

Pharmacogenetics and Pharmacokinetics of Immunosuppressants: Clinical Correlations and Disease Activity Control in Egyptian Female Patients with Lupus Nephritis.

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Abstract

Purpose

Mycophenolate mofetil (MMF) is widely used in lupus nephritis (LN), but interindividual variability in pharmacokinetics and pharmacogenetics may affect treatment response. This study investigated the relationship between MMF pharmacokinetics, key genetic polymorphisms, and therapeutic response in Egyptian female LN patients.

Methods

In this prospective study, 53 female patients with active LN (ISN/RPS class III–IV) maintained on 2 g/day MMF were enrolled at the Urology and Nephrology Center, Mansoura University, Egypt. Baseline clinical, laboratory, and histopathological data were collected. Serial blood samples were obtained over 8 hours for mycophenolic acid (MPA) quantification by LC/MS. Genomic DNA was extracted for UGT2B7 (rs7438135) and SLC01B1 (rs183624077) genotyping using TaqMan real-time PCR assays. Treatment response was classified as complete or partial remission versus non-response at 6 months. Population pharmacokinetics were analyzed using Monolix 2020R1.

Results

Considerable variability in MPA exposure was observed (mean AUC_{0-8} : $22.4 \pm 12.9 \mu\text{g}\cdot\text{h/mL}$; mean C_{max} : $12.9 \pm 5.5 \mu\text{g/mL}$). Responders exhibited higher median AUC_{0-8} than non-responders (23.1 vs $16.2 \mu\text{g}\cdot\text{h/mL}$; $p = 0.039$). SLC01B1 and UGT2B7 genotypes did not differ significantly between responders and non-responders, though TT carriers showed lower MPA AUC_{0-8} . Multivariate analysis identified biopsy class (III vs IV), induction therapy with MMF, and higher MPA AUC_{0-8} as independent predictors of response.

Conclusions

MMF exposure, biopsy class, and induction regimen significantly influence therapeutic response in LN. Pharmacokinetic monitoring of MPA may help optimize MMF therapy, while common UGT2B7 and SLC01B1 variants showed limited predictive value in this cohort.

Introduction

Mycophenolate mofetil (MMF) is a cornerstone immunosuppressive agent widely used in the management of lupus nephritis (LN), a serious renal complication of systemic lupus erythematosus that significantly contributes to morbidity and progression to end-stage kidney disease [1]. MMF is rapidly converted to its active metabolite, mycophenolic acid (MPA), which exerts immunosuppressive effects

by inhibiting inosine monophosphate dehydrogenase and suppressing lymphocyte proliferation. Despite its clinical utility, the pharmacokinetics (PK) of MPA exhibit wide inter- and intra-individual variability, which may contribute to inconsistent therapeutic responses and the risk of adverse effects in patients with LN [2].

MPA undergoes extensive hepatic and extra-hepatic metabolism, primarily through uridine diphosphate glucuronosyltransferases (UGTs) including UGT1A9 and UGT2B7, to form the inactive phenolic glucuronide (MPAG) and the acyl glucuronide (AcMPAG) metabolites [3]. AcMPAG is pharmacologically active and has been implicated in some of MMF's gastrointestinal and hematologic toxicities. In addition to metabolic pathways, MPA and its metabolites are subject to enterohepatic recirculation mediated by transporters such as multidrug resistance-associated protein 2 (MRP2) and organic anion-transporting polypeptides (OATPs), which further influence systemic drug exposure [4].

Pharmacokinetic parameters such as the area under the plasma concentration–time curve (AUC) and the maximum plasma concentration (C_{max}) provide comprehensive measures of overall drug exposure and peak levels, respectively [5]. A greater AUC has been associated with improved clinical response in LN, whereas trough concentrations (C₀) have shown only modest correlation with total exposure and substantial overlap among patients, limiting their utility as surrogate markers. Consequently, reliance on fixed dosing without consideration of individual PK variability may lead to suboptimal therapeutic outcomes [6].

An important contributor to this variability is pharmacogenetic variation in genes encoding drug-metabolizing enzymes and transporters [7]. Polymorphisms in genes such as UGT2B7 and SLC01B1 have been associated with altered MPA disposition and exposure in transplant and autoimmune populations. For example, UGT2B7 variants influence glucuronidation capacity, while SLC01B1 variants affect hepatic uptake and systemic drug levels. Despite these insights, comprehensive data on the combined effects of MPA pharmacokinetics and pharmacogenetic determinants on therapeutic response in LN patients remain limited [8].

