ORIGINAL ARTICLE

# Postoperative hyperglycemia may negatively impact cytomegalovirus infection in seropositive liver transplant recipients: a retrospective cohort study

RyungA Kang[1], Sangbin Han[1], Jong Man Kim[2], Kyo Won Lee[2], Hyo Won Park[3], Joong Hyun Ahn[4], Seonwoo Kim[4], Eun-Suk Kang[5], Gaab Soo Kim[1] & Jae-Won Joh[2]

1 Department of Anesthesiology and Pain Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea
2 Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea
3 Department of Anesthesiology and Pain Medicine, Seoul Medical Center, Seoul, Korea
4 Statistics and Data Center, Samsung Medical Center, Seoul, Korea
5 Department of Laboratory Medicine and Genetics, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

**Correspondence**
Sangbin Han, Department of Anesthesiology and Pain Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul 06351, Korea.
Tel.: +82-2-3410-2470;
fax: +82-2-3410-2461;
e-mail: hans5@skku.edu

## SUMMARY

The aim of the study was to evaluate the association between postoperative hyperglycemia and CMV infection. We analyzed 741 CMV seropositive recipients, of livers from seropositive living donors, who underwent preemptive CMV treatment without CMV prophylaxis. The primary outcome was early CMV infection within 1 month after surgery. Hyperglycemia was defined when mean postoperative blood glucose concentration was >180 mg/dl based on previous research and guidelines. Survival analysis was performed using the Fine and Gray model by accounting for the competing risk of CMV infection-unrelated death. Of the 741 recipients (hyperglycemic group, $n = 287$; nonhyperglycemic group, $n = 454$), 372 (50.2%) recipients developed cytomegalovirus (CMV) infection within 1 month after surgery. CMV infection risk was significantly higher in hyperglycemic group than in nonhyperglycemic group in univariable analysis [hazard ratio (HR) 1.34, 95% confidence interval (CI), 1.08–1.66; $P = 0.007$] and in multivariable analysis (HR 1.25, 95% CI 1.0–1.54; $P = 0.038$). CMV infection risk was also significantly associated with recipient age, graft ischemia time, model for end-stage liver disease score, and preoperative neutrophil-to-lymphocyte ratio ($P < 0.05$). In conclusion, preventing postoperative hyperglycemia appears to be an important factor decreasing the risk of CMV infection in seropositive liver transplant recipients undergoing preemptive CMV treatment.

*Transplant International* 2020; 33: 68–75

**Key words**
cytomegalovirus pp65 antigen, immunosuppression, insulin sensitivity, living donors, organ transplantation, oxidative stress

Received: 2 March 2019; Revision requested: 15 April 2019; Accepted: 15 August 2019; Published online: 9 September 2019

## Introduction

Cytomegalovirus (CMV) is transmitted via various routes including saliva, sexual contact, placental transfer, breast feeding, or blood transfusion. Accordingly, the seropositive rate is high ranging 30–70% in developed countries and >90% in developing countries [1]. Although CMV remains in a persistent state after initial infection under the establishment of long-term host immunity against the virus, viral replication can occur




doi:10.1111/tri.13496

when host immunity is compromised. Therefore, immunosuppressed liver transplant recipients are at risk of CMV replication and consequent infection, and it has been determined that more than half of seropositive recipients treated with preemptive strategy experience CMV infection [2]. Of note, most of the infections occur within 1 month post-transplant when the degree of immunosuppression is strong [3,4], suggesting the importance of infection control during this critical time window. Despite the improvement in surveillance and pharmacological strategies, post-transplant CMV infection continues to be a great cause of morbidity, economic drain, and fatal CMV disease [2,5–7]. Thus, the better understanding of factors modifying the risk of CMV infection is required.

Acute hyperglycemia is common after liver transplantation due to hepatocyte ischemia–reperfusion injury [8], surgical stress [9], and insulin resistance [10]. Acute hyperglycemia modulates the host immune response to infection [11,12]. Previous studies performed in various surgical settings have demonstrated the association between postoperative hyperglycemia and infectious complications as well as the benefit of intensive insulin therapy on preventing postoperative infections [13–16]. Previous study of liver transplant recipients also demonstrated the decrease in infectious complications after the use of postoperative intensive insulin therapy [17,18]. However, those studies of surgical patients have never focused on CMV infection; thus, it is unknown whether acute postoperative hyperglycemia affects the risk of viral replication under strong immunosuppression. Thus, we deduced that post-transplant hyperglycemia increases the risk of CMV infection and evaluated the association between postoperative hyperglycemia and CMV infection during the early post-transplant period.

