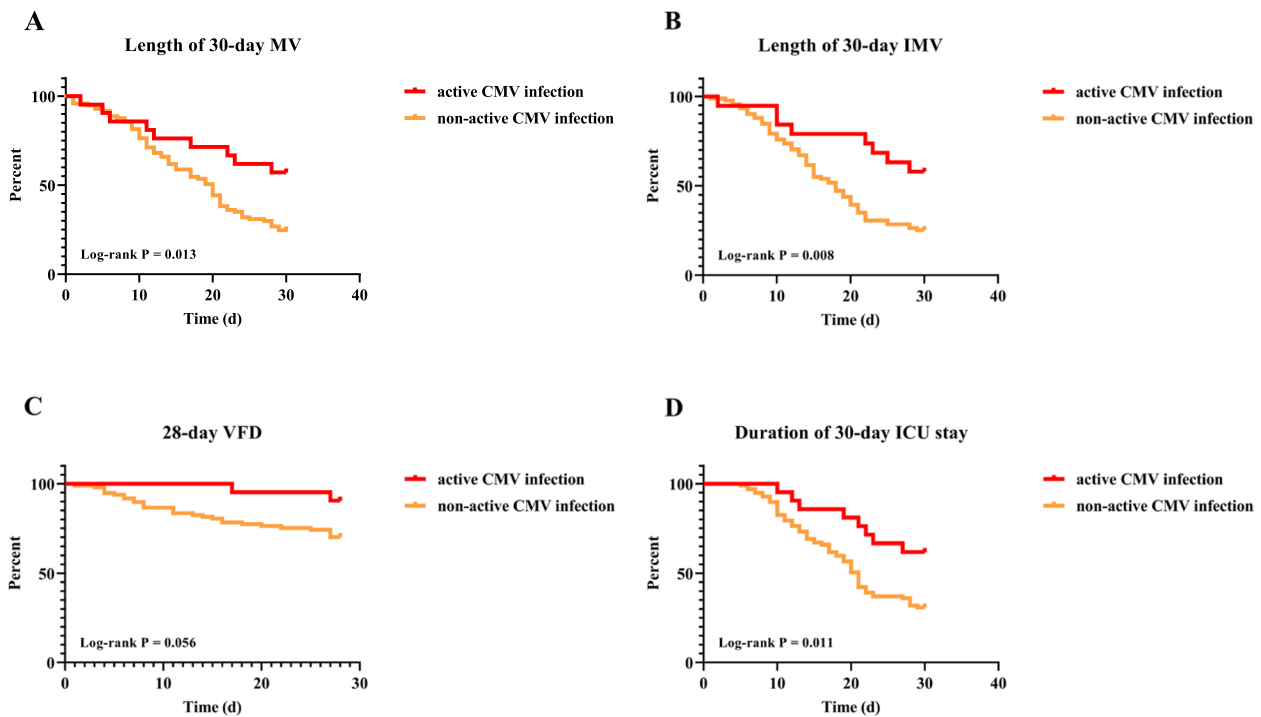
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Fig. 2 Effect of Active CMV Infection on Duration of IMV and ICU Stay. **A** Effect of active CMV infection on length of 30-day mechanical ventilation (MV); **B** Effect of active CMV infection on length of 30-day invasive mechanical ventilation (IMV); **C** Effect of active CMV infection on duration of 28-day ventilator-free days (VFD); **D** Effect of active CMV infection on duration of 30-day ICU stay
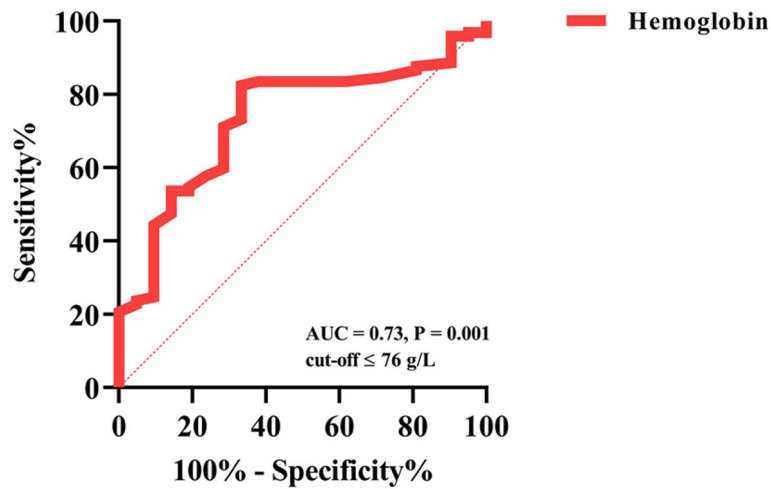