Given the complex interplay between drug metabolism, transport, and genetic variability, a more integrated analysis of MPA PK parameters and pharmacogenetic profiles may improve understanding of individual differences in drug exposure and response. Such knowledge has the potential to inform personalized MMF dosing strategies, optimizing therapeutic efficacy while minimizing toxicity in patients with lupus nephritis.

Patients and Methods

Study Design and Setting

This study was designed as a prospective study and did not involve randomization or allocation to intervention groups. This prospective study conducted at the Nephrology Clinic of the Urology and Nephrology Centre, Faculty of Medicine, Mansoura University, Egypt.

The protocol was approved by the local ethics committee, and the study was conducted in accordance with the Declaration of Helsinki (Protocol No. RP.26.02.1052).

Consent to participate

in the study: Written informed consents were signed by all participants

Participants: Eligibility criteria included Egyptian female patients with clinical, laboratory, and histopathological evidence of active lupus nephritis (ISN/RPS class III or IV). Patients were maintained on 2 g of MMF at the time of enrolment in the study. **Exclusion criteria** were male sex, pregnancy or lactation, diabetes mellitus, and concomitant autoimmune diseases (e.g., rheumatoid arthritis, scleroderma, or overlap syndromes).

Sample size: The sample size was calculated using the G-power program with α . Error = 0.05 and power 95%, and it was equal to 52 patients distributed in 2 groups according to MMF levels differences in patients with active and inactive lupus nephritis in a previous study by **Łuszczńska et al.** [9].

Methods: Baseline demographic and clinical data, including medical history, renal biopsy findings, and laboratory tests (serum creatinine, complements C3/C4, anti-dsDNA antibody, 24-hour proteinuria, and spot urine protein: creatinine ratio), were recorded at recruitment (time zero). SLE disease activity was assessed using these measures at baseline, 3 months, and 6 months.

Pharmacokinetics

Serial blood samples were collected from each patient to estimate pharmacokinetic parameters, including maximum plasma concentration (C_{max}), minimum plasma concentration (C_{min}), and area under the concentration–time curve (AUC). For MPA pharmacokinetics, blood was collected at 0, 1, 4, 8 hours, centrifuged at $1,210 \times g$ for 10 minutes, and plasma stored at -80°C . Plasma aliquots (50 μL) were mixed with 50 μL hexobarbital solution (40 $\mu\text{g}/\text{mL}$) and 125 μL acetonitrile for protein precipitation, vortexed, and centrifuged at $1,500 \times g$ for 5 minutes. Supernatants (75 μL) were combined with 50 μL of 50 mM potassium dihydrogen phosphate (pH 2.4), and 15 μL were transferred to LC/MS vials. MPA quantification was performed using an Agilent LC/MS system (1290 Infinity II with LC/MSD iQ Mass Selective Detector) equipped with a Poroshell 120 EC-C18 column (150 $\times$ 4.6 mm) and guard column. Chromatographic conditions were optimized for sensitivity and reproducibility, and standard curves were constructed using blank plasma spiked with known MPA concentrations.

Pharmacogenetics: Sample Collection and DNA Extraction: 2 mL of peripheral venous blood was collected from each patient into EDTA-containing tubes. White blood cells were isolated, and genomic DNA was extracted using the GeneJET Whole Blood Genomic DNA Purification Mini Kit (Cat. No. K0781, Thermo Scientific, USA) according to the manufacturer's instructions. DNA quality and concentration were assessed using a NanoDrop spectrophotometer (Thermo Scientific, Waltham, MA) (Table 1), and only samples with an A260/280 ratio within the optimal range were included. DNA integrity was

confirmed by 1% agarose gel electrophoresis (Fig. 1). Extracted DNA was stored at – 20°C until further analysis.

