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Risk factors for refractory and recurrent cytomegalovirus (CMV) reactivation after hematopoietic stem cell transplantation (HSCT) and solid organ transplantation (SOT): A Scoping Review

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ADMINISTRATIVE INFORMATION

Support - Takeda (China).

Review Stage at time of this submission - Data analysis.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 4 August 2025 and was last updated on 4 August 2025.

INTRODUCTION

Review question / Objective o investigate the risk factors associated with RR CMV infection following HSCT or SOT by conducting a scoping review of the published literature.

Background Cytomegalovirus (CMV) infection is one of the most common complications following hematopoietic stem cell transplantation (HSCT) and solid organ transplantation (SOT). Despite advances in monitoring and treatment, CMV infections that are refractory or recurrent (RR) to standard antiviral therapies remain a significant challenge.

The incidence of RR CMV infection varies among different transplant populations. In HSCT recipients, it has been reported that 32.03% (95% CI 22.93–41.12%) of patients with CMV infection developed refractory CMV infection and 15.42% (95% CI 7.76–30.63%) experienced CMV recurrence. RR CMV infection can significantly impair patient prognosis. They are associated with an elevated mortality risk, as the persistent viral presence can exacerbate complications and organ damage. These infections also heighten the likelihood of CMV end-organ disease, which includes severe conditions such as pneumonia, hepatitis, and gastrointestinal disease. Moreover, they can prolong illness duration, and increase healthcare resource utilization. Additionally, refractory CMV infections raise the risk of secondary bacterial and fungal infections, further complicating the clinical course and outcome for transplant patients.

Rationale There are many previous studies that have reported risk factors for refractory/recurrent CMV infection. Host-related factors include long-term antiviral therapy, previous exposure to anti-CMV drugs, recurrent infections, poor drug absorption or metabolism, T-cell depleted transplantation, delayed immune reconstitution, haploidentical or cord blood HSCT, donor CMV seronegative/recipient CMV seropositive (D^-/R^+) status, active GVHD, and immunosuppressive therapy. Virus-related factors encompass high viral

load, increased viral load during antiviral treatment (>2 weeks of adequate medication), intermittent low-level CMV viremia, recurrence of CMV viremia after initial resolution with antiviral therapy, fluctuating CMV viremia levels, and recurrence of CMV infection. Additionally, antiviral drug-related factors cannot be ignored, such as patient intolerance to anti-CMV therapeutic drugs and the development of drug resistance. For instance, patients treated with Ganciclovir (GCV) experience a 10.0% incidence of myelosuppression, a 30.0%-39.8% incidence of neutropenia, renal toxicity in approximately 11% of patients, and treatment interruption in up to 13.6% of patients. These factors may contribute to recurrent CMV infection, prolonged virus clearance time, and increased risk of CMV disease. However, a systematic summary is still lacking. This systematic review is to further summaries the risk factors for RR CMV infection and to guide the clinic to identify early patients who may progress to or at risk of RR CMV infection. It aims to guide the clinic to make timely adjustments to the management programme of CMV infection for a better patient prognosis.

METHODS

Strategy of data synthesis A systematic search of the PubMed, Embase, Cochrane Library and Web of Science databases, as well as the Chinese databases Chinese Biomedical Database (CBM), Chinese National Knowledge Infrastructure (CNKI), Wanfang Data and VIP Database for Chinese Technical Periodicals, from 2015 to April 2025, will be performed.

PubMed

#1. "Cytomegalovirus"[Mesh] OR "Cytomegalovirus Infections"[Mesh] OR Cytomegalovirus*[tw] OR cytomegalus virus*[tw] OR cytomegalusvirus*[tw] OR "Salivary Gland Virus*"[tw] OR "Human Herpesvirus 5"[tw] OR "HHV 5"[tw] OR Cytomegalic[tw] OR CMV[tw] OR HCMV[tw] OR Cytomegaly[tw] OR cytomegalia[tw] OR cytomegalo[tw] OR cytomegalus[tw] OR cytomegalusvirus*[tw] OR "human herpes virus 5"[tw] OR cytomegaloinfection*[tw] OR cytomegaloviral[tw]

#2. "Risk Factors"[MeSH Terms] OR Risk Factor*[tw] OR Risk Score*[tw] OR "Population at Risk"[tw] OR "Populations at Risk"[tw] OR "Prognosis"[Mesh] OR prognos*[tw]

