CMV IVIG modulates NK Cell phenotype in a PGD-dependent manner in lung transplant recipients

Formerly: Reduced NK Cell Activation in Lung Transplant Recipients Treated with Cytomegalovirus Immunoglobulin

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Background

Cytomegalovirus (CMV) reactivation remains a major complication after lung transplantation and is associated with increased risk of chronic lung allograft dysfunction (CLAD) and reduced long-term survival despite standard antiviral prophylaxis(1). Adjunctive therapies such as CMV intravenous immunoglobulin (IVIG) have been used to mitigate this risk, yet their immunologic effects and relationship to clinical outcomes remain incompletely understood.

Natural killer (NK) cells play a central role in CMV control through both antibody-dependent cellular cytotoxicity (via CD16) and adaptive-like responses (via NKG2C)(2). Emerging evidence suggests that NK cell phenotypes also influence transplant-related outcomes, including primary graft dysfunction (PGD) and CLAD(3-5). However, the interplay between CMV-directed therapies, NK cell biology, and PGD status has not been well characterized.

In prior work, we demonstrated that expansion of NKG2C^{+} NK cells in the bronchoalveolar lavage (BAL) occurs prior to detectable CMV DNAemia and is independently associated with increased risk of CLAD or death(6). These findings suggest that NK cell activation in the lung allograft may represent an early immunologic event linking CMV sensing to downstream graft injury, rather than simply reflecting systemic viral replication.

This raises the possibility that NK cell phenotypes are not only biomarkers of CMV exposure but active contributors to transplant outcomes. We therefore hypothesized that CMV IVIG administration is associated with distinct NK cell phenotypic profiles and that these immune alterations interact with PGD status to influence CLAD-free survival in high-risk lung transplant recipients.

Methods

We performed a retrospective cohort study of lung transplant recipients at high risk for CMV reactivation (donor CMV positive/recipient CMV negative, D+/R−; n = 37). Our center previously used CMV immunoglobulin (CMV IVIG) through 2019 for all high-risk mismatched donor and recipients (D+/R-) but stopped due to a change in protocol. We leveraged an existing biorepository and identified recipients who received CMV IVIG matched recipients who did not receive CMV IVIG based on baseline clinical characteristics.

The primary clinical outcome was CLAD-free survival, analyzed using Cox proportional hazards models. PGD status was incorporated into all analyses to account for its potential confounding and interactive effects on outcomes.

Peripheral blood samples (PBMCs and plasma) collected within 3 months post-transplant were analyzed in a subset of patients (CMV IVIG+, n = 17; CMV IVIG−, n = 20). Plasma proteomic profiling was performed to assess systemic immune signaling pathways (Olink reveal). In parallel, high-dimensional flow cytometry using a 34-marker panel was conducted to characterize NK cell phenotypes, including markers of maturation, activation, and trafficking.

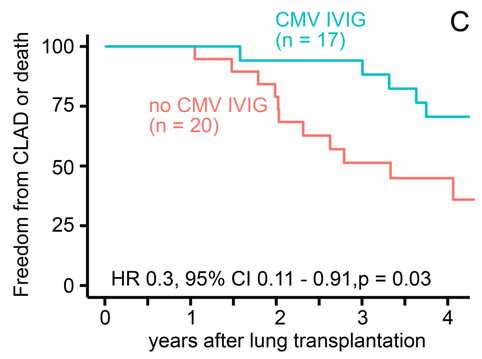
Statistical analyses included one-way and two-way ANOVA to evaluate the independent and interactive effects of CMV IVIG treatment and PGD status on immune parameters. This integrated approach enabled assessment of how CMV-directed therapy shapes NK cell biology in the context of graft injury.

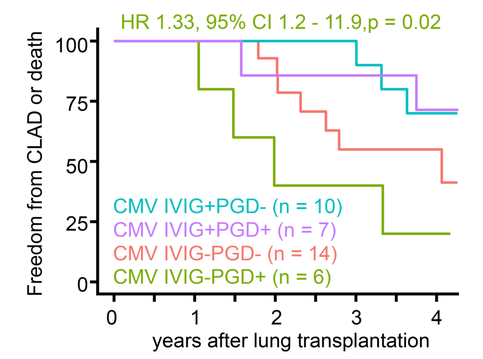
Results

CMV IVIG is associated with reduced risk for CLAD and death and interacts with PGD

A

	no CMV IgG (n = 20)	CMV IgG (n = 17)	p value
Age, mean (SD)	54.6 (14.7)	61.5 (8.3)	0.09
Female sex, N (%)	7 (35)	7 (41.2)	0.96
ILD diagnosis, N (%)	15 (75)	15 (88.2)	0.19
Double lung, N (%)	17 (85)	14 (82.4)	1
Caucasian ethnicity, N (%)	14 (70)	13 (76.5)	0.39
Sample days, mean (SD)	72.3 (28.5)	73.7 (23)	0.89
Severe PGD, N (%)	6 (30)	7 (41.2)	0.72