## Materials and methods

### Subjects and data collection

We initially reviewed the medical records of 800 recipients who underwent a first adult-to-adult living donor liver transplantation using the right hemiliver graft between May 2002 and August 2014 in our hospital. We excluded 52 recipients of grafts from seronegative donors (R+/D−) and 1 seronegative (R−/D+) recipient. We further excluded five recipients who underwent retransplantation due to early graft failure and 1 recipient with cyclosporine-based immunosuppression because of possible tacrolimus toxicity. The remaining 741 R+/D+ recipients were included in the study while there were no R−/D− recipients. All analyzed data were collected from computerized medical records or liver transplant database. The Institutional Review Board of Samsung Medical Center approved this retrospective cohort study (SMC 2017-04-080) and waived the requirement for written informed consent.

### Postoperative glycemic management

Detailed intraoperative anesthetic and surgical managements are described elsewhere [19]. Postoperative glycemic management was performed by liver transplant surgeons based on the standardized institutional protocol as follows. Postoperative blood glucose concentration (BGC) was measured on admission to the intensive care unit and every 6 h thereafter by arterial line drop sample using the blood chemistry analysis device (RAPIDLAB1265®, Siemens Healthcare Diagnostics Inc., Berlin, FRG) or by finger stick using bedside glucose meter (AccuCheck; Roche Diagnostics, Indianapolis, IN, USA). If BGC was >160 mg/dl, continuous intravenous infusion of regular insulin was initiated at the rate of 1 U/h. The rate of insulin infusion was increased by 2 U/h if BGC was 160–240 mg/dl and by 3 U/h if BGC was 240–300 mg/dl. The dose of insulin was decreased by 1 U/h if BGC was 100–140 mg/dl, and it was stopped if BGC was <100 mg/dl. If BGC was <100 mg/dl or >240 mg/dl, BGC was rechecked 2 h later. Transition to intermittent subcutaneous injection of regular insulin was generally started once the patients were stable and had begun to eat. BGC was measured once a day before breakfast by arterial line drop sample using the blood chemistry analysis device (RAPIDLAB1265®) or by finger stick using bedside glucose meter (AccuCheck). BGC was additionally measured every 6 h (before every meal and at bedtime) if patients had diabetes or the morning BGC was >200 mg/dl. The dose of insulin injection was 4, 8, and 12 U when BGC ranged from 200–250 mg/dl, 251–300 mg/dl, and 300–350 mg/dl, respectively. BGC was rechecked 2 h later if BGC was <80 mg/dl or >350 mg/dl. If BGCs were not controlled and sustained hyperglycemia occurred, we consulted an endocrinologist.

### Definition of infection and disease

Cytomegalovirus infection and CMV disease were defined based on a recently updated description [20,21]. CMV infection was when there were at least one CMV pp65 antigen-positive cells among $4 \times 10^5$ leukocytes. CMV disease presented either as CMV syndrome or

tissue-invasive end-organ disease. CMV syndrome was when CMV infection was attended with at least two of the following symptoms or signs: unexplained fever >38.3°C for at least 2 days, constitutional symptoms such as fatigue or general myalgia, leukopenia (leukocyte count $<3 \times 10^3/mm^3$), or thrombocytopenia (platelet count $<10 \times 10^9/l$). Tissue-invasive CMV disease was when CMV-associated hepatitis, pneumonitis, retinitis, or gastroenteritis was confirmed by biopsy.

### Cytomegalovirus managements

Perioperative CMV managements were performed based on the standardized institutional protocol, as described previously [2]. All recipients and corresponding donors were routinely tested for IgG seropositivity within 1 month prior to surgery. Antiviral prophylaxis was not indicated in seropositive recipients, who were considered at moderate risk of CMV infection and disease [6,22], due to the concern of the development of resistance and late-onset CMV disease [6,7]. Postoperative CMV surveillance was performed by detecting pp65 antigen using in-house immunocytochemistry staining until May 15, 2008, and thereafter, using immunofluorescence staining (CINA Kit system; Argene Biosoft, Varilhes, France). For the first week after surgery, pp65 antigen was assayed three times a week, and thereafter, it was performed weekly. After discharge, pp65 was routinely assayed once a month until 12 months post-transplant in the absence of symptoms. Patients received preemptive treatment only if viral replication reaches >10 pp65-positive cells per $4 \times 10^5$ leukocytes. If patients had 1–10 pp65-positive cells per $4 \times 10^5$ leukocytes, they did not undergo preemptive treatment and were monitored for symptoms and tested for pp65 antigen if they were symptomatic. Preemptive treatment was initiated by means of intravenous ganciclovir, and pp65 antigen was assayed three times a week until a negative result was obtained in two consecutive samples. The dose of ganciclovir was adjusted by accounting for patient renal function.