Table 1
Nanodrop results of genomic DNA extracts:

Sample no.	DNA concentration (ng/μl)	A260/280	Sample no.	DNA concentration (ng/μl)	A260/280
1	185	1.89	31	29.2	2.07
2	39.6	1.97	32	60.8	1.96
3	24.0	1.98	33	40.0	1.8
4	96.2	1.86	34	39.0	1.7
5	56.7	1.77	35	105.6	1.6
6	81.6	1.85	36	61.8	1.81
7	120.2	1.8	37	25.1	1.46
8	95.1	1.85	38	56.2	1.8
9	50.6	1.81	39	46.3	1.8
10	85.1	1.77	40	42.8	1.75
11	64.3	1.86	41	42.1	1.8
12	88.7	1.94	42	38.8	1.74
13	109.4	1.74	43	19.2	1.72
14	23.2	1.77	44	146.6	1.84
15	65.3	1.8	45	211.2	1.81
16	79.6	1.64	46	136.1	1.87
17	85.6	1.82	47	35.6	1.8
18	68.5	1.84	48	112.2	1.86
19	83	1.84	49	262.6	1.6
20	30.6	1.79	50	126.7	1.83
21	55	1.84	51	27.5	1.81
22	41.8	1.82	52	40.7	1.8
23	55.6	1.82	53	87.3	1.94
24	166.3	1.86	54	19.8	1.92
25	149.8	1.86	55	55.2	1.94
26	205.8	1.9	56	25	2.04

Sample no.	DNA concentration (ng/μl)	A260/280	Sample no.	DNA concentration (ng/μl)	A260/280
27	118.2	1.91	57	53.5	1.99
28	76.3	1.91	58	23.5	2.13
29	75.1	1.95	59	107.5	1.6
30	132.1	1.82	60	52.5	1.71
			61	107.6	1.91

Genotyping: Genotyping of UGT2B7 (rs7438135) and SLC01B1 (rs183624077) was performed using allele-specific TaqMan real-time polymerase chain reaction (PCR) assays (Thermo Scientific, USA) according to manufacturer protocols. The UGT2B7 assay employed VIC/FAM-labeled probes for the A/G alleles (Assay ID: C__26058102_10; context sequence: CCAAATAACTGTGAGGAAGTGAGTC[A/G]GAGAACAAGCTAACCTAATGATTAA), while the SLC01B1 assay targeted the A/T alleles (Assay ID: C_179227238_10; context sequence: CTCTATTTCTACAGAAGGGTCTACT[A/T]GGGCTTGTCTTCAATGTTAAGAGTC).

PCR reactions (10 μL total volume) contained 10 μL TaqMan master mix, 1 μL working assay, 5 μL genomic DNA, and 4 μL nuclease-free water. Thermal cycling was performed on an Azure Cielo 6 real-time PCR instrument (Azure, USA) under the following conditions: initial denaturation at 95°C for 10 minutes, followed by 50 cycles of 95°C for 15 seconds and 60°C for 60 seconds, with a 60°C hold for 1 second per cycle.

Outcome

The study outcome was to assess the pharmacogenetics and pharmacokinetics of MPA and their relation to response to treatment where No response was defined as failure to achieve either a partial or a complete renal response within 6–12 months of starting therapy while, Complete remission was defined by Proteinuria < 0.5 g/day or UPCR < 0.5 g/g accompanied by stable or improved renal function, reflected by an eGFR within approximately $\pm 10\%$ of baseline, and an inactive urinary sediment without cellular casts. Partial remission was defined as $\geq 50\%$ reduction in proteinuria from baseline, with an absolute proteinuria level < 1 g/day, stable renal function (eGFR within $\pm 10\text{--}20\%$ of baseline), and absence of new active sediment [10].

Statistical analysis

The population pharmacokinetic (PK) analysis was conducted using Monolix version 2020R1 (Lixoft, Antony, France), a nonlinear mixed-effects modelling platform specifically developed for the analysis of pharmacokinetic–pharmacodynamic data. PK parameters, including AUClast (area under the plasma concentration–time curve up to the last measurable concentration) and Cmax (maximum observed

plasma concentration), were evaluated in female patients with lupus nephritis to characterize drug exposure and variability.

All data were tabulated in SPSS sheet version 27. Categorical data were expressed as numbers and percentages. Normally distributed data were tested for normality of distribution using Shapiro wilk test. Normally distributed data were expressed as mean $\pm$ standard deviation. Non-parametric data were expressed as median and interquartile range. Fisher exact test was used for comparison of categorical data between 2 groups if number of events was less than 5 in any of the comparative groups. Man-Whitney U was used for the comparison of nonparametric data between 2 groups. The spearman correlation test was used for the assessment of the correlation between 2 variables of continuous variables. Binary logistic regression analysis was used to assess the predictors of response to treatment. Hardy Weinberg test was used to assess the allelic frequency equilibrium among the included patients. Receiver operator characteristics test was used to assess the accuracy of AUC and C-max in prediction of response to treatment.

