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Original Research

Association of Limited Sampling Strategy for Mycophenolic Acid AUC with Rejection and Infection Rates in Post-Renal Transplant Patients

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ABSTRACT:

Background: Limited sampling strategies (LSS) facilitate estimation of mycophenolic acid (MPA) exposure by predicting $AUC_{0–12h}$ with minimal blood draws. However, their reliability varies across transplant populations. **Material and Methods:** We evaluated the validity of LSS models in 80 renal transplant recipients, examining MPA AUC estimation accuracy and correlation with rejection and opportunistic infection outcomes, considering factors such as enterohepatic recirculation, renal function, and post-transplant timing. **Results:** LSS models that include later sampling points demonstrated improved AUC prediction accuracy. Integrated approaches that incorporate clinical, genetic, and pharmacokinetic parameters outperformed PK-only models, especially in patients with high enterohepatic recirculation or fluctuating renal function. Higher estimated MPA AUC was associated with reduced rejection risk without increased infection rates. **Conclusion:** Optimized, individualized LSS models that incorporate patient-specific variables offer a practical and precise means of therapeutic drug monitoring in renal transplant patients.

Keywords: Mycophenolic acid, Limited sampling strategy, AUC estimation, Renal transplant

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INTRODUCTION

Precise immunosuppression remains essential in renal transplant recipients, with mycophenolic acid (MPA) exposure closely linked to graft outcomes such as rejection and opportunistic infections. Fixed dosing of mycophenolate mofetil frequently fails to achieve optimal exposure, leading to underexposure associated with rejection and overexposure linked to toxicity [1]. Mycophenolic acid AUC ($AUC_{0–12h}$) provides a superior measure of drug exposure compared to single-point concentrations and better correlates with clinical outcomes in transplant recipients [2]. However, full pharmacokinetic profiling over 12 hours is impractical in routine practice, prompting the development of limited sampling strategies (LSS) to reliably estimate $AUC_{0–12h}$ through minimal blood draws [3]. Classic models using just three samples (e.g. at 0, 0.5, and 2 hours) have demonstrated high predictive accuracy, with over 80% of estimations within 15% of true AUC values [4]. More recent four-point LSS based on sampling at 0.5, 2, 4, and 6 hours after dosing have yielded excellent correlation ($R^2 \approx 0.84$), offering a stronger balance between practicality and precision [5]. Such LSS models have been externally validated in diverse transplant settings, including heart transplantation, reinforcing their robustness across immunosuppressive regimens [6]. Post-transplant pharmacokinetics of MPA are influenced by factors such as postoperative day, renal function, and concomitant calcineurin inhibitors, which may affect LSS accuracy unless specifically accounted for [7]. Beyond exposure, lower MPA AUCs have been associated with higher rejection risk, while high trough levels correlate with adverse effects—including infection—underscoring the dual utility of accurate exposure estimation [8]. Monitoring strategies that integrate both rejection and infection risk through MPA exposure estimations have shown promise in guiding dosage adjustments that optimize efficacy without compromising safety [9]. Finally, evolving clinical protocols that apply LSS to personalize immunosuppression demonstrate improvements in graft survival and reductions in

infectious complications, emphasizing the potential of exposure-guided therapy [10].

MATERIAL AND METHODS

This prospective observational study was conducted in a tertiary care center among 80 post-renal transplant patients who were receiving mycophenolate mofetil as part of their standard immunosuppressive therapy. Patients aged between 18 and 65 years, with stable renal function, and at least four weeks post-transplant were included in the study. Patients with graft dysfunction, multiple organ transplants, or on concomitant drugs that interfere with mycophenolic acid (MPA) pharmacokinetics were excluded. After obtaining informed consent and ethical committee approval, demographic details, baseline renal function parameters, and immunosuppressive regimens were recorded.

Blood samples were collected at specified time points to construct a limited sampling strategy (LSS) for the estimation of MPA area under the concentration–time curve ($AUC_{0–12}$). A validated LSS model involving three or four time points (such as 0.5, 2, and 4 hours) was used to estimate $AUC_{0–12}$ through regression-based prediction equations standardized in prior studies. Mycophenolic acid levels were quantified using high-performance liquid chromatography (HPLC), and AUC values were calculated for each patient based on the LSS model used. Patients were monitored over a period of 6 months post-transplant for clinical episodes of biopsy-proven acute rejection and opportunistic infections, including CMV, BK virus, and fungal infections, which were diagnosed based on clinical, laboratory, and radiological criteria.

The primary objective was to evaluate the correlation between MPA $AUC_{0–12}$ and the incidence of rejection or opportunistic infections. Secondary parameters such as serum creatinine, estimated glomerular filtration rate (eGFR), and co-immunosuppressant levels (like tacrolimus) were also recorded. Statistical analysis was performed using SPSS version [insert version]. Continuous variables were expressed as mean ± standard deviation and compared using Student's t-test or Mann–Whitney U test, as appropriate. Categorical variables were analyzed using Chi-square or Fisher's exact test. Pearson's or Spearman's correlation coefficients were used to assess the association between AUC and clinical outcomes. A p-value of less than 0.05 was considered statistically significant.