### Immunologic regimens

Immunosuppression was performed as described previously [19]. Basiliximab was administered intravenously during the intraoperative reperfusion phase as an induction agent. Tacrolimus, steroids, and mycophenolate mofetil were the primary agents for maintenance. Recipients were given intravenous methylprednisolone (500 mg) during the anhepatic phase and daily until postoperative day 2, followed by a tapered dose of 60 mg per day for 5 days, and then 8 mg twice per day for 1 month starting on postoperative day 8. Subsequently, recipients received 4 mg methylprednisolone twice a day for 2 months. Tacrolimus was initiated on postoperative day 3, with a trough plasma concentration of 10 ng/ml being maintained during the first month and 5–8 ng/ml thereafter. Starting on postoperative day 1, mycophenolate mofetil (750 mg) was administered twice per day. A liver biopsy was performed if acute rejection was clinically suspected. Methylprednisolone (500 mg) was administered intravenously every day for 3 days if acute rejection was confirmed by biopsy and was tapered to 60 mg/day over a period of 4 days thereafter.

### Statistical analysis

The primary outcome was post-transplant CMV infection. Survival analysis was performed using the Fine and Gray model by accounting for the competing risk of CMV infection-unrelated death and modeling the mean BGC as a time-dependent covariate [23]. Recipients were followed for a maximum of 1 month based on our previous research reporting that the median time from liver transplantation to CMV infection was 1 month [4]. The results of survival analysis were described with hazard ratio (HR) and 95% confidence interval (CI). The multivariable model was generated using the backward stepwise selection method with all variables analyzed in univariate analysis. Because the incidence of CMV infection significantly raised after the surveillance reinforcement and the introduction of immunofluorescence assay at 2008, the presence of interaction between operation period (before versus after 2008) and postoperative hyperglycemia was tested by including the interaction effect term in multivariable analysis to test the risk of bias from the difference in CMV surveillance. The cutoff mean BGC value for categorizing patients as at hyperglycemic group and nonhyperglycemic group was set at 180 mg/dl based on previous researches [24–27]. The mean BGC was calculated by an average of BGCs firstly measured at fasting state in each postoperative day during the primary admission for a maximum of 1 month. For patients who developed CMV infection before 1 month after surgery, BGCs measured before the CMV infection were used. Missing BGCs were dealt with last observation carried forward imputation [28]. Diabetes was defined when recipients had a current history of diabetes or preoperative BGC was >126 mg/dl.

Baseline characteristics were compared using Mann–Whitney test, *t*-test, or chi-square test. The continuous variables were described as mean ± standard deviations or median (25th percentile, 75th percentile) as appropriate. The categorical variables were presented as frequency (%). Statistical significance was defined as $P < 0.05$. All analyses were performed using SPSS 25 (SPSS Inc, Chicago, IL, USA), R 3.5.2 (R Development Core Team, Vienna, Austria; http://www.R-project.org/), or SAS version 9.2 (SAS institute, Cary, NC, USA).

## Results

There were no follow-up losses. Of the 741 recipients, 372 (50.2%) recipients developed CMV infection within 1 month after surgery and 8 (1.1%) recipients died because of CMV-unrelated causes. The median time to CMV infection was 20 (13–25) days and 246 of 372 infected recipients (66.1%) met the indication for preemptive treatment and underwent preemptive treatment. Despite the preemptive treatment, 30 of the 246 recipients (12.2%) progressed to CMV disease [26 syndromes and four tissue-invasive diseases (gastrointestinal tract, $n = 3$; lung, $n = 1$)] with the median time from liver transplantation to CMV disease being 17 (14–23) days. Two recipients developed CMV disease (gastrointestinal tract) at 2 and 3 weeks post-transplant, respectively, without the detection of infection. There were no clinical or pathological rejections before CMV infection in the 372 recipients. The duration of hospital stay was 37 (27–50) days in patients with CMV infection and 28 (23–40) days in patients without CMV infection. Baseline characteristics of patients are shown in Table 1.