Results and Discussion

Results

Descriptive analysis of lupus nephritis patients:

The cohort was predominantly female, with a mean age at diagnosis of 29.5 ± 8.95 years and a current mean age of 37.4 ± 10.3 years. More than half of the patients were married (58.5%). Obstetric history revealed low mean gravidity and parity, with a relatively low prevalence of previous abortion (12.0%). Hypertension was highly prevalent, affecting nearly all patients (96.2%), while diabetes mellitus was present in approximately one quarter of the cohort (24.5%). Thrombotic manifestations were observed in a notable proportion of patients, including deep venous thrombosis in 20.8%, whereas lupus cerebritis was infrequent (3.8%). Autoimmune thyroiditis was identified in a minority of cases (7.5%). Laboratory assessment demonstrated high immunological activity, with universal positivity for anti-double-stranded DNA antibodies and reduced complement levels in the majority of patients (low C3 in 86.8% and low C4 in 64.2%). Hepatitis C virus seropositivity was detected in 11.3% of patients. Histopathological evaluation revealed a predominance of proliferative lupus nephritis, with class IV accounting for 75.5% of initial biopsies, followed by class III in 24.5%. The mean activity index was 8.98 ± 4.15 , while the chronicity index averaged 2.19 ± 1.09 , indicating moderate inflammatory activity with relatively limited chronic damage. A second renal biopsy was performed in 11.3% of patients, primarily due to acute kidney injury or increased proteinuria. Among these, class IV remained the most frequent finding (50%). Regarding treatment, nearly half of the patients received pulse steroid therapy (47.2%). Mycophenolate mofetil was the predominant induction agent (84.9%), while cyclophosphamide was used in a smaller proportion (15.1%). All patients were initially maintained on steroid plus mycophenolate mofetil therapy, with most continuing this regimen during follow-up. A minority required alternative maintenance combinations (Cyclosporin: 9 patients "17%"; Tacrolimus: 1 patient "1.9%"). Plasma exchange was

infrequently utilized (3.8%). Overall, 31 patients (58.5%) achieved a therapeutic response, whereas 22 patients (41.5%) were classified as non-responders. Mycophenolate mofetil-related adverse events were reported in 15.1% of the cohort. The most frequent complication was recurrent infections, occurring in 9.4% of patients, followed by bone marrow suppression in 7.6%. Gastrointestinal intolerance attributable to mycophenolate mofetil was infrequent, being observed in only one patient (1.9%) (Supplementary table 1S).

Relationship between pharmacokinetics and LN patients' response to treatment:

Considerable interindividual variability in MPA exposure was observed. The mean AUC_{0-8} was $22.4 \pm 12.9 \mu\text{g}\cdot\text{h/mL}$, with a wide range of values (1.66–69.3 $\mu\text{g}\cdot\text{h/mL}$), reflecting marked heterogeneity in systemic drug exposure. Similarly, peak plasma concentrations demonstrated substantial variability, with a mean C_{max} of $12.9 \pm 5.52 \mu\text{g/mL}$ and values ranging from 1.01 to 21.6 $\mu\text{g/mL}$. Significant positive correlation was found between C_{max} and MPA AUC_{0-8} among lupus nephritis patients ($r: 0.747$; $p < 0.001$) (Fig. 2).

Median value of MPA AUC of 31 patients showed response to MMF was 23.1, which was significantly higher than 22 $\mu\text{g}\cdot\text{h/mL}$ in non-responder patients (median AUC of 16.2 $\mu\text{g}\cdot\text{h/mL}$) ($p = 0.039$) (Fig. 3). MPA C_{max} did not show significant differences between responders and non-responders (Fig. 4). At a cut-off value of 14.18 $\mu\text{g}\cdot\text{h/mL}$, MPA AUC_{0-8} had 80.65% sensitivity, 45.45% specificity with 62.5%, positive predictive value, 67.57% negative predictive value, and an AUC of 0.63 in the prediction of LN patients' response to MMF. At the cut-off value of 5.51 $\mu\text{g/mL}$, c_{max} had 74.19% sensitivity, 36.36% specificity, 50% negative predictive value, 62.16% positive predictive value, and AUC of 0.562 in the prediction of LN patients' response to MMF (Fig. 5).