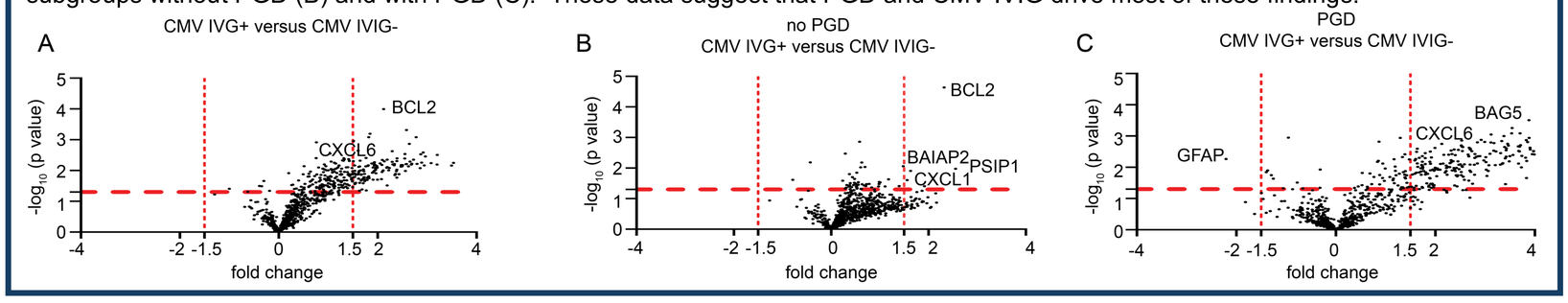




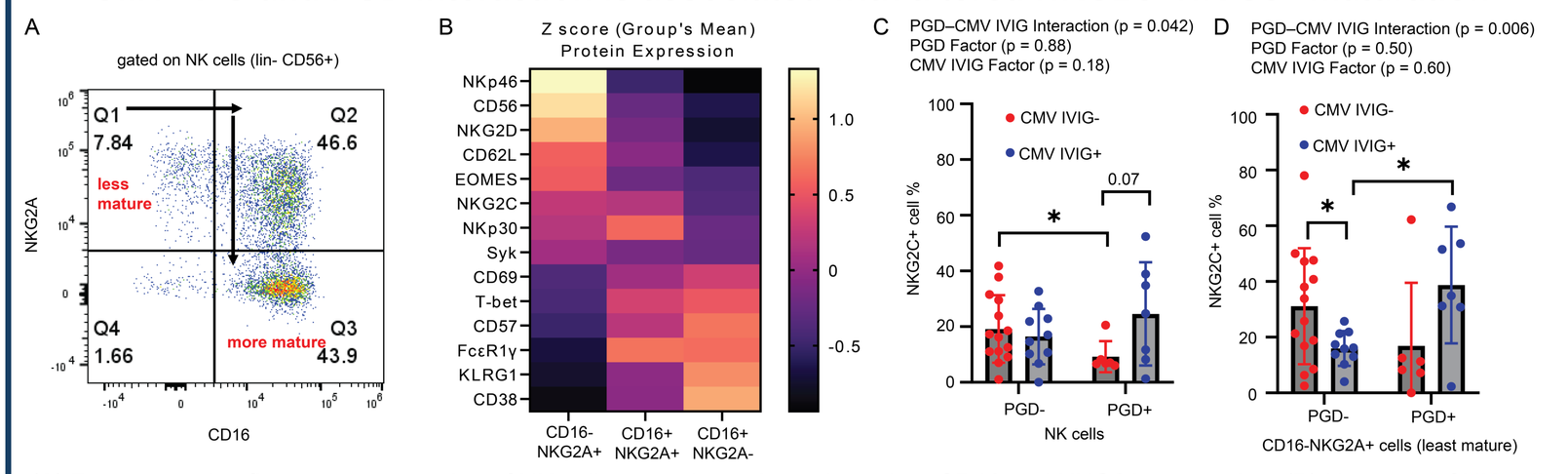
(A) Baseline demographic and clinical characteristics of lung transplant recipients stratified by CMV IVIG treatment (CMV IVIG−, n = 20; CMV IVIG+, n = 17). (B) Kaplan–Meier curve showing CLAD-free survival comparing CMV IVIG-treated and untreated groups. (C) Kaplan–Meier curves stratified by CMV IVIG treatment and primary graft dysfunction (PGD) status with increased risk for CLAD or death in the CMV IVIG- and PGD+ group.

CMV IVIG was associated with an altered protein response, accentuated in PGD+ recipients

We performed a plasma proteomic enrichment analysis and identified significant upregulation in CMV IVIG+ recipients of multiple immune and signaling pathways, including IKK/NF-κB signaling (p < 0.0001), Myddosome activation (TLR/IL-1) (p = 0.0002), T-cell receptor signaling (p = 0.0015), apoptotic execution phase (p = 0.0042), dynactin-mediated transport (p = 0.012), MAPK and stress signaling (p = 0.025), and FOXO transcriptional activity (p = 0.038). Volcano plots are shown for CMV IVIG vs no CMV IVIG (A) and the subgroups without PGD (B) and with PGD (C). These data suggest that PGD and CMV IVIG drive most of these findings.