Daily BGCs during the 1 month after surgery in hyperglycemic group and nonhyperglycemic group are shown in Fig. 1. As shown in Table 2, CMV infection risk was significantly higher in hyperglycemic group than in nonhyperglycemic group in univariable analysis (HR, 1.34, 95% CI, 1.08–1.66; $P = 0.007$) and in multivariable analysis (HR 1.25, 95% CI 1.0–1.54, $P = 0.038$). Recipient age, graft ischemia time, model for end-stage liver disease score, preoperative neutrophil-to-lymphocyte ratio, and operation period were also identified as independent prognostic factors for CMV infection ($P < 0.05$) (Table 2). The incidence of CMV infection increased in relation to the progress of operation period (2002–2008, 36.4% vs. 2008–2014, 60.9%, $P < 0.001$), suggesting the improvement in detecting CMV infection after the surveillance reinforcement and the introduction of immunofluorescence assay. Interaction analysis demonstrated that there was no interaction effect between operation period and postoperative hyperglycemia ($P = 0.969$), indicating that the effect of postoperative hyperglycemia on CMV infection did not change according to the surveillance reinforcement or the introduction of immunofluorescence assay.

The risk of CMV infection (54.1% vs. 47.8%, $P = 0.112$) was not significantly different between diabetic recipients ($n = 283$) and nondiabetic recipients ($n = 458$), indicating the dominant impact of acute hyperglycemic disturbance rather than underlying chronic glycemic status during the early post-transplant period.

## Discussion

We demonstrated the significant association between postoperative hyperglycemia and CMV infection in seropositive liver transplant recipients. Although previous studies have evaluated the association between perioperative hyperglycemia and post-transplant infectious complications [17,18], there have been no studies evaluating the role of postoperative hyperglycemia in modifying the risk of CMV infection in immunosuppressed liver transplant recipients despite the high prevalence and clinical significance of CMV infection [2]. The cutoff BGC of 180 mg/dl is clinically relevant because 180 mg/dl is a feasible target with relatively low risk of severe hypoglycemia when doing intensive insulin therapy [24–27]. Our findings suggest that maintaining post-transplant BGC <180 mg/dl complements preemptive CMV therapy and decreases the risk of CMV infection in seropositive liver transplant recipients.

The possible mechanisms underlying the association between post-transplant hyperglycemia and CMV infection can be assumed from previous studies. Experimental research has shown that acute hyperglycemia increases oxidative stress [9,29–31]. Increased oxidative stress contributes to CMV replication and virus shedding by stimulating the transcriptional regulation of the CMV promoter region, which involved in viral reactivation from latency [32–34]. Oxidative stress further deteriorates hyperglycemia by impairing insulin sensitivity and pancreatic insulin secretion [35]. In particular, acute hyperglycemia has shown stronger triggering effects on oxidative stress compared to chronic sustained hyperglycemia [36], being in agreement with our data in determining the significance of postoperative hyperglycemia and the insignificance of underlying diabetes. Second, the hyperglycemic state (a glucose-rich