Fig. 3 Predictive Value of Hemoglobin for Active CMV Infection

AST and BUN. This is further supported by evidence that CMV infection can impair both cardiac and renal functions, leading to an increase in these biochemical indicators [23, 24]. The physiological disruption caused by CMV extends beyond these parameters, potentially contributing to a broader spectrum of clinical manifestations and complications in affected patients.

Our research, through a multivariate logistic regression analysis, identified hemoglobin levels as an independent risk factor for active CMV infection, offering a moderate predictive value. This correlation seems unprecedented, as existing literature lacks similar findings for sepsis patients undergoing MV. The decline in hemoglobin may signify the severity of illness, given that critically ill

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patients are often in a state of myelosuppression, leading to a loss of hematopoietic and immune capabilities, which in turn are associated with CMV reactivation [25]. Additionally, CMV infection, particularly in sepsis or septic shock patients, is a significant cause of myelosuppression [26–28]. This situation can lead to a reduction in hemoglobin levels, increasing the risk of blood transfusions, which have been shown to be closely related to CMV reactivation through direct transmission of the virus from donors and indirect factors such as allogeneic stimulation [29]. Our study also observed a higher transfusion rate in the group with active CMV infection, which to some extent corroborates the possibility that transfusions may facilitate CMV reactivation. However, it should be noted that due to the limited sample size in this study, there exists the potential for a type II error.

Most of the findings suggested that active CMV infection was related to the clinical prognoses of non-immunosuppressed septic patients, which is consistent with our findings, including longer durations of MV, IMV, and ICU stay. The factors contributing to these unfavorable outcomes are diverse, encompassing both direct injury (such as CMV pneumonia) and indirect injury (such as immune disorder) [25]. Therefore, the treatment of active CMV infection is considered to be of significant importance. Certainly, the timing of when clinical physicians initiate antiviral therapy and the choice of medications used may impact the final outcomes. Clinical trials about prophylactic and pre-emptive antiviral treatment strategies did not evidently prove the benefit in immunocompetent critically ill patients with active CMV infection [8, 30]. Nevertheless, patients in the sepsis category may derive significant advantages from prophylactic antiviral therapy, although the therapeutic benefits must be carefully weighed against their potential side effects of the antiviral medications [8, 31].

In addition, there are several issues that warrant attention. Firstly, the assessment of CMV should be expanded to multiple specimens (lower respiratory tract specimens), and our study found that the detection rate of CMV in the lower respiratory tract is higher, and its viral load correlates with that in the blood. A study suggest that CMV positivity in the airway is closely related to adverse outcomes [32]. Secondly, the role of plasma CMV IgG positivity in septic patients could be further evaluated in the future, as recent studies have shown that CMV IgG positivity is associated with both short-term and long-term adverse clinical outcomes [33, 34]. Lastly, sepsis itself is a significant cause of induced immunosuppression, and the pathogenicity of CMV may vary at different stages of sepsis [28, 35, 36]. In summary, this study elucidates the incidence, risk factors (predictive value), and clinical outcomes of active CMV infection among mechanically ventilated patients with sepsis. These results serve as an early warning for the identification of high-risk patients, thereby ameliorating adverse clinical outcomes and providing guidance for antiviral therapy.

This study has several limitations. First, as it was retrospective in nature, it encountered limitations in pinpointing the exact time points for accurate viral detection. Meanwhile, constraints imposed by a limited sample size and the presence of unaccounted confounders contributed to the research's shortcomings. Second, the detection of CMV DNAemia indicated active infecton in most cases, so the serostatus of CMV should have been further evaluated. Third, there was an absence of robust statistical analyses to address the deficiency in CMV sampling among patients who subsequently passed away or were discharged from the facility. Fourth, as a retrospective study, it lacks assessment of CMV viral load prior to ICU admission, co-infections, and CMV-related organ failures during hospitalization. Therefore, prospective, multicenter, propensity score-matched studies are to be carried out. More importantly, subsequent studies should evaluate the efficacy and therapeutic timing of prophylactic and preemptive anti-CMV therapies in immunocompetent mechanically ventilated patients with sepsis.