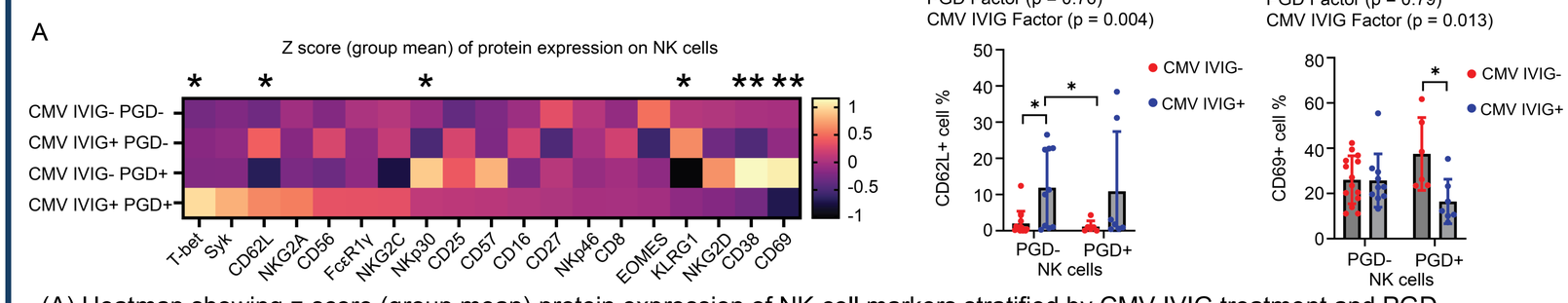


CMV IVIG and PGD interaction is associated with altered NKG2C NK Cell maturation



(A) Representative flow cytometry gating of NK cell maturation subsets based on CD16 and NKG2A expression. (B) Heatmap of NK cell marker expression across subsets (z-score). (C–D) Quantification of NKG2C+ NK cells across PGD and CMV IVIG groups, including subset-specific analysis of less mature NK cells.

CMV IVIG and PGD+ NK cells have increased CD62L and T-bet but reduced CD69



(A) Heatmap showing z-score (group mean) protein expression of NK cell markers stratified by CMV IVIG treatment and PGD status. (B–C) Quantification of NK cell subset frequencies across PGD− and PGD+ groups, stratified by CMV IVIG treatment, with corresponding interaction and main effect p-values indicated.

Conclusions

- CMV IVIG treatment is associated with improved CLAD free survival, especially blunting the effects of PGD
- CMV IVIG was associated with shifts in NK cell phenotype, including changes in maturation and activation marker expression
- Significant CMV IVIG × PGD interactions indicate that NK cell responses differ depending on graft injury status
- Less mature NK cell subsets (CD16^{-}/NKG2A^{+}) are particularly influenced by CMV IVIG in the context of PGD
- CMV IVIG is associated with reduced activation marker expression (e.g., CD69, CD38) and altered trafficking/maturation profiles
- These data suggest CMV IVIG modulates NK cell biology in a PGD-dependent manner, with potential relevance to transplant outcomes

Limitations:

- Small sample size, especially in subgroup analyses
- Retrospective, non-randomized design with potential confounding
- Single-center cohort limits generalizability
- Peripheral blood may not reflect allograft immune biology

The story continues in this session:

Board #112: CMV reactivation after PGD in >2000 recipients
Board #061: mouse models of CMV reactivation after IRI
Board #122: CMV IgG → improved CLAD-free survival and lung function

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CMV Immunoglobulin is Associated with Improved Peak Lung Function and Better CLAD-free Survival

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Background

Cytomegalovirus (CMV) is a ubiquitous herpesvirus that establishes lifelong latency following primary infection and remains a major contributor to morbidity after lung transplantation. CMV seropositivity is highly prevalent worldwide, and in the transplant setting, donor-recipient serostatus is a key determinant of risk. Lung transplant recipients with donor-positive/recipient-negative (D+/R−) mismatch represent the highest-risk group for CMV infection, reactivation, and associated complications[1,4].

Despite the routine use of antiviral prophylaxis, CMV reactivation remains common after lung transplantation and has been consistently associated with adverse outcomes, including chronic lung allograft dysfunction (CLAD) and increased mortality[2,5]. Importantly, CMV-related injury may not be fully explained by direct viral cytopathic effects alone. Emerging evidence suggests that CMV contributes to long-term graft dysfunction through immunomodulatory mechanisms, including activation and expansion of CMV-specific natural killer (NK) cells and alterations in adaptive immune responses, which may promote chronic alloimmune injury[1,3].

CMV immunoglobulin (IVIG) has historically been used as an adjunctive therapy in high-risk transplant populations, including kidney and lung recipients, with the goal of reducing CMV-related complications. However, its use has declined in many centers due to uncertainty regarding its clinical benefit in the modern era of effective antiviral prophylaxis. Notably, CMV IVIG may exert effects beyond viral neutralization, including modulation of innate and adaptive immune responses, which could influence long-term graft outcomes[1,3].

At our institution, CMV IVIG was previously administered per protocol to high-risk recipients but was discontinued in February 2019. This change in practice created a natural experiment to evaluate the clinical impact of CMV IVIG exposure. We therefore sought to determine whether CMV IVIG administration is associated with differences in CLAD-free survival and peak lung function among CMV D+/R− lung transplant recipients in the contemporary era.

Methods

We performed a retrospective cohort study of consecutive, consenting, adult lung transplant recipients at a single center from 2016 to 2022 under an approved protocol. Primary outcomes were freedom from CLAD or death, peak lung function, and freedom from CMV DNAemia. Survival differences between groups were determined by Cox proportional hazards models adjusted for baseline characteristics. Peak lung function was defined as the mean of the highest two FEV1 or FVC values after transplant. Differences in peak lung function in liters across groups were determined by linear regression adjusted for baseline characteristics. Inclusion was limited to CMV D+/R− recipients.

To evaluate potential confounding by transplant era, additional analyses compared outcomes across CMV serotype groups (D+/R+, D−/R+, D−/R−). CMV DNAemia was assessed to determine whether differences in outcomes were attributable to virologic control. CMV IVIG was administered per institutional protocol prior to February 2019 and subsequently discontinued, allowing stratification by CMV IVIG exposure.

All recipients received standard antiviral prophylaxis with intravenous ganciclovir or oral valganciclovir. Baseline demographic and clinical characteristics were compared between groups.