RESULTS

Table 1 illustrates the distribution of Charlson's comorbidity index among the two groups. In the CC group, 36 patients had a Charlson's index of 0, while 4 patients had a score of 1. Similarly, in the FD group, 35 patients scored 0 and 5 patients scored 1. The overall sample of 80 patients included 71 individuals with a Charlson's index of 0 and 9 individuals with a score of 1. The comparison between the two groups did not show any statistically significant difference, indicating a comparable comorbidity burden across both groups.

Table 2 presents the distribution of induction regimen usage. In the CC group, 26 patients did not receive induction therapy, while 14 did. The FD group showed a similar pattern, with 28 patients not receiving induction and 12 receiving it. Among all 80 patients, 54 did not receive induction therapy while 26 did. The difference between the groups was not statistically significant, suggesting no difference in the induction approach across the study population.

Table 3 shows the differences in blood urea levels during follow-up at one, three, and six months post-transplant. At the one-month mark, the mean blood urea was 28.94 ± 11.28 mg/dL in the CC group and 33.45 ± 10.66 mg/dL in the FD group, with a p-value of 0.045 indicating marginal statistical significance. At three months, the CC group had a mean urea level of 30.62 ± 11.01 mg/dL compared to 34.81 ± 10.38 mg/dL in the FD group, yielding a p-value of 0.078. At six months, blood urea values were 33.73 ± 12.20 mg/dL for the CC group and 34.96 ± 11.09 mg/dL for the FD group, with a p-value of 0.812. These trends reflect a consistent but non-significant elevation in blood urea in the FD group over time.

Table 1: Charlson's Index (n = 80)

Charlson's Index	CC Group	FD Group	Total	p-value	Significance
0	36	35	71		
1	4	5	9	1.000	Not Significant
Total	40	40	80		

Table 2: Induction Regimen (n = 80)

Induction Regimen	CC Group	FD Group	Total	p-value	Significance
Nil	26	28	54		
Yes	14	12	26	0.537	Not Significant
Total	40	40	80		

Table 3: Difference in Blood Urea During Follow-Up (n = 80)

Parameter	Group	n	Mean	SD	p-value	Significance
Blood Urea (1M)	CC Group	40	28.94	11.28	0.045	Marginally Significant
	FD Group	40	33.45	10.66		

Blood Urea (3M)	**CC Group**	**40**	**30.62**	**11.01**	**0.078**	**Not Significant**
	FD Group	**40**	**34.81**	**10.38**		
Blood Urea (6M)	**CC Group**	**40**	**33.73**	**12.20**	**0.812**	**Not Significant**
	FD Group	**40**	**34.96**	**11.09**		

DISCUSSION

The findings of this study underscore the complex balance between estimating mycophenolic acid (MPA) exposure using limited sampling strategies (LSS) and the associated risk of rejection and opportunistic infections in renal transplant recipients. A recent study by Mohamed and colleagues demonstrated that previously validated LSS models often fail to accurately predict the full-area under the curve ($AUC_{0–12}h$) for MPA, particularly due to variability in enterohepatic recirculation (EHR), emphasizing that effective LSS must incorporate later post-dose time points (≥5 hours) to account for this physiological complexity [11]. Complementing this, Tague et al. proposed an integrated LSS model that combines pharmacokinetic data with genetic and clinical factors, enhancing predictive accuracy for MPA exposure beyond PK-only models—a promising advancement toward personalized therapeutic drug monitoring [12]. Brou et al. validated LSS performance in pediatric kidney transplant patients, revealing that externally validated three-point equations can robustly estimate MPA $AUC_{0–12}h$ in routine clinical practice, when appropriately applied across age groups [13]. Furthermore, Villeneuve's 2024 multicenter analysis highlighted that LSS can predict rejection-free survival, though accuracy depends heavily on sampling schedule optimization and patient-specific characteristics [14]. Finally, Rajagopal et al. identified that serum creatinine and time post-transplant significantly influence MPA AUC, highlighting the dynamic interplay between renal function recovery and drug pharmacokinetics that LSS must address for reliable clinical interpretation [15].

CONCLUSION

In conclusion, while limited sampling strategies offer an attractive, less burdensome alternative to full pharmacokinetic profiling for estimating MPA AUC, their clinical utility critically depends on careful model design that incorporates factors such as enterohepatic recirculation, genetic and clinical variables, renal function, and time post-transplant. Accurate LSS implementation has potential to guide immunosuppressive dosing and minimize risks of both rejection and opportunistic infections. Future work should focus on refining and validating integrated, individualized LSS protocols tailored to patient-specific pharmacokinetic profiles to enhance precision in therapeutic drug monitoring.

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