

UCLA Mycophenolate mofetil dosing impacts humoral and cellular responses to SARS-CoV-2 in patients hospitalized with COVID-19

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Background

COVID-19 poses significant risks for solid organ transplant (SOT) recipients, who have atypical immune responses to SARS-CoV-2.

Maintenance immunosuppression with mycophenolate mofetil (MMF) significantly reduces the risk of acute rejection but is also associated with increased infection risk. Furthermore, MMF therapy appears to be a major contributing factor in ineffective immune responses to infection and vaccination.

Therefore, we sought to study the impact of MMF therapy, and its dosing, on early immune responses in patients hospitalized with COVID-19 prior to vaccination.

Methods

We studied 27 SOT recipients and 56 non-SOT controls from UCLA enrolled in the multicenter IMPACC study at days 1-3 post-admission.

SOT recipients were grouped based on MMF dosing at admission into ≤ 1000 mg/day or > 1000 mg/day and compared with non-SOT controls not receiving MMF.

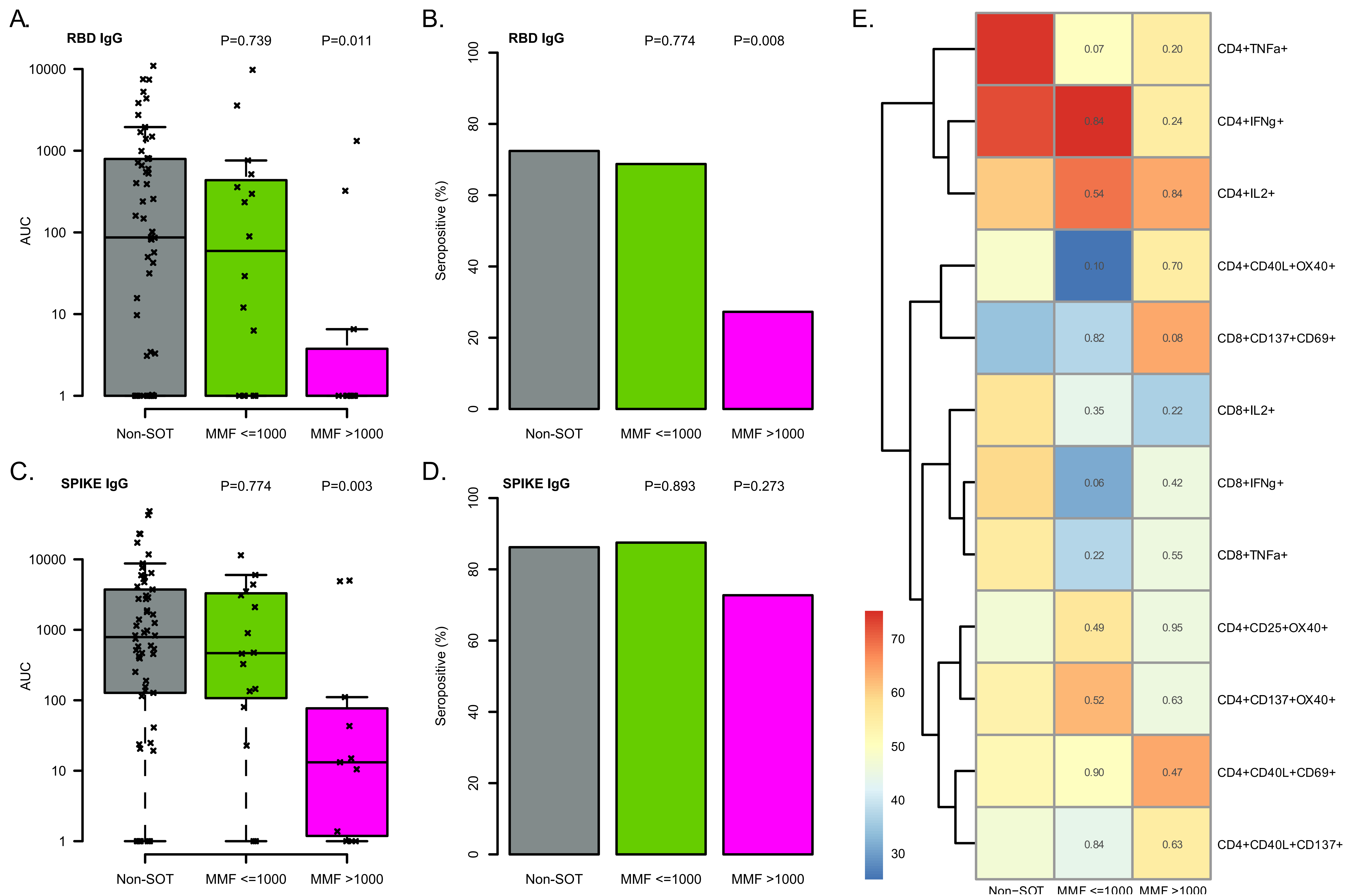
Anti-RBD and spike IgG levels were measured in serum. Peripheral blood mononuclear cells were stimulated with a SARS-CoV-2 spike-specific peptide pool and memory T cells were profiled by flow cytometry for activation-induced markers and cytokine production.