Conclusions

Active CMV infection is frequently observed to be correlated with several adverse clinical outcomes in mechanically ventilated patients with sepsis. A low hemoglobin level may serve as a risk factor and valuable predictor for CMV reactivation. To improve the poor prognosis in those patients, further prospective studies are necessary to establish the efficacy of initiating preventive and preemptive antiviral therapies.

Abbreviations

ICU	Respiratory Intensive Care Unit
CMV	Cytomegalovirus
DNAemia	DNA detection by quantitative polymerase chain reaction (qPCR) on peripheral blood samples
qPCR	Quantitative Polymerase Chain Recation
BMI	Body Mass Index
APACHE II	Acute Physiology and Chronic Health Evaluation II
SOFA	Sequential Organ Failure Assessment
sCAP	Severe Community-acquired Pneumonia
COPD	Chronic Obstructive Pulmonary Disease
CVA	Cerebrovascular Accident
CKD	Chronic Kidney Disease
ILD	Interstitial Lung Disease
PT	Prothrombin Time
APTT	Activated Partial Thromboplastin Time
NT-proBNP	N-terminus Precursor of B-Type Natriuretic Peptide
AST	Aspartate Aminotransferase
T-BIL	Total Bilirubin
Scr	Serum Creatinine
BUN	Serum Urea Nitrogen
IMV	Invasive Mechanical Ventilation
CRRT	Continuous Renal Replacement Therapy
ECMO	Extracorporeal Membrane Oxygenation

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ARF	Acute Respiratory Failure
MODS	Multiple Organ Dysfunction Syndrome
AKI	Acute Kidney Failure
ARDS	Acute Respiratory Distress Syndrome
AECOPD	Acute Exacerbation of Chronic Obstructive Pulmonary Disease
AHF	Acute Heart Failure
DIC	Disseminated Intravascular Coagulation
VFD	Ventilator-Free Days
ETA	Endotracheal Aspirates
BALF	Bronchoalveolar Lavage Fluid
β	Regression Coefficient
OR	Odds Ratio
95% CI	95% Confidence Interval
AUC	Area Under Curve

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12879-024-10304-4.

Supplementary Material 1.

Accordance statement
All methods were performed in accordance with the relevant guidelines and regulations.

Authors' contributions
ZHZ, XQL, and YML conceived and designed the study; ZHZ, JRZ, SD, XYF, YHL, JLS, LSC, TTS, SZL, JJZ, XSL, RZ, DDL, and YHX collected and aggregated data; ZHZ, JRZ, SD, XYF, and YHL analyzed the data and wrote the manuscript; XQL and YML reviewed and revised the manuscript. XQL and YML contributed equally to this work. All authors read and approved the final manuscript.

Data availability
The datasets generated during and analyzed during the current study are not publicly available due to patients privacy but are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The Ethics Committees of the First Affiliated Hospital of Guangzhou Medical University approved the protocol (No. ES-2024-K084-01). Due to the retrospective nature of this study, the Ethics Committee of the First Affiliated Hospital of Guangzhou Medical University also waived the requirement for informed consent.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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References

