Active Cytomegalovirus Infection in Acute Respiratory Distress Syndrome Patients: Incidence, Risk Factors, and Clinical Outcomes

Zhihui Zhang

the First Affiliated Hospital of Guangzhou Medical University

Rujian Li

the First Affiliated Hospital of Guangzhou Medical University

Yongxin Zheng

the First Affiliated Hospital of Guangzhou Medical University

Qianyi Zhan

the First Affiliated Hospital of Guangzhou Medical University

Qing Zang

the First Affiliated Hospital of Guangzhou Medical University

Ruixue Zhao

the First Affiliated Hospital of Guangzhou Medical University

Qing Rao

the First Affiliated Hospital of Guangzhou Medical University

Jierong Zhang

the First Affiliated Hospital of Guangzhou Medical University

Yongbo Huang

the First Affiliated Hospital of Guangzhou Medical University

Xiaoqing Liu

the First Affiliated Hospital of Guangzhou Medical University

Yimin Li (✉ dryiminli@vip.163.com)

the First Affiliated Hospital of Guangzhou Medical University

Research Article

Keywords: Cytomegalovirus, Acute Respiratory Distress Syndrome, Incidence, Risk Factors, Clinical Outcomes

Posted Date: June 4th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-576066/v1>

Abstract

Background: Acute respiratory distress syndrome (ARDS) patients have been reported to have a high seroprevalence of cytomegalovirus (CMV). However, the role of active CMV infection in ARDS patients has not been clearly established.

Objective: This study aimed at determining the incidence, risk factors, and clinical outcomes of active cytomegalovirus (CMV) infection in acute respiratory distress syndrome (ARDS) patients.

Methods: We retrospectively reviewed medical records for ARDS patients who had been admitted to the intensive care unit (ICU) from January 1st, 2018 to December 31st, 2020 at a national teaching hospital in China. Study participants were divided into active CMV infection and non-active 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 168 ARDS patients, 31 (18.5%) exhibited active CMV infection within the 28-day hospitalization period in ICU. In multivariate logistic regression analysis, monocyte counts, hemoglobin levels, blood transfusion, and septic shock were significantly independently associated with active CMV infection ($p < 0.05$). Oxygenation ($\text{PaO}_2/\text{FiO}_2$) of active CMV infection patients was worse than for non-active CMV infection ($p < 0.05$). Duration of invasive mechanical ventilation, 28-day ventilator-free days, length of ICU stay, and 28-day all-cause mortality rates in active CMV infection patients were significantly higher than in those without active CMV infection ($p < 0.05$).

Conclusions: Active CMV infection is common among critically ill ARDS patients. Monocytes, hemoglobin, blood transfusion, and septic shock are risk factors for active CMV infection, which has a negative effect on oxygenation. Moreover, active CMV infection is associated with several adverse prognoses. Prospective studies should be performed to evaluate the impact of prophylactic antiviral therapy for prognoses among ARDS patients.

Background

As a latent viral infection, cytomegalovirus (CMV) is prevalent in the general population [1]. Under certain circumstances, CMV may reactivate, and its hazardous nature has been proven, especially in immunosuppressed patients, such as those under organ transplantation or with HIV infection [2]. Over the past 20 years, active CMV infection has also been shown to occur in immunocompetent patients with critical illness [3]. Among these patients, incidences of active CMV infection are more than 30%, and are correlated with prolonged duration of mechanical ventilation, increased length of hospital stay, and high case fatality [4].

Acute respiratory distress syndrome (ARDS) is a common disease in the intensive care unit (ICU). The major cause of ARDS is severe pneumonia, in which viral pneumonia plays an important role [5]. Furthermore, atypical pathogens (herpes simplex virus and CMV) may also be responsible for infection in

ARDS patients [6]. However, studies have not elucidated on the role of active CMV infection in ARDS patients. Moreover, there is a need to establish their clinical incidences, risk factors, and prognoses. Therefore, this study aimed at investigating the incidences, risk factors, and clinical outcomes of active CMV infection in ARDS patients.

Methods

2.1 Study participants

We retrospectively reviewed medical records for ARDS patients who had been admitted to the ICU between January 1st, 2018 and December 31st, 2020 at the First Affiliated Hospital of Guangzhou Medical University, China. Detection of active CMV infection was done using real-time PCR with blood plasma as the sample. Study participants were divided into active CMV infection (CMV DNAemia ≥ 500 copies/mL) and non-active infection groups (CMV DNAemia < 500 copies/mL) within 28-day hospitalization period in the ICU. The Ethics Committee of the First Affiliated Hospital of Guangzhou Medical University approved the study protocol (No. GY-2021-K04). The need for an informed consent was waived due to the retrospective nature of the study.

2.2 Data collection

Clinical data for 168 cases were extracted from the electronic records by two independent researchers who subsequently cross-checked the data for accuracy, including clinical features, laboratory findings, treatments, complications, and clinical outcomes. Disagreements between the two researchers were further adjudicated by a third independent reviewer who was an expert in critical care medicine. Data were entered into an electronic database for statistical analysis.