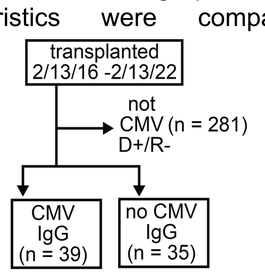

Figure 1. CONSORT diagram

Results

CMV IVIG exposure was associated with significantly improved CLAD-free survival.

In multivariable-adjusted Cox proportional hazards modeling, CMV IVIG conferred a **60% reduction in the risk of CLAD or death compared to no CMV IVIG**: Hazard ratio (HR) 0.41 (95% CI 0.20–0.82), p = 0.01. This effect is demonstrated in Kaplan–Meier analysis (Figure 2)

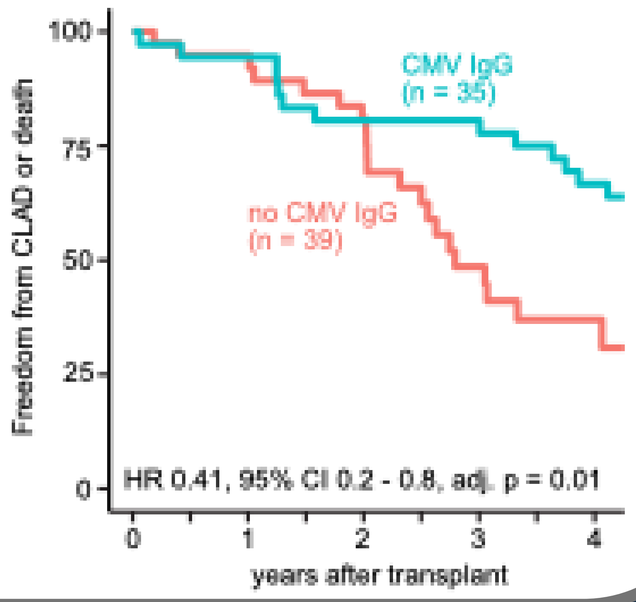

Figure 2. CLAD-free survival for the CMV IVIG group (n=35) and the no CMV IVIG group (n=39). Differences in CLAD-free survival were calculated with Cox Proportional Hazards model were calculated with generalized linear modeling, adjusted for baseline characteristics of age, sex, transplant type, transplant indication, race or ethnicity.

CMV IVIG-treated recipients achieved significantly higher peak lung function compared to those who did not receive CMV IVIG, with significantly higher peak FEV1 (p = 0.009) (Figure 3A) and a trend toward higher peak FVC (p = 0.06) (**Figure 3B**). These findings suggest improved allograft functional recovery among CMV IVIG recipients.

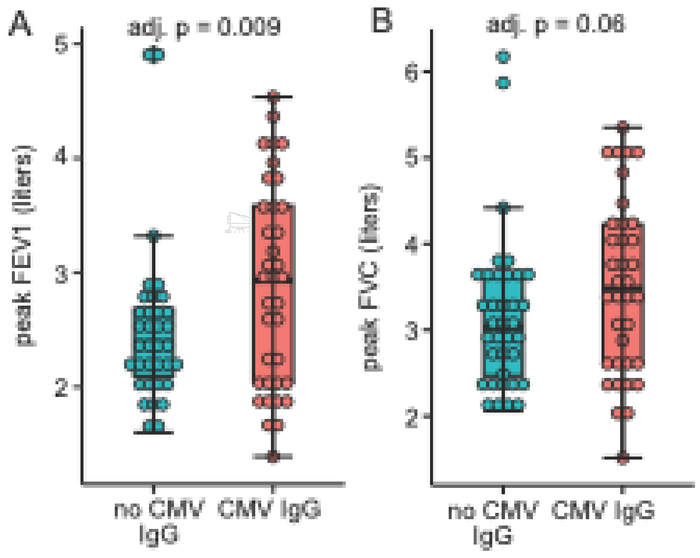

Figure 3. Peak Lung function by CMV IVIG group. Differences in peak FEV1 (Figure 3A) and FVC (Figure 3B) were calculated with Cox Proportional Hazards model were calculated with generalized linear modeling, adjusted for baseline characteristics of age, sex, transplant type, transplant indication, race or ethnicity. .

To deconvolute the effect of transplant era, we compared LTR who received CMV IVIG to LTR with other CMV serotypes (D+/R+, D−/R+, D−/R−) across eras and found no difference in CLAD-free survival (HR 0.77, 95% CI 0.48–1.24, p = 0.29), suggesting that broader improvements in care did not account for the observed benefit. (Figure 4A) In contrast, D+/R− LTR who did not receive CMV IVIG had over a two-fold increased risk of CLAD or death compared to LTR with other serotypes (HR 1.92, 95% CI 1.24–2.97, p = 0.003) (Figure 4A). Finally, these differences were not explained by CMV DNAemia rates, supporting that the benefit of CMV IVIG is not solely attributable to improved virologic control.

