Association Between *Cytomegalovirus* Infection/Disease and Morbidity and Mortality in Kidney Transplantation: A Systematic Literature Review of Observational Studies

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Introduction

- Cytomegalovirus (CMV) is the most common viral infection post-transplant among kidney transplantation recipients (KTR), affecting as high as 82% of KTRs without any preventive approach and up to 54% even with preventive antiviral agent use[1]
- Literature suggests that CMV infection/disease may increase the risk of opportunistic infections due to its immunomodulatory actions. In addition, replication of CMV may lead to immunoactivation, leading to increased risk for acute or chronic rejection. Collectively, CMV infection/disease may lead to an increase in mortality and morbidity[2]
- The extent to which CMV affects morbidity, such as acute rejection, graft loss, or other opportunistic infections, or mortality in KTRs has not been evaluated using a systematic review framework

Objective

- To examine the association between CMV infection/disease and indirect outcomes (related to mortality and morbidity) among KTRs using a systematic review of observational studies

Methods

- This systematic literature review (SLR) was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines[3]

Criteria for Study Selection and Literature Search

- Inclusion criteria: Retrospective or prospective cohort, case-control observational studies with adults aged ≥18 years and single-organ kidney transplant recipients with defined CMV serostatus
- Exclusion criteria: Studies reporting CMV infection/disease without information on CMV status of donor and recipients for the study population; no report on CMV antiviral treatment approach; with ABO-incompatible donors, HLA mismatch donors, or human immunodeficiency virus; participants undergoing multiple transplant procedures
- Primary outcomes: Indirect outcomes
  - All-cause mortality
  - Graft outcomes: Acute rejection, graft loss, decline in renal function
  - Opportunistic infections
  - Hospitalizations and cost

Literature Search

- Medline and EMBASE were searched to identify relevant studies published between January 2008 and November 2018, without any geographic restriction

Data Screening and Extraction

- Titles and abstracts of studies were screened for eligibility; subsequently, full-text article screening was performed to confirm inclusion of eligible publications during abstract screening
- Relevant data from included studies on baseline characteristics, CMV treatment, and outcomes were extracted into a data extraction template

Statistical Analysis

- All analyses were carried out in R Foundation for Statistical Computing, Vienna, Austria (version 3.5.1), using the "meta" packages

Results

- Of 1,860 retrieved citations, 23 studies with a total of 6,994 KTRs met inclusion criteria (**Figure 1**)

Participant Characteristics

- Sample size in the included studies varied widely, with a mean of 304 participants per included study
- The majority of studies were retrospective cohort (N=20), were conducted in Europe (N=14), and included participants regardless of donor/recipient CMV serostatus (N=14) (**Figure 2**)

Indirect Effect of CMV Infection/Disease

- CMV infection/disease was also associated with increased odds of mortality (**Figure 3**) (pOR, 1.73; 95% CI, 1.23, 2.44; *P*-value <0.01; I^2=22%; 12 studies; 4,873 KTRs) compared to the absence of CMV infection/disease, without significant heterogeneity (**Figure 4**)
- Those with CMV infection/disease were twice as likely to have graft loss (pOR, 1.59; 95% CI, 1.13, 2.23; *P*-value <0.01; I^2=22%; 11 studies; 3,528 KTRs) without significant heterogeneity and acute rejection (pOR, 2.40; 95% CI, 1.69, 3.40; *P*-value <0.01; I^2=69%; 14 studies; 3,532 KTRs) as compared to those without CMV infection/disease (**Figure 5**), albeit with significant heterogeneity
- Three studies reported estimated glomerular filtration rate (eGFR). All of them reported that lower mean eGFR was found among those with CMV infection/disease compared to those without CMV infection
- In the four studies with reported outcomes on serum creatinine level, mixed findings were observed with respect to CMV infection/disease
- A single study reported a greater mean number of opportunistic infection episodes with CMV infection/disease; also, a single study reported that a higher proportion of individuals with CMV disease (88%) had all-cause hospital readmissions compared to those with CMV infection (50%) or without CMV infection/disease (51%)
- None of the included studies examined healthcare cost by CMV infection/disease in KT recipients