2.3 Study definitions

The inclusion criteria were: i. Patients that met the diagnostic criteria for ARDS (Berlin definition 2012) [7] and ii. Patients aged > 18 years. The exclusion criteria were: i. Pregnant or lactating patients; ii. Survival time < 72 h; iii. Lack of CMV detection; and iv. Patients administered with antiviral therapy before ICU entry.

According to the World Health Organization Standard, active CMV infection was defined as viral load greater than or equal to 500 copies/mL in plasma [8]. Screening for CMV viral load in plasma was part of routine clinical practice in the hospital.

2.4 Study outcomes

Assessed outcomes included incidences, risk factors, and prognoses of the study participants. Moreover, we assessed the impact of CMV infection on oxygenation ($\text{PaO}_2/\text{FiO}_2$).

2.5 Statistical analysis

Continuous variables were expressed as Mean $\pm$ SD or Median (interquartile ranges, IQRs) and compared using the Wilcoxon rank-sum test. Categorical variables were expressed as counts and percentages, and compared using the Fisher's exact test. Risk factors for active CMV infection were screened in the univariate logistic regression model, variables with $p \leq 0.05$ were considered potential risk factors and were further imported into the multivariate logistic regression analysis. Active CMV infection risk model was established by calculating the regression coefficient (β), odds ratios (OR), and 95% confidence interval (CI). The receiver operating characteristic (ROC) curve was used to evaluate the predictive value of active CMV infection. The area under ROC curve (AUC), 95% CI, p-value, cut-off, sensitivity, and specificity were calculated. The significance threshold was set at a two-sided $p \leq 0.05$. All statistical analyses or charting were performed using SPSS version 25.0 (SPSS Inc., USA) and GraphPad Prism 8.0 (Graphpad Software Inc., USA).

Results

3.1 Active CMV infection

During the study period, a total of 4,261 patients were admitted to the ICU. Among them, 4,022 patients were initially excluded for reasons that included: i. Not meeting the ARDS diagnostic criteria ($n=3,987$); ii. Survived for less than 72 h ($n=23$); iii. Pregnant or lactating women ($n=7$), and iv. Younger than 18 years ($n=5$). Preliminarily, 239 ARDS patients were screened, however, 71 were excluded for; i. Lacking CMV detection ($n=69$) and ii. Receiving antiviral therapy before entering the ICU ($n=2$). Finally, a total of 168 ARDS patients were enrolled (**Figure 1**)

Among the 168 enrolled ARDS patients, there were 31 (18.5%) cases of active CMV infections within the 28-day ICU hospitalization period (**Figure 1**). A total of 25 (80.7%) of the 31 cases with active CMV infection exhibited positive results at ICU admission, moreover, 4 cases at day 14 and 2 cases at day 21.

3.2 Clinical features

We recruited 168 patients with complete data, among whom 111 were male (66.1%). The mean age for all study participants was 58 ± 15 years. Based on the median scores for APACHE II (20) and SOFA (9), the disease was very severe. Patients with mild, moderate, and severe ARDS were 32 (19.0%), 66 (39.3%), and 70 (41.7%), respectively. The main cause of ARDS was pneumonia (91.7%). Patients' heart and respiratory rates were higher. The main comorbidities were hypertension ($n=47$, 28.0%), cardiovascular diseases ($n=47$, 28.0%), and connective tissue diseases ($n=31$, 18.5%). Except for connective tissue disease [35.5% vs. 14.6% (n), $p=0.011$], differences in these clinical characteristics between the two groups were not significant (**Table 1**).

Moreover, the active CMV infection group exhibited low monocyte counts (median: 0.2 vs. 0.5 (109/L), $p=0.006$), hemoglobin levels (median: 82 vs. 97 (g/L), $p=0.009$), platelet counts (median: 102 vs. 145 (109/L), $p=0.012$), and T-helper lymphocytes/T-suppressor lymphocytes (Th/Ts) counts (median: 0.98 vs.

1.32, $p=0.030$). There were no significant differences for other laboratory findings between the two groups (**Table 2**).

3.3 Risk factors

In the multivariate regression model, monocytes [OR: 0.182, 95% CI: 0.054-0.617, $p=0.006$], hemoglobin [OR: 0.974, 95% CI: 0.953-0.996, $p=0.020$], blood transfusion [OR: 3.790, 95% CI: 1.407-10.210, $p=0.008$], and septic shock [OR: 4.889, 95% CI: 1.018-23.478, $p=0.047$] were independently associated with active CMV infection in ARDS patients. Based on the regression coefficient (β), monocytes [β : -1.702] and hemoglobin [β : -0.026] were inhibitory factors for active CMV infection. However, blood transfusion [β : 1.332] and septic shock [β : 1.587] were found to facilitate active CMV infection (**Table 3**).