Relationship between pharmacogenomics, pharmacokinetics and LN patients' response to treatment:

For UGT2B7, the heterozygous AG genotype predominated (96.1%), while the AA and GG homozygotes were rare (1.96% each), yielding a significant deviation from equilibrium ($p < 0.001$). No results were obtained for UGT2B7 in 2 patients. Similarly, for SLC01B1, the AT genotype was most frequent (81.6%), the TT genotype was less common (18.4%), and the AA genotype was absent, also resulting in significant deviation from HWE ($p < 0.001$). No results were obtained for SLC01B1 gene in 15 patients. These findings reflect marked skewing in genotype distributions, which may be attributed to the lupus nephritis-specific allele frequencies (Table 2). For UGT2B7, the AG genotype was the most frequent in both non-responders (95.2%) and responders (96.7%), while the AA and GG genotypes were rare. Similarly, for SLC01B1, the AT genotype predominated in non-responders (75%) and responders (86.4%), with TT observed less frequently, and AA absent with no statistically significant differences between responders and non-responders (Table 3). cross the total cohort, patients with the TT genotype had a

lower median MPA AUC_{0-8} (14.0 $\mu\text{g}\cdot\text{h}/\text{mL}$; range 1.66–44.2) compared with those carrying the AT genotype (24.2 $\mu\text{g}\cdot\text{h}/\text{mL}$; range 10.4–69.3), although this difference was not statistically significant ($p = 0.214$). Among responders, median AUC_{0-8} was 34.6 $\mu\text{g}\cdot\text{h}/\text{mL}$ (TT) versus 25.5 $\mu\text{g}\cdot\text{h}/\text{mL}$ (AT), with no significant difference ($p = 0.94$). Among non-responders, median AUC_{0-8} was 13.9 $\mu\text{g}\cdot\text{h}/\text{mL}$ (TT) versus 21.8 $\mu\text{g}\cdot\text{h}/\text{mL}$ (AT) ($p = 0.17$). Comparison between responders and non-responders revealed a significant difference for patients with the TT genotype (**$p = 0.005$**), whereas no significant difference was observed for the AT genotype ($p = 0.224$) (Table 4).

Table 2

Hardy-Weinberg equilibrium of the *UGT2B7* and *SLC01B1* among 51 of the included lupus nephritis patients:

Genotype	Observed count	Observed proportion	Expected count (HWE)	Expected proportion	p value
UGT2B7					
AA	1	1.96%	13	25%	< 0.001
AG	49	96.1%	25	50%	
GG	1	1.96%	13	25%	
Total	51	100%	51	100%	
SLC01B1					
AA	0	0%	7	16.7%	< 0.001
AT	31	81.6%	18	48.3%	
TT	7	18.4%	13	35.0%	
Total	38	100%	38	100%	
HWE: Hardy Weinberg equilibrium; Test of association; Goodness of Fit; UDP-glucuronosyltransferases 2B7; SLC01B1: Solute Carrier Organic Anion Transporter Family Member 1B					

Table 3
Association between genotypes and response of lupus nephritis patients to MMF:

Non- responders (n = 22) n (%)		Responders (n = 31) n, (%)	p value ^{HWE}
UGT2B7			
AA	1 (4.8%)	0 (0%)	0.345
AG	20 (95.2%)	29 (96.7%)	
GG	0 (0%)	1 (3.3%)	
SLC01B1			
AT	12 (75%)	19 (86.4%)	0.372
TT	4 (25%)	3 (13.6%)	
Fisher exact test; UDP-glucuronosyltransferases 2B7; SLC01B1: Solute Carrier Organic Anion Transporter Family Member 1B; HWE Hardy Weinberg equilibrium			

Table 4
Effect of *SLC01B1* on MPA AUC₀₋₈ among lupus nephritis patients:

Among total patients	TT Median (min, max)	AT Median (min, max)	p value
	14 (1.66, 44.2)	24.2 (10.4, 69.3)	0.214
Among responders	34.6 (1.66, 44.2)	25.5 (11, 69.3)	0.94
Among non- responders	13.9 (11.5, 17.9)	21.8 (10.4, 47)	0.17
P value between responders and non-responders	0.005	0.224	
Man Whitney U test; UGT2B7: SLC01B1: Solute Carrier Organic Anion Transporter Family Member 1B			