Figure 1. PRISMA Flow Diagram for Study Selection

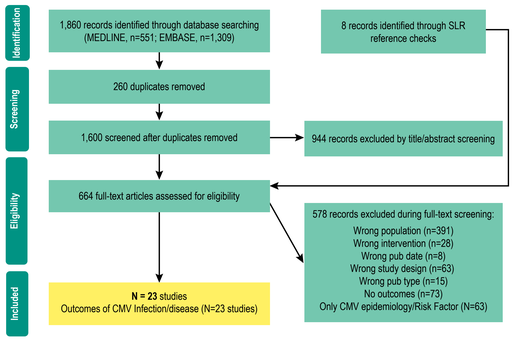


Figure 2. Characteristics of Included Studies

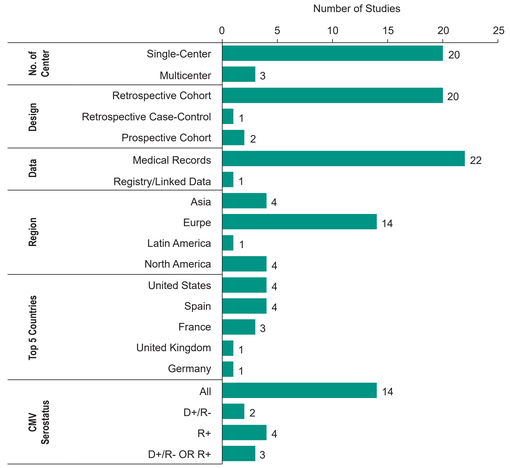


Figure 3. Forest Plot on Pooled Odds Ratios With 95% Confidence Interval for All-Cause Mortality by CMV Infection/Disease

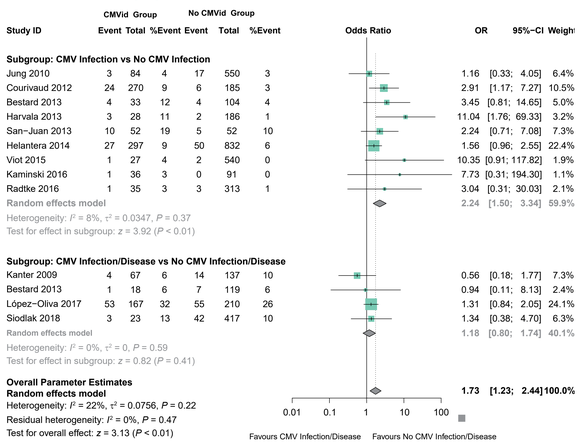


Figure 4. Forest Plot on Pooled Odds Ratios With 95% Confidence Interval for Graft Loss by CMV Infection/Disease

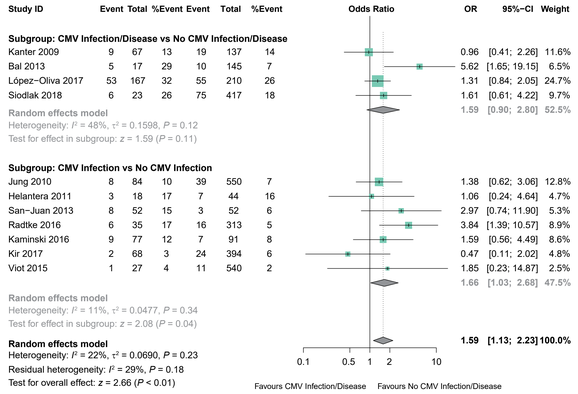
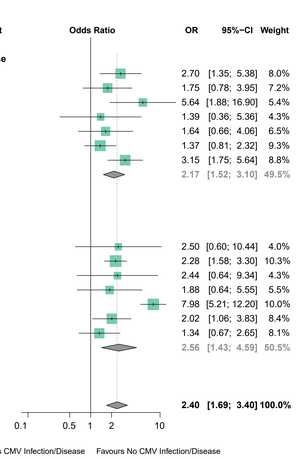


Figure 5. Forest Plot on Pooled Odds Ratios With 95% Confidence Interval for Acute Rejection by CMV Infection/Disease



Discussion

- Our study aimed to understand the association between CMV infection/disease and mortality/morbidity outcomes using data of 23 observational cohort studies
- We found a positive association between CMV infection/disease and mortality and graft loss without heterogeneity between studies
- The association between CMV and acute rejection were similar in direction but with high heterogeneity, limiting the robustness of the conclusion
- To our knowledge, this is the first systematic review of the largest number of included observational studies published across the globe to summarize epidemiological association between CMV infection/disease and indirect outcomes in KT recipients
- Reported data on the association between opportunistic infections or kidney function and CMV infection/disease were limited. Because antiviral dose changes are often done in response to renal function indicators, evaluating the association between CMV infection/disease or prevention strategies and renal function in real-world data is complicated
- Limitations of our study include the limited availability of studies reporting renal function-related outcomes and opportunistic infection; heterogeneity in pooled estimates shows the need for further long-term studies

Conclusion

- CMV infection/disease was associated with increased mortality and graft loss in adults with KT
- Our analysis underscores the importance of interventions to reduce the incidence of CMV infection/disease, thereby reducing the burden of the indirect outcomes associated with CMV infection/disease in KTRs, even in the current era

References

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2. Pérez-Sola MJ, et al. *Enferm Infecc Microbiol Clin.* 2008;26(1):38-47.
3. Liberati A, et al. *BMJ.* 2009;339:b2700.

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Disclosure

Raval, Tang, and Murata are employees of MSD.
Kistler was an employee of Evidera, Inc., at the time of study conduct.

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