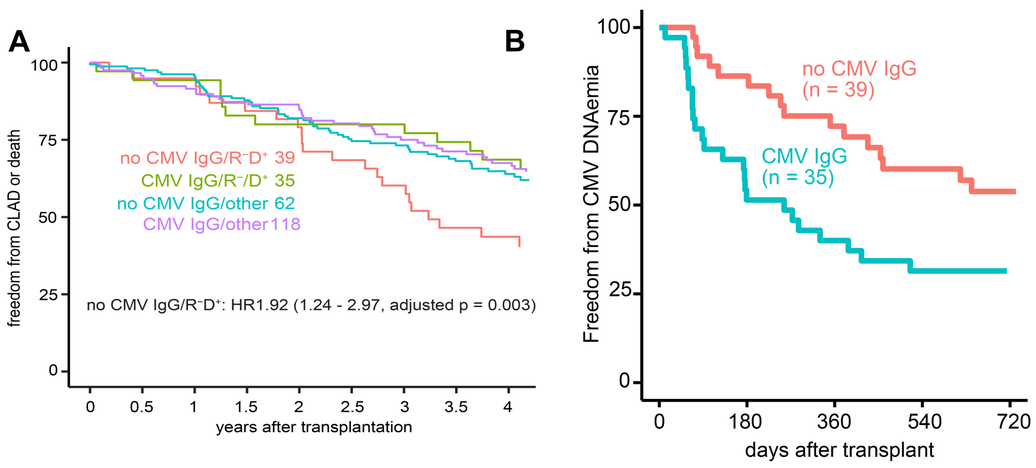

Figure 4. CLAD-free survival by CMV serostatus and CMV IVIG exposure. (A) CLAD-free survival stratified by CMV serotype and CMV IVIG exposure. CMV D+/R− recipients who did not receive CMV IVIG demonstrated significantly worse CLAD-free survival compared to other groups, with an approximately two-fold increased risk of CLAD or death (HR 1.92, 95% CI 1.24–2.97, p = 0.003) In contrast, outcomes among recipients receiving CMV IVIG were similar across serotype groups, suggesting attenuation of risk associated with D+/R− status. **(B)** CMV DNAemia-free survival stratified by CMV IVIG exposure. There was no clear separation between CMV IVIG-treated recipients (n = 35) and those who did not receive CMV IVIG (n = 39). These findings suggest that the observed clinical benefits of CMV IVIG are not explained by differences in CMV DNAemia and are unlikely to be solely attributable to improved virologic control.

Baseline characteristics

Baseline demographic and clinical characteristics were similar between groups, with no significant differences in recipient age, sex, transplant indication, or other key variables (**Table 1**)

	no CMV IgG n = 39	CMV IgG n = 35	p-value
Age, mean (SD)	57.4 (12.7)	57.5 (12.4)	0.95
Female sex, N (%)	23 (59)	21 (58.3)	1
Double lung Tx, N (%)	35 (89.7)	33 (91.7)	1
ILD, N (%)	28 (71.8)	30 (83.3)	0.36
Race/Ethnicity			0.69
Caucasian	28 (71.8)	28 (77.8)	
African American	2 (5.1)	1 (2.8)	
Asian	6 (15.4)	6 (16.7)	
Other	3 (7.7)	1 (2.8)	

Conclusions

In this retrospective cohort of high-risk CMV D+/R− lung transplant recipients, CMV IVIG exposure was associated with significantly improved clinical outcomes, including reduced risk of CLAD or death and higher peak lung function. These findings were observed despite no measurable differences in CMV DNAemia, suggesting that the benefit of CMV IVIG may not be mediated solely through viral suppression.

Instead, these data support a model in which CMV contributes to chronic allograft injury through immunologic pathways, and CMV IVIG may exert protective effects through immunomodulation, potentially influencing NK cell and T cell responses implicated in graft dysfunction.

Importantly, recipients who did not receive CMV IVIG had substantially worse outcomes compared to both CMV IVIG-treated recipients and other CMV serotype groups, reinforcing the clinical relevance of this high-risk population and the potential role of CMV IVIG as a targeted intervention.

These findings should be interpreted in the context of a single-center retrospective design and potential residual confounding, including transplant era effects. However, additional analyses suggest that the observed associations are not solely attributable to era-related differences.

Overall, CMV IVIG may represent a clinically meaningful adjunctive therapy to improve long-term graft outcomes in high-risk lung transplant recipients. These results provide a strong rationale for prospective, randomized controlled trials to definitively evaluate the efficacy and mechanism of CMV IVIG in the modern transplant era.

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Funding

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The story continues in this session:

Board #112: CMV reactivation after PGD in >2000 recipients
Board #50: CMV IVIG in humans modulates NK cells
Board #061: Mouse models of IRI and mCMV

Lung ischemia reperfusion injury is amplified by latent cytomegalovirus in an NK cell-dependent manner

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Background

Human cytomegalovirus (CMV) is a ubiquitous β-herpesvirus that establishes lifelong latency and remains a major driver of morbidity after lung transplantation despite modern antiviral strategies (1).

Natural killer (NK) cells are key innate lymphocytes for CMV immune surveillance, and CMV exposure imprints long-lived, virus-adapted and memory-like NK subsets with enhanced cytotoxicity and effector function(2, 3).

Lung ischemia-reperfusion injury (IRI) results from epithelial and endothelial dysfunction immediately after transplantation with graft damage ensuing from innate immune activation. Primary graft dysfunction (PGD) is the clinical syndrome from IRI that is associated with early morbidities, poor peak lung function, and mortality(4).

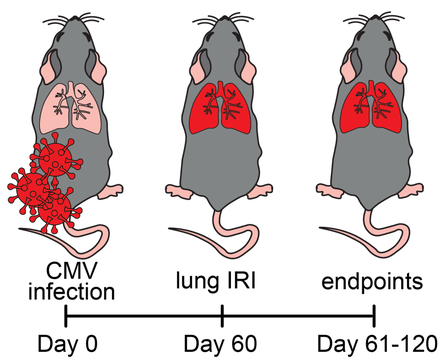
Our group has shown a prominent role for NK cells in mediating the lung damage of IRI dependent upon graft stress recognized by the NKG2D receptor and trafficking to the alveolar compartment via CCR5(5-7). We have previously shown that CMV-specific NK cells (NKG2C+) in the bronchoalveolar lavage after transplant were associated with increased risk for CLAD or death, as opposed to CMV protection(8).

