

# Mycophenolate mofetil-related diarrhea reports and beta-glucuronidase expression following kidney transplantation.

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## INTRODUCTION

- Mycophenolate mofetil (MMF) is associated with diarrhea.
- Recipients developing diarrhea are generally managed with lower MMF daily doses or dividing the same daily dose into three times a day dosing.
- Shorter dosing intervals are associated with reduced adherence to immunosuppression and poorer outcomes.

## HYPOTHESIS

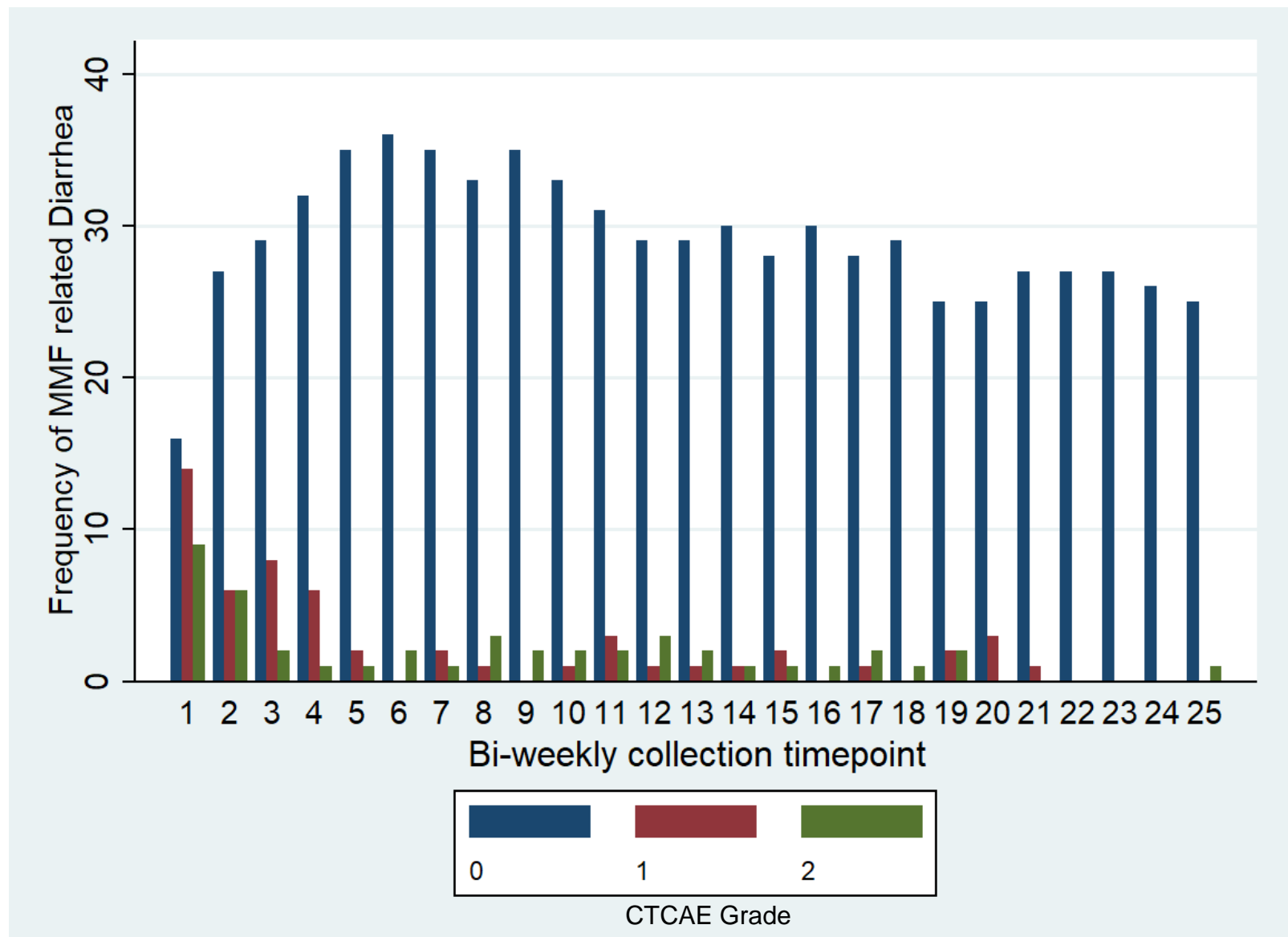
- We hypothesized that bacterial beta-glucuronidase expression in the stool, which is a key enzyme in MMF enterohepatic recirculation, is associated with diarrhea occurrence.