1. Zuhair M, Smit GSA, Wallis G, et al. Estimation of the worldwide seroprevalence of cytomegalovirus: a systematic review and meta-analysis[J]. Rev Med Virol. 2019;29(3):e2034. https://doi.org/10.1002/rmv.2034.
2. Al-Omari A, Aljamaan F, Alhazzani W, et al. Cytomegalovirus infection in immunocompetent critically ill adults: literature review[J]. Ann Intensive Care. 2016;6(1):110. https://doi.org/10.1186/s13613-016-0207-8.
3. Li X, Huang Y, Xu Z, et al. Cytomegalovirus infection and outcome in immunocompetent patients in the intensive care unit: a systematic review and meta-analysis[J]. BMC Infect Dis. 2018;18(1):289. https://doi.org/10.1186/s12879-018-3195-5.
4. Zhang Z, Li R, Chen Y, et al. Association between active cytomegalovirus infection and lung fibroproliferation in adult patients with acute respiratory distress syndrome: a retrospective study[J]. BMC Infect Dis. 2022;22(1):788. https://doi.org/10.1186/s12879-022-07747-y.
5. Zhang Z, Liu X, Sang L, et al. Cytomegalovirus reactivation in immunocompetent mechanical ventilation patients: a prospective observational study[J]. BMC Infect Dis. 2021;21(1):1026. https://doi.org/10.1186/s12879-021-06698-0.
6. Marandu T, Dombek M, Cook CH. Impact of cytomegalovirus load on host response to sepsis[J]. Med Microbiol Immunol. 2019;208(3–4):295–303. https://doi.org/10.1007/s00430-019-00603-y.
7. Imlay H, Dasgupta S, Boeckh M, et al. Risk factors for cytomegalovirus reactivation and association with outcomes in critically ill adults with sepsis: a pooled analysis of prospective studies[J]. J Infect Dis. 2021;223(12):2108–12. https://doi.org/10.1093/infdis/jiaa697.
8. Limaye AP, Stapleton RD, Peng L, et al. Effect of ganciclovir on IL-6 levels among cytomegalovirus-seropositive adults with critical illness: a randomized clinical trial[J]. JAMA. 2017;318(8):731–40. https://doi.org/10.1001/jama.2017.10569.
9. von Elm E, Altman DG, Egger M, et al. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies[J]. Lancet. 2007;370(9596):1453–7. https://doi.org/10.1016/S0140-6736(07)61602-X.
10. Fryer JF, Heath AB, Anderson R, et al. Collaborative study to evaluate the proposed 1st WHO International Standard for Human Cytomegalovirus (HCMV) for nucleic acid amplification (NAT)-based assays[S]. WHO/BS/10/2138. World Health Organization, Geneva, Switzerland.
11. Ljungman P, Chemaly RF, Khawaya F, et al. Consensus definitions of cytomegalovirus (cmv) infection and disease in transplant patients including resistant and refractory cmv for use in clinical trials: 2024 update from the transplant associated virus infections forum[J]. Clin Infect Dis. 2024;ciae321. https://doi.org/10.1093/cid/ciae321.
12. Kotton CN, Kumar D, Caliendo AM, et al. The third international consensus guidelines on the management of cytomegalovirus in solid-organ transplantation[J]. Transplantation. 2018;102(6):900–31. https://doi.org/10.1097/TP.0000000000002191.
13. Singer M, Deutschman CS, Seymour CW, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3)[J]. JAMA. 2016;315(8):801–10. https://doi.org/10.1001/jama.2016.0287.
14. Cook CH, Trgovcich J, Zimmerman PD, et al. Lipopolysaccharide, tumor necrosis factor alpha, or interleukin-1beta triggers reactivation of latent cytomegalovirus in immunocompetent mice[J]. J Virol. 2006;80(18):9151–8. https://doi.org/10.1128/JVI.00216-06.
15. Cook CH, Zhang Y, McGuinness BJ, et al. Intra-abdominal bacterial infection reactivates latent pulmonary cytomegalovirus in immunocompetent mice[J]. J Infect Dis. 2002;185(10):1395–400. https://doi.org/10.1086/340508.
16. Domart Y, Trouillet JL, Fagon JY, et al. Incidence and morbidity of cytomegaloviral infection in patients with mediastinitis following cardiac surgery[J]. Chest. 1990;97(1):18–22. https://doi.org/10.1378/chest.97.1.18.

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17. Kutza AS, Muhl E, Hackstein H, et al. High incidence of active cytomegalovirus infection among septic patients[J]. Clin Infect Dis. 1998;26(5):1076–82. https://doi.org/10.1086/520307.

18. von Müller L, Klemm A, Weiss M, et al. Active cytomegalovirus infection in patients with septic shock[J]. Emerg Infect Dis. 2006;12(10):1517–22. https://doi.org/10.3201/eid1210.060411.

19. Heininger A, Haeberle H, Fischer I, et al. Cytomegalovirus reactivation and associated outcome of critically ill patients with severe sepsis[J]. Crit Care. 2011;15(2):R77. https://doi.org/10.1186/cc10069.

20. Walton AH, Muenzer JT, Rasche D, et al. Reactivation of multiple viruses in patients with sepsis[J]. PLoS ONE. 2014;9(2):e98819. https://doi.org/10.1371/journal.pone.0098819.