3.4 Treatments, complications, and clinical outcomes

Most of the patients (96.8%) with active CMV infection were administered with antiviral therapy [96.8% vs. 0% (n), $p<0.01$] after ICU admission. Moreover, compared to the group without active CMV infection, immunosuppressive drugs [29.0% vs. 9.5% (n), $p=0.007$] and blood transfusion [38.7% vs. 13.1% (n), $p=0.003$] were found to have been highly administered in the group with active CMV infection before ICU admission. Other therapeutic measures were not significantly different between the two groups (**Table 4**).

Severe pneumonia with a prevalence of 91.7% was found to be a major complication in ARDS patients. Compared to the non-active CMV infection group, the number of ARDS patients diagnosed with septic shock [90.3% vs. 71.5% (n), $p=0.037$] in the active CMV infection group was higher. Although statistical significance was not reached, the rate of AECOPD was low in cases without (11.7%) than in cases with (22.6%) active CMV infection (**Table 4**).

Length of invasive mechanical ventilation (IMV) [median: 42 vs. 29 (d), $p=0.045$], 28-day ventilator-free days (VFD) [median: 0 vs. 0 (d), $p=0.039$], ICU length of stay [median: 32 vs. 22 (d), $p=0.047$], and the 28-day all-cause mortality rate [51.6% vs. 26.3% (n), $p=0.009$] in the active CMV infection group were significantly higher than in the non-active CMV infection group (**Table 4**).

3.5 Oxygenation influence

Continuous observation of arterial oxygenation over 7 days of active infection with CMV revealed that the CMV group exhibited worse outcomes in oxygenation within 5-day hospitalization in ICU than the non-active CMV infection group. On day 5, oxygenation was significantly worse in the active CMV group than in the non-active CMV infection group [median: 179 vs. 193 (P/F), $p=0.046$] (**Figure 2**).

Discussion

We evaluated the incidence, risk factors, and clinical outcomes of active CMV infection in ARDS patients. Among ARDS patients, the incidence rate of active CMV infection was 18.5%. Clinical features, including connective tissue disease, monocytes, hemoglobin, platelet, Th/Ts, immunosuppressive drugs and blood

transfusion, and septic shock were associated with active CMV infection. Monocytes, hemoglobin, blood transfusion, and septic shock were found to be independent risk factors for active CMV infection. Moreover, active CMV infection had a negative effect on oxygenation and was associated with adverse prognoses.

Active CMV infection is not a rare phenomenon among patients admitted to the ICU. It has been reported that the incidence of active CMV infection in critically ill patients is 31% [4]. However, the population included in most of the current studies did not differentiate between specific disease types, especially ARDS. Two prospective studies revealed that the incidence of active CMV infection in ARDS patients was 18.6%-22.0% [9, 10], which was comparable to our findings. We found that most of the patients had active CMV infections at the time of ICU admission, implying that active CMV infection was likely to have been present before ICU admission. Therefore, detection of active CMV infection should not be restricted to ICU post-admission but should be extended to ICU pre-admission.

Active CMV infection has previously been associated with several conditions, including immunosuppressive drugs, blood transfusion, and septic shock [3, 10-12], consistent with our results. Immune dysfunction is closely correlated with the occurrence of active CMV infection [2, 13]. Immunosuppressive drugs result in suppressed immune cell (especially T lymphocytes) levels, which inhibits viral clearance, making latent CMV infection more susceptible to active infection, as seen mostly in transplant patients [3, 13-15]. Active CMV infection through transfusion is a challenge in the treatment of critically ill patients. It has been reported that donations from new CMV-IgG-positive donors bear the highest risk for transmitting CMV infections because they contain elevated CMV-DNA levels, which is a risk factor for active CMV infection [16]. Leucocyte depletion of cellular blood products and selection of CMV-IgG-negative donations might reduce the occurrence of active CMV infection [16, 17]. Sepsis induces active CMV infection through sepsis-related cytokine storm, which triggers transcriptional CMV replication, a mechanism that has been confirmed in animal models [18, 19]. Furthermore, several studies have shown that active CMV infection impairs hematopoiesis and immune function [20, 21], suppressing multiple blood cell levels, consistent with our results. The reason for this association is correlated with direct pathological damage caused by CMV infection and the indirect damage caused by inflammatory factors.

Active CMV infection has been strongly associated with sepsis, mechanical ventilation, as well as hypertension induced by glucocorticoids and catecholamines. Besides, there was no correlation for disease scores, such as the APACHE and SOFA scores. There is no evidence that CMV reactivation is age-related, and whether it is gender-related or not has not been established [3]. Moreover, risk factors for active CMV infection in ARDS patients have not been clearly elucidated. We found that monocytes, hemoglobin, blood transfusion, and septic shock were independent risk factors for active CMV infection in ARDS patients. The mechanisms through which hemoglobin, blood transfusion, and septic shock cause active CMV infection have been described above. Monocytes are essential for effective control and clearance of viral infections, especially their direct involvement in non-specific immunity and indirect regulation of specific immunity [22]. Monocytes play a pivotal role in viral dissemination to organ tissues

during primary infections and the following reactivation from latency [23]. Main targets of CMV are monocytes, where they induce their differentiation into macrophages [23, 24]. Once CMV infected monocytes differentiate into macrophages, expression of immediate early viral genes are detectable, followed by viral replication and long term infectious viral particle release [23]. Furthermore, CMV have been shown to alter the expression of monocyte transcripts and are involved in inflammatory responses, which enhances CMV replication [23-25]. Therefore, suppressed monocyte levels directly affect CMV clearance and indirectly reflect elevated CMV replication levels.