Multivariate analysis of the predictors of response of lupus nephritis patients to MMF:

Biopsy class (III vs IV) and type of induction therapy (MMF vs cyclophosphamide) were significantly associated with treatment response, with patients having class III biopsy demonstrating higher odds of response (OR = 54.98, 95% CI: 1.46–206.68, **p = 0.030**), and those receiving MMF induction showing greater likelihood of response compared with cyclophosphamide (OR = 42.82, 95% CI: 1.26–1461.0, **p =**

0.037). MPA exposure, measured by AUC_{0-8} , was also a significant predictor, with higher AUC_{0-8} associated with increased odds of response (OR = 1.05, 95% CI: 1.97–2.14, **p = 0.023**) (Table 5).

Table 5

Multivariate analysis of the predictors of response of lupus nephritis patients to MMF maintenance therapy:

S. creatinine	Lower 95% CI	Upper 95% CI	Estimate	Odds ratio	p value
	0.73	15.18	1.2018	3.33	0.121
Proteinuria	0.95	1.87	0.2844	1.33	0.101
Biopsy class (III vs IV)	1.46	206.68	4.007	54.98	0.030
Activity index	0.78	1.19	-0.0400	0.96	0.710
Chronicity index	0.34	1.72	-0.2710	0.76	0.514
Type of induction (MMF vs cyclophosphamide)	1.26	1461.0	3.7571	42.82	0.037
AUC_{0-8}	1.97	2.14	0.0516	1.05	0.023
SLCO1B1 (AT vs TT)	0.09	15.88	0.1771	1.19	0.893
Binary logistic regression; Solute Carrier Organic Anion Transporter Family Member 1B.					

Discussion:

This prospective study aimed to explore the relationship between MMF pharmacokinetics, pharmacogenetics, and therapeutic outcomes in Egyptian female patients with active LN. Our findings revealed marked interindividual variability in MPA exposure, with a mean AUC_{0-8} of 22.4 ± 12.9 $\mu\text{g}\cdot\text{h}/\text{mL}$ and a mean C_{max} of 12.9 ± 5.5 $\mu\text{g}/\text{mL}$ on a standard 2 g daily dose. Multivariate analysis showed that higher MPA AUC_{0-8} , an initial biopsy class III (vs. class IV), and induction therapy with MMF were independent predictors of a positive therapeutic response at 6 months. Although TT carriers had lower MMF AUC_{0-8} , genetic polymorphisms in the SLCO1B1 and UGT2B7 genes did not differ significantly between clinical responders and non-responders in this study.

Our observation that clinical responders to MMF had a significantly higher median MPA AUC_{0-8} (23.1 $\mu\text{g}\cdot\text{h}/\text{mL}$) than non-responders (16.2 $\mu\text{g}\cdot\text{h}/\text{mL}$) underscore the potential value of therapeutic drug monitoring in LN. This variability in MPA exposure aligns with the known challenges of fixed-dose regimens, where factors such as enterohepatic recirculation and transporter-mediated uptake contribute to inconsistent systemic levels [4, 11]. Although TDM of MPA is widely practiced in many organ

transplantation centers to prevent allograft rejection, its routine use in LN has not been clearly defined. However, recent literature closely aligns with our findings. A thorough meta-analysis by Wuttiputhanun and his study group, which evaluated 16 studies comprising 433 LN patients, found that patients who achieved a clinical response had significantly higher MPA AUC than non-responders, with a weighted mean difference of 16.83 mg·h/L ($p < 0.001$). Moreover, the meta-analysis identified a significant link between MPA trough concentrations (C0) and clinical response, with responders exhibiting a mean C0 of 2.50 mg/L, compared to 1.51 mg/L in non-responders [6].

Furthermore, Kiyokawa and his colleagues illustrated that maintaining high plasma MPA concentrations during the early induction phase can predict better long-term renal outcomes in patients with class III or IV LN [12]. Additionally, a Japanese study found that MPA concentrations during the induction phase can be reduced by various clinical factors, including high steroid doses, hypoalbuminemia, and decreased creatinine clearance [13]. These interactions make fixed-dose MMF often insufficient. Consequently, our data do not support a fixed 2 g/day dose, as it can lead to underexposure in a subset of patients; however, individualized dosing could enhance remission rates.