## METHODS

- The Microbiome and Immunosuppression in Kidney Transplantation (MISSION) study assessed diarrhea posttx using bi-weekly text-based survey (Mosio Inc, Seattle, WA) in the first 3 months posttx.
- Diarrhea events were defined using the V 5.0 definition of the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE).
- Diarrhea events of CTCAE grade 2 (increase of 4-6 stools per day compared to the previous week) were the primary outcome.
- Each participant provided a single stool sample at baseline, which underwent metatranscriptomics analysis on NovaSeq. The data were processed using HUMAnN 3.0, and beta-glucuronidase transcripts were determined using level-4 enzyme commission (EC) categories.
- In an exploratory analysis, we used polytomous logistic regression to model the association between diarrhea events and beta-glucuronidase transcripts after controlling for age, gender, race, diabetes and BMI at baseline.

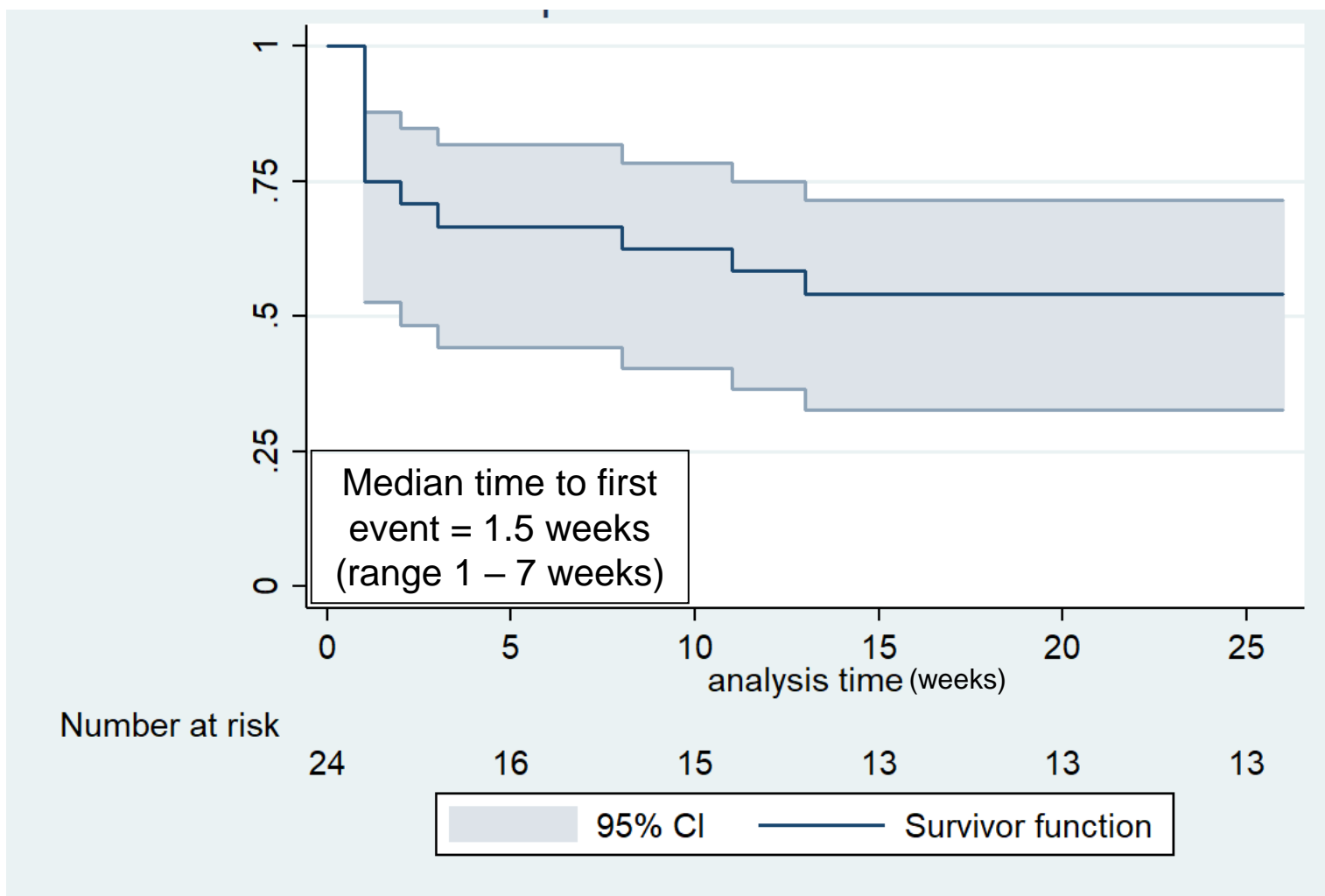
## RESULTS

**Figure 1: Frequency of MMF-related diarrhea during the first 3 months of follow up**



During the first 3 months of follow up, we observed 31 CTCAE grade 1 (5.3% of responses) and 25 CTCAE grade 2 (4.3% of responses) diarrhea events.

**Figure 2: Kaplan Meier curve for diarrhea events of CTCAE grade 2+ events during follow up**



Data represent the Kaplan Meier estimates for the time to first severe diarrhea event over the first 6 months of follow up. 33% of the study participants reported a CTCAE grade 2 diarrhea event in the first 30 days of follow up.

**Table 1: Demographic & clinical characteristics of the study participants**

Baseline Demographics	Did not develop CTCAE grade 2 Diarrhea (N=13)	Developed CTCAE grade 2 diarrhea* (N=11)