Active CMV infection is associated with adverse prognoses for critically ill patients, consistent with our findings, including prolonged duration of mechanical ventilation, increased length of hospitalization, and mortality [2-4, 9-12, 18]. These adverse prognoses are associated with various factors, including direct injury (such as CMV pneumonia) and indirect injury (such as immune disorders) [18, 26]. We found that active CMV infection is associated with poor oxygenation in ARDS patients, as previously reported [12]. This mechanism may be involved in the initiation of pulmonary fibrosis by CMV and has been validated in in vivo experiments [27]. CMV may be a potential factor in the development of pulmonary fibrosis in ARDS patients.

This study has several limitations. First, as a retrospective study, the time points at which accurate viral detections were made were impossible to be determined. Second, since CMV positive cases were present at ICU admission, only active infection incidences and not reactivation incidences could be assessed. Third, due to the lack of CMV detection in the airways, we could not establish the clinical significance of CMV on oxygenation among ARDS patients. Therefore, prospective, multicenter studies are needed in future. Further analysis of the effect of CMV in the airways of ARDS patients is needed, and evaluation of CMV reactivation needs to be extended to the entire hospitalization period and not limited to the ICU stay period.

Conclusion

Active CMV infection is a common phenomenon in ARDS patients. Monocytes, hemoglobin, blood transfusion, and septic shock are risk factors for active CMV infection, which has a negative effect on oxygenation. Moreover, active CMV infection is associated with several adverse clinical outcomes. Prospective studies should aim at evaluating the impact of prophylactic antiviral therapy on the prognosis of ARDS patients.

Abbreviations

CMV: Cytomegalovirus; ICU: Intensive Care Unit; ARDS: Acute Respiratory Distress Syndrome; LPS: Lipopolysaccharide; BMI: Body Mass Index; APACHE II: Acute Physiology and Chronic Health Evaluation; SOFA: Sequential Organ Failure Assessment; P/F: PaO₂/FiO₂; QRT-PCR: Quantitative Real-time Polymerase Chain Reaction; COPD: Chronic Obstructive Pulmonary Disease; AECOPD: Acute Exacerbation of Chronic Obstructive Pulmonary Disease; Th1/Th2: Helper T Lymphocyte 1&2; PT: Prothrombin Time;

APTT: Activated Partial Thromboplastin Time; NT-proBNP: N-terminal Pro-B-type Natriuretic Peptide; AST: Aspartate Aminotransferase; ALT: Alanine Transaminase; T-BIL: Total Bilirubin; Scr: Serum Creatinine; BUN: Serum Urea Nitrogen; Hb: Hemoglobin; Th: T-helper Lymphocytes; Ts: T-suppressor Lymphocytes; IL: Interleukin; TNF: Tumor Necrosis Factor; INF: Interferon; CRRT: Continuous Renal Replacement Therapy; ECMO: Extracorporeal Membrane Oxygenation; AHF: Acute Heart Failure; AKI: Acute Kidney Failure; DIC: Disseminated Intravascular Coagulation; IMV: Invasive Mechanical Ventilation; VFD: Ventilator-free Days; IQRs: Interquartile Ranges; β : Regression Coefficient; OR: Odds Ratio; ROC: Receiver Operating Curve; AUC: Area Under Curve; CI: Confidence Interval.

Declarations

Authors' contributions

Zhihui Zhang, Yimin Li, and Xiaoqing Liu conceived and designed the study; Zhihui Zhang, Rujian Li, Yongxin Zheng, Qianyi Zhan, Qing Zang, and Ruixue Zhao collected and aggregated data; Zhihui Zhang, Rujian Li, Qianyi Zhan, Qing Zang, Ruixue Zhao, Qing Rao, and Jierong Zhang analyzed the data and wrote the manuscript; Yimin Li, Xiaoqing Liu, and Yongbo Huang reviewed and revised the manuscript. All authors read and approved the final manuscript.

Funding

The study was funded by the National Science and Technology Major Project (No. 2017ZX10204401), National Natural Science Foundation of China (Nos. 81970071, 82070084), Clinical Research and Cultivation Project of Guangzhou Medical University (No. B185004064), Science and Technology Program of Guangzhou (No. 202102010366), and Guangzhou Medical University Students Extracurricular Academic Technology Project (Nos. 2020A012, 2021A016).