This biology raises the possibility that CMV-primed NK cells may respond aberrantly to IRI, amplifying graft injury even in the absence of active viral replication.

We hypothesized that lung IRI unmasks CMV latency associated immunopathology and exacerbates lung injury in an NK cell dependent manner.

Methods

Animals
C57BL/6 mice obtained from Jackson Laboratories (Bar Harbor, ME) were used for all experiments. Animal work was conducted in accordance with approved institutional protocols.



CMV infection
Mice were infected intraperitoneally with murine cytomegalovirus (MCMV; Smith strain) at a dose of 1 × 10^3 plaque-forming units (PFU, **Figure**). Mock-infected control mice received an equivalent volume of sterile saline. Mice were allowed to recover and progress to viral latency for 60 days following primary infection. CMV latency was confirmed by the absence of detectable infectious virus and low-level viral gene expression in tissues.

Warm hilar clamp versus sham IRI procedures
At 60 days post-CMV latency achievement, mice underwent either lung ischemia–reperfusion injury (IRI or sham surgery as previously described. Injury was quantified via arterial oxygen (PaO_2), lavage protein, histopathology and inflammation measures. Lymphocytes were deeply profiled with spectral flow cytometry focused on phenotyping NK cells and T cells. In select experiments, mice received intraperitoneal ganciclovir, pooled immunoglobulin from latently infected mice, anti-NK1.1 monoclonal antibody, or an isotype control antibody 24 hours preceding planned IRI procedures.

Statistical Analysis
Group-wise differences in overall population distributions were assessed using chi-square tests, while pairwise comparisons of individual populations or continuous outcomes were performed using two-tailed Student's t-tests. Survival analysis was conducted using Kaplan–Meier curves with log-rank testing.

Individual datapoints (at least n = 5 per condition)are shown with data summarized in box and whisker plots with medians shown by bisecting lines and whiskers representing the 25th and 75th percentiles. All analyses and data plots were performed using R statistical programming software.

Results

Lung IRI leads to robust reactivation of CMV in the blood and the lung

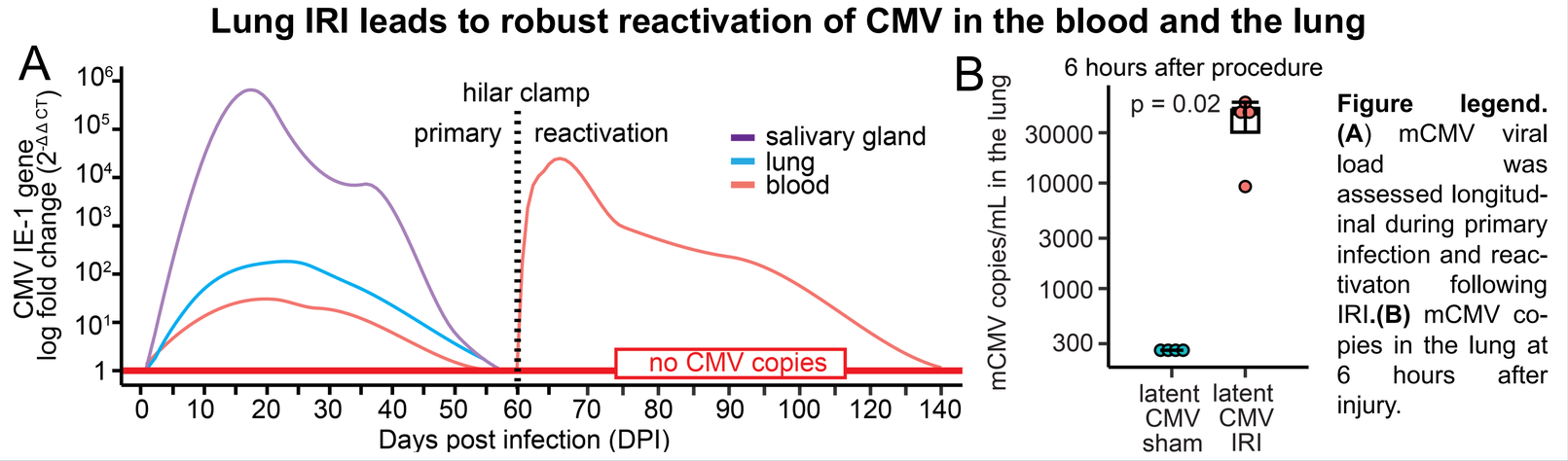


Figure legend. (A) mCMV viral load was assessed longitudinal during primary infection and reactivaton following IRI.**(B)** mCMV copies in the lung at 6 hours after injury.