**Table 1.** Comparison of clinical characteristics between nonhyperglycemic and hyperglycemic recipients.

| Characteristics | Overall (*n* = 741) | Nonhyperglycemic (*n* = 454) | Hyperglycemic (*n* = 287) | *P* value |
|---|---|---|---|---|
| Donor factors | | | | |
| Age (years) | 32.7 ± 11.1 | 33.1 ± 11.1 | 32.2 ± 11.2 | 0.314 |
| Male sex | 494 (66.7) | 314 (69.2) | 180 (62.7) | 0.078 |
| Macrosteatosis > 5% | 361 (48.7) | 217 (47.8) | 144 (50.2) | 0.547 |
| Graft ischemia time (minutes) | 119 [98–143] | 118 [97–142] | 122 [98–146] | 0.157 |
| Graft-to-recipient weight ratio (%) | 1.0 [0.9–1.2] | 1.1 [0.9–1.3] | 1.0 [0.9–1.2] | 0.017 |
| ABO incompatibility | 69 (9.3) | 42 (9.3) | 27 (9.4) | >0.999 |
| Recipient factors | | | | |
| Age (years) | 51.3 ± 8.5 | 51.0 ± 9.2 | 51.8 ± 7.2 | 0.162 |
| Male sex | 583 (78.7) | 346 (76.2) | 237 (82.6) | 0.043 |
| Body mass index (kg/m$^2$) | 24.3 ± 3.5 | 24.3 ± 3.6 | 24.3 ± 3.2 | 0.813 |
| CMV surveillance era | | | | 0.255 |
| Immunocytochemistry (2002–2008) | 324 (43.7) | 191 (42.1) | 133 (46.3) | |
| Immunofluorescence (2008–2014) | 417 (56.3) | 263 (57.9) | 154 (53.7) | |
| MELD score | 18.8 ± 10.1 | 18.0 ± 10.4 | 20.0 ± 9.4 | 0.008 |
| Hypertension | 82 (11.1) | 46 (10.1) | 36 (12.5) | 0.337 |
| Diabetes | 283 (38.2) | 113 (24.9) | 170 (59.2) | <0.001 |
| Preoperative Blood glucose (mg/dl) | 125.5 ± 62.8 | 109.9 ± 42.8 | 150.3 ± 79.4 | <0.001 |
| Preoperative neutrophil-to-lymphocyte ratio | 2.5 [1.5–4.8] | 2.3 [1.5–4.0] | 2.9 [1.7–5.7] | 0.002 |
| Nonviral etiology | 132 (17.8) | 85 (18.7) | 47 (16.4) | 0.432 |
| Disease progression | | | | 0.106 |
| Acute | 36 (4.9) | 28 (6.2) | 8 (2.8) | |
| Acute on chronic | 33 (4.5) | 21 (4.6) | 12 (4.2) | |
| Chronic | 672 (90.7) | 405 (89.2) | 267 (93.0) | |
| Refractory ascites | 496 (66.9) | 276 (60.8) | 220 (76.7) | <0.001 |
| Hepatic encephalopathy grade III-IV | 37 (5.0) | 17 (3.7) | 20 (7.0) | 0.057 |
| Surgical stress-related factors | | | | |
| Operative time (minutes) | 579.7 ± 106.9 | 581.3 ± 108.6 | 577.3 ± 104.2 | 0.617 |
| Salvaged RBCs (ml) | 1032 [703–1754.5] | 956.5 [615–1551.5] | 1230 [760–2084] | <0.001 |
| Intraoperative RBC transfusion (units) | 2 [0–4] | 2 [0–4] | 2 [0–4] | 0.311 |
| Postoperative intensive care unit stay (days) | 8 [7–9] | 7 [7–9] | 8 [7–10] | <0.001 |
| Acute kidney injury (ICA-AKI criteria*) | 221 (29.8) | 121 (26.7) | 100 (34.8) | 0.021 |
| Postoperative immunosuppressive status and co-infections | | | | |
| Tacrolimus level (ng/ml) | 9.8 [8.6–10.9] | 9.9 [8.7–11.1] | 9.8 [8.5–10.7] | 0.146 |
| Other viral infection† | 15 (2.0) | 10 (2.2) | 5 (1.7) | 0.792 |
| Other bacterial and fungal infection | 72 (9.7) | 35 (7.7) | 37 (12.9) | 0.022 |

Data are presented as median (25th percentile, 75th percentile) or frequency (%). Salvaged RBCs represent the amount of intraoperative blood loss.

CMV, cytomegalovirus; MELD, model for end-stage liver disease; RBC, red blood cell; SMD, standardized mean differences.

*ICA-AKI criteria, International Club of Ascites diagnostic criteria of acute kidney injury in patients with cirrhosis.

†Other viral infection includes herpes simplex virus and varicella zoster virus.

environment) is necessary to maintain the infectivity of CMV. CMV requires a large amount of energy to synthesize viral proteins, which is supplied by increasing the utilization of glucose and glutamine in infected cells [37]. Actually, glucose uptake and consumption were significantly increased in the CMV -infected cell compared to the noncytomegalovirus-infected cell [37]. A specific mechanism to increase glucose uptake in infected cells is to replace the glucose transporter (GLUT) 1 to GLUT 4 [38]. The GLUT 4 is the major glucose transporter in adipose tissue and has glucose transport capacity three times higher than GLUT 1.