Availability of data and materials

Data sharing will be considered only on a collaborative basis with the principal investigators, after evaluation of the proposed study protocol and statistical analysis plan.

Ethical approval and consent to participate

The Ethics Committees of the First Affiliated Hospital of Guangzhou Medical University approved the protocol and exempted consent forms (No. GY-2021-K04).

Consent for publication

Not applicable.

Competing interests

None of the authors has any conflict of interest to report.

Statement

All methods were carried out in accordance with relevant guidelines and regulations in the manuscript.

Acknowledgments

Not applicable.

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 May;29(3):e2034. DOI: 10.1002/rmv.2034.
2. Griffiths P. Burden of disease associated with human cytomegalovirus and prospects for elimination by universal immunisation[J]. *Lancet Infect Dis*. 2012 Oct;12(10):790-8. DOI: 10.1016/S1473-3099(12)70197-4.
3. Al-Omari A, Aljamaan F, Alhazzani W, et al. Cytomegalovirus infection in immunocompetent critically ill adults: literature review[J]. *Ann Intensive Care*. 2016 Dec;6(1):110. DOI: 10.1186/s13613-016-0207-8.
4. 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 Jun;18(1):289. DOI: 10.1186/s12879-018-3195-5.
5. Shah RD, Wunderink RG. Viral Pneumonia and Acute Respiratory Distress Syndrome[J]. *Clin Chest Med*. 2017 Mar;38(1):113-125. DOI: 10.1016/j.ccm.2016.11.013.
6. Luyt CE, Bouadma L, Morris AC, et al. Pulmonary infections complicating ARDS[J]. *Intensive Care Med*. 2020 Dec;46(12):2168-2183. DOI: 10.1007/s00134-020-06292-z.
7. ARDS Definition Task Force, Ranieri VM, Rubenfeld GD, et al. Acute respiratory distress syndrome: the Berlin Definition[J]. *JAMA*. 2012 Jun;307(23):2526-33. DOI: 10.1001/jama.2012.5669.
8. Fryer JF, Heath AB, Anderson R, Minor PD, Collaborative Study Group. 2010. Collaborative study to evaluate the proposed 1st WHO International Standard for Human Cytomegalovirus (HCMV) for nucleic acid amplification (NAT)-based assays. WHO/BS/10/2138. World Health Organization, Geneva, Switzerland.
9. 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 Mar;42(3):333-341. DOI: 10.1007/s00134-015-4071-z.
10. Vergara A, Cilloniz C, Luque N, et al. Detection of human cytomegalovirus in bronchoalveolar lavage of intensive care unit patients[J]. *Eur Respir J*. 2018 Feb;51(2):1701332. DOI: 10.1183/13993003.01332-2017.

11. Frantzeskaki FG, Karampi ES, Kottaridi C, et al. Cytomegalovirus reactivation in a general, nonimmunosuppressed intensive care unit population: incidence, risk factors, associations with organ dysfunction, and inflammatory biomarkers[J]. *J Crit Care*. 2015 Apr;30(2):276-81. DOI: 10.1016/j.jcrc.2014.10.002.
12. 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. DOI: 10.1186/cc10069.
13. Pawelec G. Immunosenescence: role of cytomegalovirus. *Exp Gerontol*. 2014 Jun;54:1-5. DOI: 10.1016/j.exger.2013.11.010.
14. Klenerman P, Oxenius A. T cell responses to cytomegalovirus. *Nat Rev Immunol*. 2016 Jun;16(6):367-77. DOI: 10.1038/nri.2016.38. Epub 2016 Apr 25.
15. Yong MK, Lewin SR, Manuel O. Immune Monitoring for CMV in Transplantation[J]. *Curr Infect Dis Rep*. 2018 Mar;20(4):4. DOI: 10.1007/s11908-018-0610-4.
16. Ziemann M, Thiele T. Transfusion-transmitted CMV infection - current knowledge and future perspectives[J]. *Transfus Med*. 2017 Aug;27(4):238-248. DOI: 10.1111/tme.12437.
17. AABB, Clinical Transfusion Medicine Committee, Heddle NM, et al. AABB Committee Report: reducing transfusion-transmitted cytomegalovirus infections[J]. *Transfusion*. 2016 Jun;56(6 Pt 2):1581-7. DOI: 10.1111/trf.13503.
18. Laurent Papazian, Sami Hraiech, Samuel Lehingue, et al. Cytomegalovirus reactivation in ICU patients[J]. *Intensive Care Med*. 2016 Jan;42(1):28-37. DOI: 10.1007/s00134-015-4066-9.
19. Charles H Cook, Joanne Trgovcich, Peter D Zimmerman, et al. Lipopolysaccharide, tumor necrosis factor alpha, or interleukin-1beta triggers reactivation of latent cytomegalovirus in immunocompetent mice[J]. *J Virol*. 2006 Sep;80(18):9151-8. DOI: 10.1128/JVI.00216-06.
20. Renzaho A, Podlech J, Kühnapfel B, et al. Cytomegalovirus-Associated Inhibition of Hematopoiesis Is Preventable by Cytoimmunotherapy With Antiviral CD8 T Cells[J]. *Front Cell Infect Microbiol*. 2020 Apr;10:138. DOI: 10.3389/fcimb.2020.00138.
21. Reddehase MJ. Mutual Interference between Cytomegalovirus and Reconstitution of Protective Immunity after Hematopoietic Cell Transplantation[J]. *Front Immunol*. 2016 Aug;7:294. DOI: 10.3389/fimmu.2016.00294.
22. Shi C, Pamer EG. Monocyte recruitment during infection and inflammation[J]. *Nat Rev Immunol*. 2011 Oct;11(11):762-74. DOI: 10.1038/nri3070.
23. Min CK, Shakya AK, Lee BJ, et al. The Differentiation of Human Cytomegalovirus Infected-Monocytes Is Required for Viral Replication[J]. *Front Cell Infect Microbiol*. 2020 Jul;10:368. DOI: 10.3389/fcimb.2020.00368.
24. Rice GP, Schrier RD, Oldstone MB. Cytomegalovirus infects human lymphocytes and monocytes: virus expression is restricted to immediate-early gene products[J]. *Proc Natl Acad Sci U S A*. 1984 Oct;81(19):6134-8. DOI: 10.1073/pnas.81.19.6134.
25. Nikitina E, Larionova I, Choinzonov E, et al. Monocytes and Macrophages as Viral Targets and Reservoirs[J]. *Int J Mol Sci*. 2018 Sep;19(9):2821. DOI: 10.3390/ijms19092821.