Lung IRI in latently infected animals is more severe

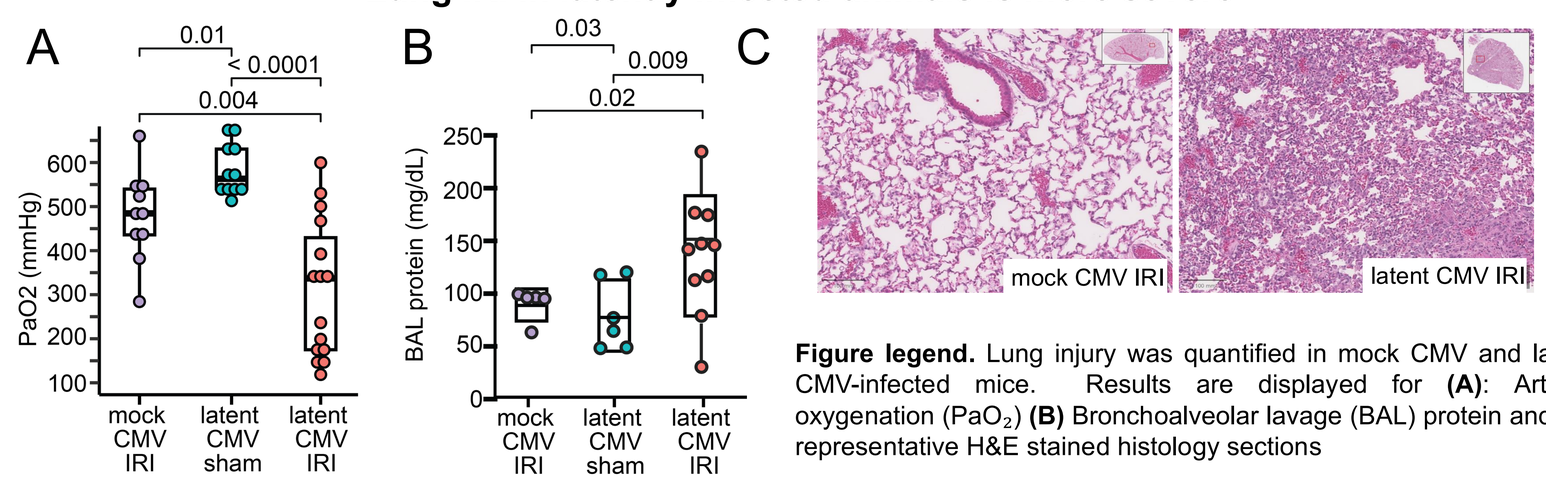


Figure legend. Lung injury was quantified in mock CMV and latent CMV-infected mice. Results are displayed for **(A)**: Arterial oxygenation (PaO_2) **(B)** Bronchoalveolar lavage (BAL) protein and **(C)** representative H&E stained histology sections

Lung injury induces long-lived lung resident NK cell memory expansion

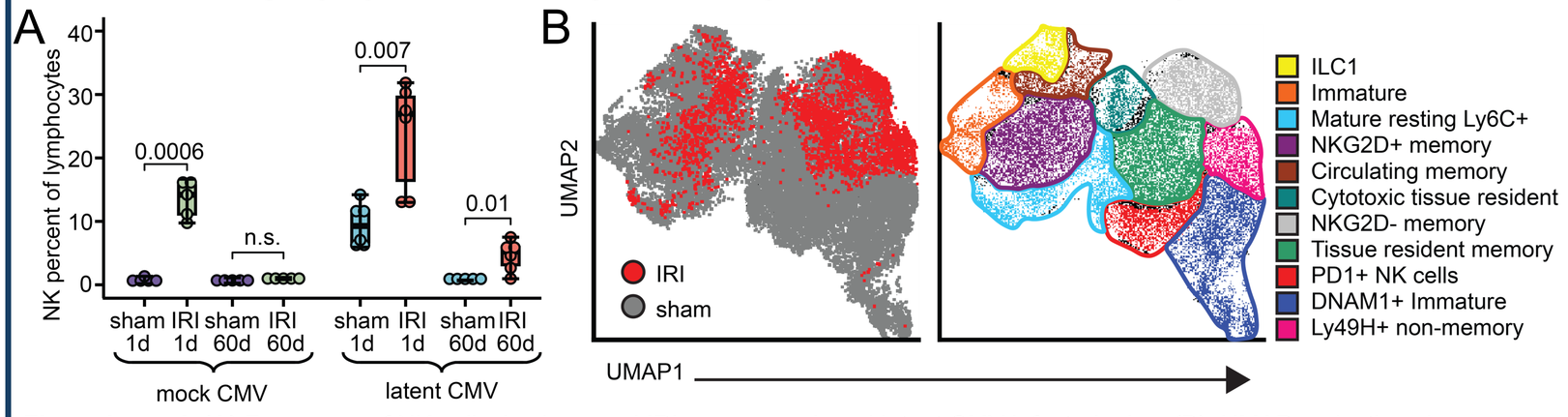


Figure legend: (A) Frequency of NK cells in sham and IRI across mock and latent CMV infected mice. (B) UMAP projection shows distinct clustering of NK cells in IRI versus sham conditions at 1 day following procedures