Our study has advantages in terms of data homogeneity and reliability. First, we only included seropositive liver transplant recipients, who are considered at intermediate risk of CMV infection. The effects of acute

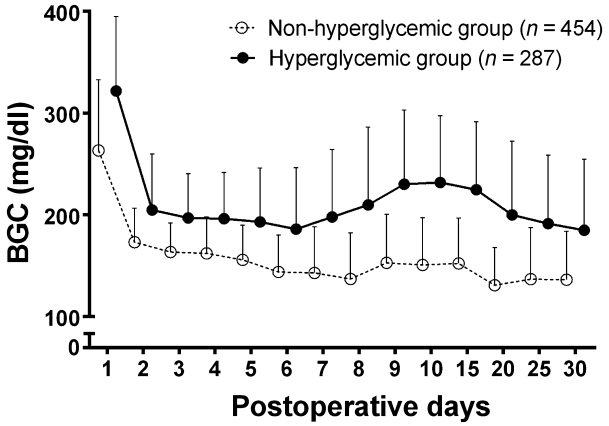


**Figure 1** This plot provides information about the development of blood glucose concentration (BGC) of recipients in hyperglycemic group and recipients in nonhyperglycemic group during the first month after transplantation. Black and white circles indicate mean and upper whisker indicates standard deviations.

hyperglycemia on CMV infection may differ in high risk R−/D+ recipients [39]. Second, a single transplant team performed anesthesia, surgical procedures, and perioperative cares as well as CMV surveillance and management according to the standardized institutional protocols. In particular, the bias from transfusion-transmitted CMV infection might have been minimal despite frequent perioperative transfusion because all transfused blood cell products were leukoreduced as described elsewhere [40]. Furthermore, the amount of red blood cell transfusion was controlled via multivariable analysis. Third, possible factors which may modify the risk of post-transplant CMV infection such as the degree of the immunosuppression, co-infections, and postoperative renal insufficiency were thoroughly taken into account [22]. Finally, the sufficient sample size carried additional advantages: The power of expected HR for the primary outcome was 80%.

**Table 2.** Multivariable analysis of risk factors for CMV infection.

| | Hazard ratio (95% CI) | *P* value |
|---|---|---|
| Postoperative hyperglycemia | 1.25 (1.01–1.54) | 0.038 |
| CMV surveillance era (vs. 2002–2008) | | |
| Immunofluorescence (2008–2014) | 2.53 (2.01–3.19) | <0.001 |
| Graft ischemia time (minutes) | 1.003 (1.001–1.004) | 0.006 |
| Recipient age (years) | 1.02 (1.00–1.03) | 0.013 |
| MELD score | 1.04 (1.03–1.05) | <0.001 |
| Preoperative neutrophil-to-lymphocyte ratio | 1.04 (1.03–1.05) | <0.001 |

CMV, cytomegalovirus; MELD, model for end-stage liver disease.

This study has several limitations. First, as a retrospective study, we could not exclude the possibility of bias from unobserved (unmeasured or unmeasurable) variables. Although there are no currently known confounders that would be lacking, we cannot rule out that other confounders may exist. Also, the mechanisms underlying the association between post-transplant hyperglycemia and CMV infection remained unknown, although some of them can be assumed from previous research. Second, our center used antigenemia assay quantitating leukocytes positive for pp65 for CMV surveillance. Quantitative polymerase chain reaction was recently recommended to monitor CMV after transplantation [41], but antigenemia assay has shown also reliable, rapid, and sensitive results [1]. Moreover, antigenemia assay is still commonly used in clinical practice and research [20]. Third, it is indistinguishable whether CMV infection was due to endogenous CMV reactivation or exogenous infection with a new strain because viral genome sequencing was not performed.

The risk of CMV infection early after living donor liver transplantation increased in relation to the development of postoperative acute hyperglycemia in seropositive recipients who were treated with CMV preemptive pharmacological treatment. Thus, this retrospective study suggests that, despite methodological limitations, preventing early post-transplant hyperglycemia may complement the current CMV therapy and prevent CMV infection.

## Authorship

RK: designed the study, collected data, analyzed data and wrote the manuscript. SH: designed the study, collected, analyzed, interpreted data and wrote the manuscript. JMK: interpreted data and provided critical revisions. KWL: interpreted data and provided critical revisions. HWP: interpreted data, collected data and wrote the manuscript. JHA: analyzed data, interpreted data and gave critical revisions. SK: analyzed data, interpreted data and gave critical revisions. E-SK: interpreted data and gave critical revisions. GSK: contributed to conception, acquisition of data and interpretation of data. J-WJ: contributed to conception, acquisition of data and revisions.