21. Ong DSY, Spitoni C, Klein Klouwenberg PMC, et al. Cytomegalovirus reactivation and mortality in patients with acute respiratory distress syndrome[J]. Intensive Care Med. 2016;42(3):333–41. https://doi.org/10.1007/s00134-015-4071-z.

22. Singh N, Inoue M, Osawa R, et al. Inflammasome expression and cytomegalovirus viremia in critically ill patients with sepsis[J]. J Clin Virol. 2017;93:8–14. https://doi.org/10.1016/j.jcv.2017.05.012.

23. Wang H, Peng G, Bai J, He B, Huang K, Hu X, et al. Cytomegalovirus infection and relative risk of cardiovascular disease (ischemic heart disease, stroke, and cardiovascular death): a meta-analysis of prospective studies up to 2016[J]. J Am Heart Assoc. 2017;6(7):e005025. https://doi.org/10.1161/JAHA.116.005025.

24. Raval AD, Kistler KD, Tang Y, Murata Y, Snydman DR. Epidemiology, risk factors and outcomes associated with cytomegalovirus in adult kidney transplant recipients: a systematic literature review of real-world evidence[J]. Transpl Infect Dis. 2020;e13483. https://doi.org/10.1111/tid.13483.

25. Papazian L, Hraiech S, Lehingue S, et al. Cytomegalovirus reactivation in ICU patients[J]. Intensive Care Med. 2016;42(1):28–37. https://doi.org/10.1007/s00134-015-4066-9.

26. Zhang H, Rodriguez S, Wang L, et al. Sepsis induces hematopoietic stem cell exhaustion and myelosuppression through distinct contributions of TRIF and MYD88[J]. Stem Cell Reports. 2016;6(6):940–56. https://doi.org/10.1016/j.stemcr.2016.05.002.

27. Skirecki T, Drechsler S, Jeznach A, et al. An early myelosuppression in the acute mouse sepsis is partly outcome-dependent[J]. Front Immunol. 2021;12:708670. https://doi.org/10.3389/fimmu.2021.708670.

28. Hotchkiss RS, Moldawer LL, Opal SM, et al. Sepsis and septic shock[J]. Nat Rev Dis Primers. 2016;2:16045. https://doi.org/10.1038/nrdp.2016.45.

29. Ziemann M, Thiele T. Transfusion-transmitted CMV infection - current knowledge and future perspectives[J]. Transfus Med. 2017;27(4):238–48. https://doi.org/10.1111/tme.12437.

30. Papazian L, Jaber S, Hraiech S, et al. Preemptive ganciclovir for mechanically ventilated patients with cytomegalovirus reactivation[J]. Ann Intensive Care. 2021;11(1):33. https://doi.org/10.1186/s13613-020-00793-2.

31. Cowley NJ, Owen A, Shiels SC, et al. Safety and efficacy of antiviral therapy for prevention of cytomegalovirus reactivation in immunocompetent critically ill patients: a randomized clinical trial[J]. JAMA Intern Med. 2017;177(6):774–83. https://doi.org/10.1001/jamainternmed.2017.0895.

32. Huang L, Zhang X, Pang L, et al. Viral reactivation in the lungs of patients with severe pneumonia is associated with increased mortality, a multicenter, retrospective study[J]. J Med Virol. 2023;95(1):e28337. https://doi.org/10.1002/jmv.28337.

33. Unterberg M, Ehrentraut SF, Bracht T, et al. Human cytomegalovirus seropositivity is associated with reduced patient survival during sepsis[J]. Crit Care. 2023;27(1):417. https://doi.org/10.1186/s13054-023-04713-1.

34. Huang X, Meng Y, Hu X, et al. Association between cytomegalovirus seropositivity and all-cause mortality: an original cohort study[J]. J Med Virol. 2024;96(2):e29444. https://doi.org/10.1002/jmv.29444.

35. Hotchkiss RS, Monneret G, Payen D. Sepsis-induced immunosuppression: from cellular dysfunctions to immunotherapy[J]. Nat Rev Immunol. 2013;13(12):862–74. https://doi.org/10.1038/nri3552.

36. Ong DSY, Chong GM, Chemaly RF, et al. Comparative clinical manifestations and immune effects of cytomegalovirus infections following distinct types of immunosuppression[J]. Clin Microbiol Infect. 2022;28(10):1335–44. https://doi.org/10.1016/j.cmi.2022.05.034.

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