26. Paul Griffiths, Ilona Baraniak, Matt Reeves. The pathogenesis of human cytomegalovirus. J Pathol[J]. 2015 Jan;235(2):288-97. DOI: 10.1002/path.4437.

27. Cook CH, Zhang Y, Sedmak DD, et al. Pulmonary cytomegalovirus reactivation causes pathology in immunocompetent mice[J]. Crit Care Med. 2006 Mar;34(3):842-9. DOI: 10.1097/01.ccm.0000201876.11059.05.

Tables

Table 1. Clinical features of the study participants

	Overall	Active CMV infection		
	N=168	Yes (n=31, 18.5%)	No (n=137, 81.5%)	P
Age (yr)	58 ± 15	62 ± 12	57 ± 15	0.104
Sex, n (%)				0.062
Male	111 (66.1)	25 (80.7)	86 (62.8)	-
Female	57 (33.9)	6 (19.3)	51 (37.2)	-
Weight (kg)	60.0 (52.5-67.0)	60.0 (51.0-67.5)	60.0 (53.3-67.0)	0.870
BMI (kg/m ²)	22.4 (19.9-24.2)	22.5 (19.0-23.3)	22.1 (20.0-24.8)	0.541
Score of disease severity				
APACHE II	20 (15-25)	20 (16-28)	20 (15-25)	0.469
SOFA	9 (7-12)	9 (8-12)	9 (7-12)	0.532
qSOFA	2 (1-3)	2 (1-2)	2 (1-3)	0.511
ARDS severity, n (%)				
Mild	32 (19.0)	5 (16.1)	27 (19.7)	0.802
Moderate	66 (39.3)	14 (45.2)	52 (38.0)	0.542
Severe	70 (41.7)	12 (38.7)	58 (42.3)	0.841
Main causes of ARDS, n (%)				0.471
Pneumonia	154 (91.7)	30 (96.8)	124 (90.5)	-
Other	14 (8.3)	1 (3.2)	13 (9.5)	-
Vital signs				
Average blood pressure (mmHg)	77 (63-91)	78 (64-89)	76 (63-92)	0.841
Heart rate (bp)	105 (89-123)	100 (86-123)	105 (91-122)	0.827
Respiratory rate (t/m)	25 (21-31)	24 (21-30)	25 (20-31)	0.835
Temperature (°C)	37.1 (36.5-38)	37.0 (36.2-38.0)	37.2 (36.5-38.0)	0.333
Comorbidities, n (%)				
Hypertension	47 (28.0)	13 (41.9)	34 (24.8)	0.080
Cardiovascular diseases	47 (28.0)	9 (29.0)	38 (27.7)	> 0.99
Connective tissue disease*	31 (18.5)	11 (35.5)	20 (14.6)	0.011

Bronchial asthma	30 (17.9)	9 (29.0)	21 (15.3)	0.116
Malignancy	28 (16.7)	7 (22.6)	21 (15.3)	0.422
Diabetes	28 (16.7)	7 (22.6)	21 (15.3)	0.422
COPD	23 (13.7)	7 (22.6)	16 (11.7)	0.145
Cerebral thrombosis	20 (11.9)	3 (9.7)	17 (12.4)	> 0.99
Bronchiectasis	14 (8.3)	3 (9.7)	11 (8.0)	0.724

^a, $P < 0.05$; Continuous variables were expressed as Mean $\pm$ SD or Median (IQRs); *, mainly included Systemic Lupus Erythematosus, Rheumatoid Arthritis, Dermatomyositis, Still's Disease and Sjogren's Syndrome. Bold font indicates the difference was statistically significant. BMI: Body Mass Index; APACHEII: Acute Physiology and Chronic Health Evaluation; SOFA: Sequential Organ Failure Assessment; qSOFA: Quick Sequential Organ Failure Assessment; COPD: Chronic Obstructive Pulmonary Disease.