## Funding

The authors have declared no funding.

## Conflict of interest

The authors have declared no conflicts of interest.

## REFERENCES

1. Gandhi MK, Khanna R. Human cytomegalovirus: clinical aspects, immune regulation, and emerging treatments. *Lancet Infect Dis* 2004; **4**: 725.
2. Kim JM, Kim SJ, Joh JW, *et al.* Is cytomegalovirus infection dangerous in cytomegalovirus-seropositive recipients after liver transplantation? *Liver Transpl* 2011; **17**: 446.
3. Wadhawan M, Gupta S, Goyal N, *et al.* Cytomegalovirus infection: its incidence and management in cytomegalovirus-seropositive living related liver transplant recipients: a single-center experience. *Liver Transpl* 2012; **18**: 1448.
4. Kim JM, Kwon CH, Joh JW, *et al.* Oral valganciclovir as a preemptive treatment for cytomegalovirus (CMV) infection in CMV-seropositive liver transplant recipients. *PLoS ONE* 2015; **10**: e0123554.
5. Kim WR, Badley AD, Wiesner RH, *et al.* The economic impact of cytomegalovirus infection after liver transplantation. *Transplantation* 2000; **69**: 357.
6. Marcelin JR, Beam E, Razonable RR. Cytomegalovirus infection in liver transplant recipients: updates on clinical management. *World J Gastroenterol* 2014; **20**: 10658.
7. Herman D, Han H. Cytomegalovirus in liver transplant recipients. *Curr Opin Organ Transplant* 2017; **22**: 345.
8. Han S, Sangwook Ko J, Jin SM, *et al.* Glycemic responses to intermittent hepatic inflow occlusion in living liver donors. *Liver Transpl* 2015; **21**: 180.
9. Dungan KM, Braithwaite SS, Preiser JC. Stress hyperglycaemia. *Lancet* 2009; **373**: 1798.
10. Tietge UJ, Selberg O, Kreter A, *et al.* Alterations in glucose metabolism associated with liver cirrhosis persist in the clinically stable long-term course after liver transplantation. *Liver Transpl* 2004; **10**: 1030.
11. Jafar N, Edriss H, Nugent K. The effect of short-term hyperglycemia on the innate immune system. *Am J Med Sci* 2016; **351**: 201.
12. Kwoun MO, Ling PR, Lydon E, *et al.* Immunologic effects of acute hyperglycemia in nondiabetic rats. *JPEN J Parenter Enteral Nutr* 1997; **21**: 91.
13. Frisch A, Chandra P, Smiley D, *et al.* Prevalence and clinical outcome of hyperglycemia in the perioperative period in noncardiac surgery. *Diabetes Care* 2010; **33**: 1783.
14. Ramos M, Khalpey Z, Lipsitz S, *et al.* Relationship of perioperative hyperglycemia and postoperative infections in patients who undergo general and vascular surgery. *Ann Surg* 2008; **248**: 585.
15. Ambiru S, Kato A, Kimura F, *et al.* Poor postoperative blood glucose control increases surgical site infections after surgery for hepato-biliary-pancreatic cancer: a prospective study in a high-volume institute in Japan. *J Hosp Infect* 2008; **68**: 230.
16. van den Berghe G, Wouters P, Weekers F, *et al.* Intensive insulin therapy in critically ill patients. *N Engl J Med* 2001; **345**: 1359.
17. Wallia A, Parikh ND, O'Shea-Mahler E, *et al.* Glycemic control by a glucose management service and infection rates after liver transplantation. *Endocr Pract* 2011; **17**: 546.
18. Wallia A, Schmidt K, Oakes DJ, *et al.* Glycemic control reduces infections in post-liver transplant patients: results of a prospective, randomized study. *J Clin Endocrinol Metab* 2017; **102**: 451.
19. Han S, Park HW, Song JH, *et al.* Association between intraoperative platelet transfusion and early graft regeneration in living donor liver transplantation. *Ann Surg* 2016; **264**: 1065.
20. Ljungman P, Boeckh M, Hirsch HH, *et al.* Definitions of cytomegalovirus infection and disease in transplant patients for use in clinical trials. *Clin Infect Dis* 2017; **64**: 87.
21. Kotton CN, Kumar D, Caliendo AM, *et al.* The third international consensus guidelines on the management of cytomegalovirus in solid-organ transplantation. *Transplantation* 2018; **102**: 900.
22. McDevitt LM. Etiology and impact of cytomegalovirus disease on solid organ transplant recipients. *Am J Health Syst Pharm* 2006; **63**: S3.
23. Fine JPGR. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc* 1999; **94**: 496.
24. Kang R, Han S, Lee KW, *et al.* Portland intensive insulin therapy during living donor liver transplantation: association with post-reperfusion hyperglycemia and clinical outcomes. *Sci Rep* 2018; **8**: 16306.
25. Akhtar S, Barash PG, Inzucchi SE. Scientific principles and clinical implications of perioperative glucose regulation and control. *Anesth Analg* 2010; **110**: 478.
26. Moghissi ES, Korytkowski MT, DiNardo M, *et al.* American Association of Clinical Endocrinologists and American Diabetes Association consensus statement on inpatient glycemic control. *Diabetes Care* 2009; **32**: 1119.
27. Finney SJ, Zekveld C, Elia A, Evans TW. Glucose control and mortality in critically ill patients. *JAMA* 2003; **290**: 2041.
28. Shao J, Zhong B. Last observation carry-forward and last observation analysis. *Stat Med* 2003; **22**: 2429.
29. Martin A, Rojas S, Chamorro A, Falcon C, Bargallo N, Planas AM. Why does acute hyperglycemia worsen the outcome of transient focal cerebral ischemia? Role of corticosteroids, inflammation, and protein O-glycosylation. *Stroke* 2006; **37**: 1288.
30. Hirose R, Xu F, Dang K, *et al.* Transient hyperglycemia affects the extent of ischemia-reperfusion-induced renal injury in rats. *Anesthesiology* 2008; **108**: 402.
31. Behrends M, Martinez-Palli G, Niemann CU, Cohen S, Ramachandran R, Hirose R. Acute hyperglycemia worsens hepatic ischemia/reperfusion injury in rats. *J Gastrointest Surg* 2010; **14**: 528.
32. Cinatl J Jr, Vogel JU, Kotchetkov R, Scholz M, Doerr HW. Proinflammatory potential of cytomegalovirus infection. specific inhibition of cytomegalovirus immediate-early expression in combination with antioxidants as a novel treatment strategy? *Intervirology* 1999; **42**: 419.