Immunomodulation and not viral suppression improves survival

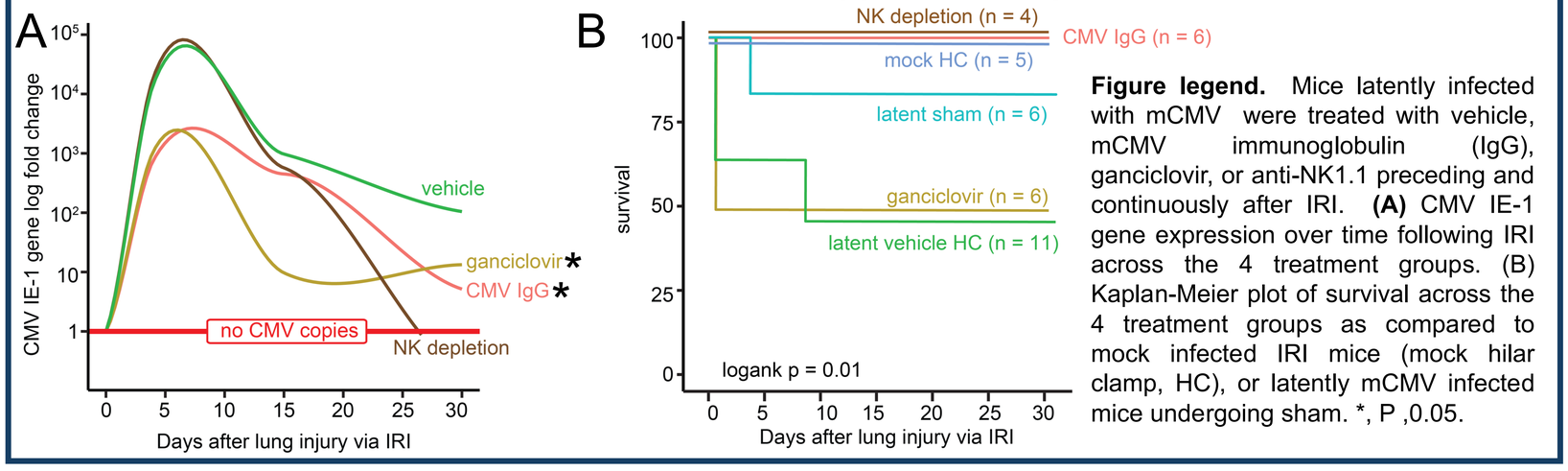


Figure legend. Mice latently infected with mCMV were treated with vehicle, mCMV immunoglobulin (IgG), ganciclovir, or anti-NK1.1 preceding and continuously after IRI. **(A)** CMV IE-1 gene expression over time following IRI across the 4 treatment groups. (B) Kaplan-Meier plot of survival across the 4 treatment groups as compared to mock infected IRI mice (mock hilar clamp, HC), or latently mCMV infected mice undergoing sham. *, P ,0.05.

Conclusions

- Pulmonary IRI triggers CMV reactivation from latency
- Latent CMV worsens acute lung injury as evidenced by ↓ oxygenation, ↑ permeability
- NK cells are increased in lung tissue long-term after IRI with a skewing towards cytotoxic memory populations
- Survival was improved with immunomodulatory but not viral suppressive therapy alone.
- These findings suggest that NK immunomodulation may prove a useful clinical adjunct to CMV viral suppressive therapy in improving lung transplant outcomes.

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Cytogam [Cytomegalovirus Immune Globulin Intravenous (Human)]

Cytogam® is an intravenous immunoglobulin containing standardized amount of antibody to cytomegalovirus.

Indication and Usage:

It is indicated for the prophylaxis of cytomegalovirus disease associated with transplantation of kidney, lung, liver, pancreas and heart. In transplants of these organs other than kidney from CMV seropositive donors into seronegative recipients, prophylactic CMV-IGIV should be considered in combination with ganciclovir.

Important Safety Information:

Cytogam® is contraindicated in individuals with a history of a prior severe reaction associated with the administration of this or other human immunoglobulin preparations. Persons with selective immunoglobulin A deficiency have the potential for developing antibodies to immunoglobulin A and could have anaphylactic reactions to subsequent administration of blood products that contain immunoglobulin A, including Cytogam.

Immune Globulin Intravenous (Human) products have been reported to be associated with renal dysfunction, acute renal failure, osmotic nephrosis, and death. Patients predisposed to acute renal failure include patients with any degree of preexisting renal insufficiency, diabetes mellitus, age greater than 65, volume depletion, sepsis, paraproteinemia, or patients receiving known nephrotoxic drugs. Especially in such patients, IGIV products should be administered at the minimum concentrations available and the minimum rate of infusion practicable. Those containing sucrose as a stabilizer, like Cytogam, account for a disproportionate share of the total number of reports of renal dysfunction and acute renal failure when given at daily doses of 350 mg/kg or greater.
During administration, the patient's vital signs should be monitored continuously, and careful observation made for any symptoms throughout the infusion. Epinephrine and diphenhydramine should be available for the treatment of an acute and anaphylactic reactions.

Increases in serum creatinine and blood urea nitrogen (BUN) have been observed as soon as one to two days following IGIV infusion. Progression to oliguria or anuria requiring dialysis has been observed.

Immune Globulin Intravenous (Human) products can contain blood group antibodies which may act as hemolysins and induce in vivo coating of red blood cells with immunoglobulin, causing a positive direct antiglobulin reaction and, rarely, hemolysis.

Thrombotic events have been reported in association with IGIV. Patients at risk may include those with a history of atherosclerosis, multiple cardiovascular risk factors, advanced age, impaired cardiac output, and/or known or suspected hyperviscosity. The potential risks and

benefits of IGIV should be weighed against those of alternative therapies for all patients for whom IGIV administration is being considered. Baseline assessment of blood viscosity should be considered in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/markedly high triacylglycerols (triglycerides), or monoclonal gammopathies.

Cytogam® is derived from human plasma. As with all plasma-derived products, the risk of transmission of infectious agents, including viruses and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent, cannot be completely eliminated.

Minor reactions, such as flushing, chills, muscle cramps, back pain, fever, nausea, vomiting, arthralgia, and wheezing, were the most frequent adverse reactions observed during the clinical trials for Cytogam.

Please see full Prescribing Information for full prescribing details.

To report SUSPECTED ADVERSE REACTIONS, contact Kamada at pharmacovigilance@kamada.com or 1-(866)-916-0077 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.