Table 2. Laboratory findings of the study subjects at the time of ICU admission.

	Overall	Active CMV Infection		
	N=168	Yes (n=31, 18.5%)	No (n=137, 81.5%)	<i>P</i>
Laboratory Findings				
White blood cells (10 ⁹ /L)	10.7 (7.0-15.2)	9.8 (6.9-14.1)	10.8 (7.0-15.7)	0.594
Neutrophils (10 ⁹ /L)	9.9 (5.9-14.8)	9.2 (5.9-13.2)	10.0 (5.9-15.3)	0.734
Lymphocytes (10 ⁹ /L)	0.4 (0.2-0.8)	0.3 (0.1-0.7)	0.4 (0.2-0.8)	0.110
Monocytes (10⁹/L)	0.4 (0.1-0.9)	0.2 (0.1-0.5)	0.5 (0.2-0.9)	0.006
Hemoglobin (g/L)	95 (80-113)	82 (72-102)	97 (84-114)	0.009
Platelet (10⁹/L)	136 (75-209)	102 (51-141)	145 (90-222)	0.012
Procalcitonin (ng/mL)	1.48 (0.28-10.85)	1.11 (0.28)	1.62 (0.31-10.85)	0.487
Blood lactate (mmol/L)	2.1 (1.5-2.9)	2.4 (1.5-2.9)	2.0 (1.5-3.1)	0.704
PT (s)	16.1 (15.0-18.4)	16.6 (15.2-18.8)	15.9 (14.9-18.3)	0.282
APTT (s)	43.3 (38.2-55.4)	43.9 (37.3-64.2)	43.1 (38.3-54.3)	0.828
Cardiac troponins (ng/ml)	0.08 (0.03-0.58)	0.08 (0.03-0.17)	0.08 (0.04-1.02)	0.265
NT-proBNP (pg/mL)	1738 (560-4787)	2593 (571-5785)	1718 (568-4335)	0.386
AST (U/L)	51.5 (33.6-102.6)	42.7 (32.0-62.0)	55.2 (34.2-105.1)	0.078
ALT (U/L)	28.6 (17.7-60.4)	24.1 (17.8-43.0)	30.9 (17.8-62.2)	0.086
Albumin (g/L)	31.0 (27.8-33.9)	30.5 (27.8-32.6)	30.8 (27.9-33.9)	0.456
T-BIL (μmol/L)	15.2 (10.0-27.7)	18.0 (10.5-26.5)	15.0 (10.2-28.0)	0.694
D-BIL (μmol/L)	5.0 (3.0-13.2)	6.7 (3.6-10.7)	5.0 (3.0-14.8)	0.867
Scr (μmol/L)	101 (72-172)	128 (77-193)	102 (75-166)	0.305
BUN (mmol/L)	10.4 (6.1-17.5)	12.1 (6.7-20.6)	10.4 (6.2-16.7)	0.204
T lymphocytes (%)	65.9 (53.9-74.5)	64.9 (50.8-80.8)	66.5 (57.2-73.5)	0.516
Th lymphocytes (%)	34.6 (25.1-45.7)	27.2 (24.3-35.6)	34.9 (26.8-46.4)	0.053
Ts lymphocytes (%)	24.5 (17.0-33.9)	30.5 (22.0-37.6)	23.8 (17.1-33.4)	0.066
Th/Ts	1.41 (0.89-2.33)	0.98 (0.84-1.42)	1.32 (0.87-2.50)	0.030

IL-2 (pg/mL)	0.96 (0.58-1.31)	0.68 (0.48-1.20)	0.88 (0.58-1.30)	0.484
IL-4 (pg/mL)	1.37 (0.80-2.04)	0.87 (0.66-1.78)	1.48 (0.86-2.12)	0.211
IL-6 (pg/mL)	53.23 (14.14-163.67)	64.49 (18.20-178.96)	51.24 (12.84-142.75)	0.273
IL-10 (pg/mL)	6.88 (3.82-17.86)	6.80 (4.85-22.75)	6.98 (3.69-11.60)	0.560
TNF- α (pg/mL)	1.04 (0.74-1.65)	0.90 (0.64-1.16)	1.06 (0.73-1.58)	0.114
INF- γ (pg/mL)	1.20 (0.68-2.41)	1.14 (0.65-3.09)	1.16 (0.70-2.11)	0.891

^a, $P < 0.05$; Continuous variables were expressed as Mean $\pm$ SD or Median (IQRs); Bold font indicates the difference was statistically significant. PT: Prothrombin Time; APTT: Activated Partial Thromboplastin Time; NT-proBNP: N-terminus Precursor of B-Type Natriuretic Peptide; AST: Aspartate Aminotransferase; ALT: Alanine Transaminase; T-BIL: Total Bilirubin; D-BIL: Direct Bilirubin; Scr: Serum Creatinine; BUN: Serum Urea Nitrogen; Th: T-helper Lymphocytes; Ts: T-suppressor Lymphocytes; IL: Interleukin; TNF: Tumor Necrosis Factor; INF: Interferon.