Results

Compared to non-SOT controls (5.2%), higher MMF dosing was associated with increased baseline lymphopenia (≤ 1000 mg/day: 18.8%, $P=0.098$; > 1000 mg/day: 36.4%, $P=0.006$). There was no significant difference in 28-day mortality for SOT recipients on ≤ 1000 mg/day MMF ($P=0.963$) or > 1000 mg/day ($P=0.778$).

Anti-RBD and spike IgG levels were lower in SOT recipients on > 1000 g/day MMF (**Panels A+C**), as was anti-RBD seropositivity (**Panel B**).

Activated and cytokine-producing spike-specific T cells were detectable in most patients regardless of SOT status (non-SOT: 81.0%) or MMF dosing (≤ 1000 mg/day: 81.3%, $P=0.984$; > 1000 mg/day: 90.9%, $P=0.440$). However, differences were observed for specific T cell subsets (**Panel E**). Cytokine-producing spike-specific CD4 T cells were less common in SOT recipients on > 1000 g/day MMF, while equivalent CD8 T cells were less common in all SOT recipients. Conversely, spike-specific T cells expressing CD69 were more common in SOT recipients on > 1000 g/day MMF.



In a cohort of patients hospitalized with PCR-confirmed SARS-CoV-2 infection, non-solid organ transplant (SOT) recipients (grey) were compared to SOT recipients receiving no MMF or ≤ 1000 mg/day ("MMF ≤ 1000 ", green) compared with those receiving > 1000 mg/day ("MMF > 1000 ", purple).

A) Boxplot of baseline RBD IgG levels in serum measured by area under the curve (AUC). **B)** Barplot of baseline RBD IgG seropositivity. **C)** Boxplot of baseline spike IgG levels in serum measured by area under the curve (AUC). **D)** Barplot of baseline spike IgG seropositivity. **E)** Peripheral blood mononuclear cells were stimulated with 253 overlapping peptides covering the entire sequence of the ancestral SARS-CoV-2 spike protein and T memory cell responses were quantified by immunostaining for activation-induced markers (AIM) and intracellular cytokines (ICS) and evaluated by flow cytometry. Percent of patients per group with detectable spike-specific memory T cells, defined as spike-stimulated frequencies $>$ the negative control, are shown for each gate.

Linear regression (**panels A and C**) and binomial logistic regression (**panels B, D, and E**) were used to compare non-SOT patients to SOT recipients on variable levels of MMF, P-values are indicated above the plots (**panels A-D**) or within the heatmap (**panel E**).

Conclusions

Despite increased lymphopenia and diminished antibody responses, MMF dosing did not significantly hinder initial induction of anti-spike T cells in SOT recipients hospitalized with COVID-19. However, higher MMF doses were associated with less cytokine-producing T cells but increased CD69 expression. These findings suggest a nuanced impact of MMF on development of cellular immunity to SARS-CoV-2 that may be missed by less comprehensive phenotypic profiling.