Age (Mean (STD))	45.6 (15.3)	50.3 (12.1)
BMI (Mean (STD))	28.8 (3.3)	28.9 (5.9)
White (%)	6 (46.1%)	9 (81.8%)
Male (%)	8 (61.5%)	9 (81.8%)
Diabetes at baseline (%)	4 (30.1%)	2 (18.2%)

\*CTCAE grade 1 indicates loose stool, but no increase in frequency. CTCAE grade 2 was the main outcome of this analysis

**Table 2: Association between beta-glucuronidase transcripts and MMF related diarrhea events using multinomial regression**

Diarrhea CTCAE Grade	Number of diarrhea events	Beta_Glucuronidase Mean copies per million (standard deviation)	Relative Risk	p-value
CTCAE grade 0	526	107.4 (200.8)	Reference	
CTCAE grade 1	31	60.5 (98.8)	0.997 (0.995 - 1.000)	0.13
CTCAE grade 2	25	71.2 (118.9)	0.999 (0.995 - 1.001)	0.38

The multinomial logistic regression model was adjusted for age at transplant, sex, race, diarrhea reported timepoint, bmi and diabetes status at baseline.

## CONCLUSIONS

- 33% (8 out of 24 participants) reported a CTCAE grade 2 diarrhea event within the first 30 days of follow up.
- Although beta-glucuronidase expression in the stool was lower among participants who developed CTCAE grade 2 diarrhea (mean of 71.2 cpm, vs 107.4 cpm in CTCAE grade 0 participants) we did not observe an association between beta-glucuronidase transcripts and diarrhea (RR: 0.999, p-value: 0.38) (Table 2).
- A larger sample size is needed to simultaneously collect longitudinal microbiome data and MMF adverse events to understand the interplay between the gut microbiome and MMF adverse events in kidney transplantation.

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