#3. "Organ Transplantation"[Mesh] OR Grafting*[tw] OR Transplant*[tw] OR Organ Grafting*[tw] OR Organ Transplant*[tw] OR Heart Grafting*[tw] OR Heart Transplant*[tw] OR Cardiac Transplant*[tw] OR Lung Grafting*[tw] OR Lung Transplant*[tw] OR Liver Grafting*[tw] OR Liver Transplant*[tw] OR Hepatic Transplant*[tw] OR Renal Transplant*[tw] OR Kidney Grafting*[tw] OR Kidney Transplant*[tw] OR Intestine Transplant*[tw] OR multivisceral Transplant*[tw] OR Intestine Grafting*[tw] OR "Stem Cell Transplantation"[Mesh] OR "Bone Marrow Transplantation"[Mesh] OR "Bone Marrow Grafting"[tw] OR "Bone Marrow Cell Transplant*"[tw] OR "Bone Marrow Transplant*"[tw] OR "stem cell Transplant*"[tw] OR "hematopoietic cell Transplant*"[tw] OR "stem cell Grafting"[tw] OR "Haploidentical Transplant*"[tw] OR "unrelated donor Transplant*"[tw] OR "Cord Blood Stem Cell Transplantation"[Mesh] OR "Cord Blood Transplant*"[tw] OR "Umbilical cord blood Transplant*"[tw] OR "Umbilical blood Transplant*"[tw] OR "Semicongruent Transplant*"[tw] OR Halfmatched[tw] OR "Half matched"[tw] OR "allo-HSCT"[tw] OR Peripheral blood Transplant*[tw] OR "matched sibling donor"[tw] OR "matched unrelated donor"[tw] OR "haplo transplantation*"[tw] OR "haploidenticaltransplantation*"[tw] OR"matched related donor"[tw]

#4. #1 AND #2 AND #3

#5. "Review Literature as Topic"[Mesh] OR "Review" [Publication Type] OR Review[ti] OR "Case Reports as Topic"[Mesh] OR "Case Reports" [Publication Type] OR "case report"[ti] OR "a case"[ti] OR ("Animals"[Mesh] NOT ("Humans"[Mesh] AND "Animals"[Mesh]))

#6. #4 NOT #7

#7. "Recurrence"[Mesh] OR Relaps*[tw] OR Recurrenc*[tw] OR Recrudescenc*[tw] OR Refractor*[tw] OR Recrudescen*[tw] OR "second-line"[tw] OR "2nd-line"[tw] OR "2 line"[tw] OR "2L"[tw] OR "2-L"[tw] OR after[tiab] OR failure[tiab] OR fail[tiab] OR "first line progress*"[tw] OR "1st line progress*"[tw] OR "previously treated"[tw] OR pretreated[tw] OR pre-treated[tw] OR "re-treated"[tw] OR "third line"[tw] OR "3rd line"[tw] OR "3 line"[tw] OR "fourth line"[tw] OR "4th line"[tw] OR "4 line"[tw]

#8. #6 AND #7.

Eligibility criteria Population: HSCT or SOT recipient at all age. Patients who have not received HSCT or SOT will be excluded.

Factors: transplantation-related factors: blood transplantation, organ transplantation. Factors associated with blood transplantation include haplo-HSCT, matched sibling, matched unrelated, mismatched unrelated, cord blood, T-cell depleted transplant, etc. Factors associated with organ transplantation include lung transplantation, kidney transplantation, liver transplantation, heart transplantation, etc.; viral-related factors: serologic status, persistent low level CMV viremia, high level CMV viremia, recurrent episodes of CMV, etc.;

drug-related factors: preconditioning regimen, myeloablative regimen, sub-therapeutic exposure, dose interruption/adjustment, prolonged drug exposure; etc.; host-related factors: lymphocytopenia, poor immune recovery, GvHD, rejection, or other comorbidities/complications, primary disease, etc..
Time: Refractory/recurrent CMV infection. The definitions of refractory/recurrent CMV infection follow the original. Publications without reported outcomes will be excluded.
Study design: Cohort studies, case-control studies and cross-sectional studies. Literatures related to intervention efficacy or systemic review or meta-analysis study or clinical guideline or animal study or case report will be excluded.
Conference abstract, studies written in other language rather than English or Chinese and full text not available will be excluded.

Source of evidence screening and selection The titles and abstracts of the retrieved search records will be independently screened by two reviewers, followed by full text examination of potential eligible citations. If data on the same populations is reported by more than one publication, only the latest results will be retained. Disagreements will be resolved by discussion, with assistance from a third reviewer if necessary. A PRISMA flow diagram will be constructed to show the full study-selection process.

Data management Two reviewers will independently extract data from each study using a standardized data extraction form. Any disagreement will be resolved by discussion, with the assistance from a third reviewer if necessary. If information relating to a potentially eligible study is lacking, the study authors will be contacted to request this information. We will extract the data as follows: (1) characteristics of the included studies and populations, including information on first author name, year of publication, country, study design, age, gender distribution, sample size, and transplantation type; (2) all exposure variables (risk factors), such as age, gender, serologic status of donors and recipients, transplantation type, pretreatment method before transplantation etc.; (3) outcome variables (refractory and recurrent CMV reactivation), methods employed for outcome assessment, the primary adjusted risk estimate (expressed as hazard ratios (HR), odds ratios (OR), or relative risks (RR) along with 95% confidence intervals (95% CI), and the adjusted confounding variables.

Language restriction No restriction.

Country(ies) involved China.

Keywords cytomegalovirus, hematopoietic stem cell transplantation, organ transplantation, recurrent, refractory, risk factor.

Contributions of each author
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