Table 3. Risk factors for active CMV infection in ARDS patients.

Variables	β	OR (95% CI)	P
Univariate logistic regression			
Connective tissue disease	1.169	3.217 (1.341-7.721)	0.009
Monocytes	-1.383	0.251 (0.083-0.755)	0.014
Hemoglobin	-0.024	0.976 (0.958-0.995)	0.015
Platelet	-0.005	0.995 (0.990-0.999)	0.027
Immunosuppressive drugs ^b	1.362	3.902 (1.489-10.225)	0.006
Blood transfusion ^b	1.429	4.175 (1.738-10.030)	0.001
Septic shock	1.312	3.714 (1.067-12.927)	0.039
Multivariate logistic regression			
Monocytes	-1.702	0.182 (0.054-0.617)	0.006
Hemoglobin	-0.026	0.974 (0.953-0.996)	0.020
Blood transfusion ^b	1.332	3.790 (1.407-10.210)	0.008
Septic shock	1.587	4.889 (1.018-23.478)	0.047

^b, Before ICU Admission. β : Regression Coefficient; OR: Odds Ratio; CI: Confidence Interval.

Table 4. Treatments, complications, and clinical outcomes.

	Overall	Active CMV Infection		
	N=168	Yes (n=31, 18.5%)	No (n=137, 81.5%)	P
Treatment, n (%)				
Before ICU admission				
Glucocorticoids	74 (44.1)	15 (48.4)	59 (43.1)	0.689
Immunosuppressive drugs[^]	22 (13.1)	9 (29.0)	13 (9.5)	0.007
Gamma globulin infusions	25 (14.9)	6 (19.4)	19 (13.9)	0.414
Blood transfusion	30 (17.9)	12 (38.7)	18 (13.1)	0.003
After ICU admission				
Glucocorticoids	46 (27.4)	10 (32.3)	36 (26.3)	0.509
Immunosuppressive drugs [^]	8 (4.8)	2 (6.5)	6 (4.4)	0.641
Gamma globulin infusions	32 (19.1)	8 (25.8)	24 (17.5)	0.314
Blood transfusion	74 (44.1)	18 (58.1)	56 (40.9)	0.109
Antiviral therapy[#]	30 (17.9)	30 (96.8)	0 (0)	< 0.01
CRRT	60 (35.7)	13 (41.9)	47 (34.3)	0.537
ECMO	26 (15.5)	6 (19.4)	20 (14.6)	0.582
Complications, n (%)				
Septic shock	126 (75.0)	28 (90.3)	98 (71.5)	0.037
AKI	83 (49.4)	17 (54.8)	66 (48.2)	0.554
DIC	42 (25.0)	9 (29.0)	33 (24.1)	0.646
AHF	32 (19.1)	7 (22.6)	25 (18.3)	0.614
AECOPD	23 (13.7)	7 (22.6)	16 (11.7)	0.145
Clinical Outcomes				
Length of IMV (d)	31 (12-68)	42 (29-123)	29 (10-59)	0.045
28-day VFD (d)	0 (0-15)	0 (0-0)	0 (0-18)	0.039
ICU length of stay (d)	24 (13-50)	32 (16-82)	22 (12-49)	0.047
Length of hospital stay (d)	35 (20-59)	37 (22-90)	35 (19-58)	0.222
28-day all-cause mortality, n (%)	52 (31.0)	16 (51.6)	36 (26.3)	0.009

^a, $P < 0.05$; Continuous variables were expressed as Mean $\pm$ SD or Median (IQRs); [#], mainly included Ganciclovir, Valganciclovir, or Sodium Phosphate; [^], mainly included Cyclophosphamide, Methotrexate, and Mycophenolate Mofetil. Bold font indicates the difference was statistically significant. CRRT: Continuous Renal Replacement Therapy; ECMO: Extracorporeal Membrane Oxygenation; AHF: Acute Heart Failure; AKI: Acute Kidney Failure; DIC: Disseminated Intravascular Coagulation; IMV: Invasive Mechanical Ventilation; VFD: Ventilator-free Days.

Figures

Figure 1

Flowchart for patient enrollment.

Figure 2

Oxygenation levels for the study participants * $p < 0.05$

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [2OnlinesupplementResults.doc](#)