33. Scholz M, Cinatl J, Gross V, *et al*. Impact of oxidative stress on human cytomegalovirus replication and on cytokine-mediated stimulation of endothelial cells. *Transplantation* 1996; **61**: 1763.
34. Jaganjac M, Matijevic T, Cindric M, *et al*. Induction of CMV-1 promoter by 4-hydroxy-2-nonenal in human embryonic kidney cells. *Acta Biochim Pol* 2010; **57**: 179.
35. Paolisso G, Giugliano D. Oxidative stress and insulin action: is there a relationship? *Diabetologia* 1996; **39**: 357.
36. Monnier L, Mas E, Ginet C, *et al*. Activation of oxidative stress by acute glucose fluctuations compared with sustained chronic hyperglycemia in patients with type 2 diabetes. *JAMA* 2006; **295**: 1681.
37. Chambers JW, Maguire TG, Alwine JC. Glutamine metabolism is essential for human cytomegalovirus infection. *J Virol* 2010; **84**: 1867.
38. Yu Y, Maguire TG, Alwine JC. Human cytomegalovirus activates glucose transporter 4 expression to increase glucose uptake during infection. *J Virol* 2011; **85**: 1573.
39. Katsolis JG, Bosch W, Heckman MG, *et al*. Evaluation of risk factors for cytomegalovirus infection and disease occurring within 1 year of liver transplantation in high-risk patients. *Transpl Infect Dis* 2013; **15**: 171.
40. Han S, Kwon JH, Jung SH, *et al*. Perioperative fresh red blood cell transfusion may negatively affect recipient survival after liver transplantation. *Ann Surg* 2018; **267**: 346.
41. Kotton CN, Kumar D, Caliendo AM, *et al*. Updated international consensus guidelines on the management of cytomegalovirus in solid-organ transplantation. *Transplantation* 2013; **96**: 333.