Additionally, our multivariate analysis showed that patients presenting with an initial biopsy of class III LN had higher odds of therapeutic response than those with class IV LN. This finding is highly consistent with a prospective cohort study involving 75 Korean patients with LN, which similarly identified class III LN as a strong predictor of complete renal response at 6 months, with an odds ratio of 1.48 [14].

The pharmacogenetic aspect of our study investigated whether specific polymorphisms in the SLC01B1 and UGT2B7 genes, which encode key transporters and metabolizing enzymes for MPA, could predict clinical response. Although we observed that TT carriers had a lower MPA AUC₀₋₈, the overall genotype distribution did not differ significantly between responders and non-responders. This observation contrasts with findings in some other populations, particularly Asians, where MPA-related genetic variants have demonstrated pronounced clinical consequences. In a study by Shu et al. involving 120 Chinese patients with autoimmune diseases, the SLC01B1 521T > C polymorphism was significantly correlated with dose-adjusted MPA trough concentrations and a higher incidence of anemia [15]. The difference between these findings and ours could be attributed to ethnic variations in allele frequencies. Moreover, our sample of 53 patients may lack the statistical power to detect subtle, multifactorial pharmacogenetic influences on overall clinical outcomes.

Safety considerations in our cohort revealed MMF-related adverse events in 15.1% of patients, predominantly recurrent infections (9.4%), bone marrow suppression (7.6%), and gastrointestinal intolerance (1.9%). This profile is consistent with Egyptian LN studies, in which MMF induction showed comparable efficacy to cyclophosphamide but fewer severe adverse effects [16]. The high comorbidity burden in our patients may amplify risks, as evidenced by universal anti-dsDNA positivity and frequent hypocomplementemia, aligning with global data showing that MMF increases diarrhea but reduces leukopenia compared to cyclophosphamide [17]. These findings advocate for routine monitoring of hematologic and infectious complications in similar populations.

Our study has some limitations. First, the sample size was relatively small ($n = 53$) and was constricted to Egyptian female patients, which may limit the generalizability of our results to males or other populations worldwide. Second, the 6-month follow-up period is adequate to evaluate early remission but precludes the study of long-term outcomes, such as lupus flares or kidney disease progression. Finally, we analyzed only a limited set of SNPs; investigating a wider range of genetic variants within the UGT, SLCO, and IMPDH gene families could provide a more comprehensive understanding of the pharmacogenomic landscape in this population.

In conclusion, our prospective study emphasizes the importance of MPA pharmacokinetics, baseline histological classification, and the choice of induction therapy in shaping clinical outcomes in lupus nephritis. The strong association between higher MPA AUC and better therapeutic responses supports consideration of therapeutic drug monitoring as part of standard LN management, moving away from uniform dosing strategies. Although the investigated UGT2B7 and SLCO1B1 polymorphisms did not significantly predict clinical response in our study, further large-scale, multiethnic, and multicenter studies are warranted to fully understand the role of pharmacogenetics in tailoring immunosuppressive treatment for lupus nephritis.

Declarations

Conflict of interest: All authors declared no conflict of interest.

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Authorship contribution: **Ahmed Yahia Elmowafy:** Conceptualization of the study, study design, patient recruitment, clinical data collection, interpretation of results, and manuscript drafting. **Salwa Elwasif:** Patient recruitment, clinical assessments, follow-up, and contribution to data analysis and manuscript revision. **Rasha Samir Shemies:** Laboratory investigations, renal biopsy interpretation, and contribution to data acquisition. **Ahmed Mansour Abdel-Rahman:** Clinical data collection and manuscript drafting. **Mahmoud M. Zakaria:** Biochemical assays, quality control of laboratory data, and interpretation of pharmacokinetic results. **Sameha Ashraf:** Statistical analysis, population pharmacokinetic modelling, and data visualization. **Randa El-Gamal:** Molecular biology support, genomic DNA extraction, SNP genotyping, and methodological validation. **Nehal Mohamed Ramadan:** Pharmacogenetic analysis, LC/MS assay oversight, and interpretation of pharmacokinetic–pharmacogenetic correlations. **Hala Abdel Malek:** Study supervision, project administration, critical revision of the manuscript for intellectual content, and final approval of the submitted version. All authors have read and approved the final manuscript and agree to be accountable for all aspects of the work, ensuring accuracy and integrity.

Data availability statement: All data are available via the corresponding author upon reasonable request.

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Figures

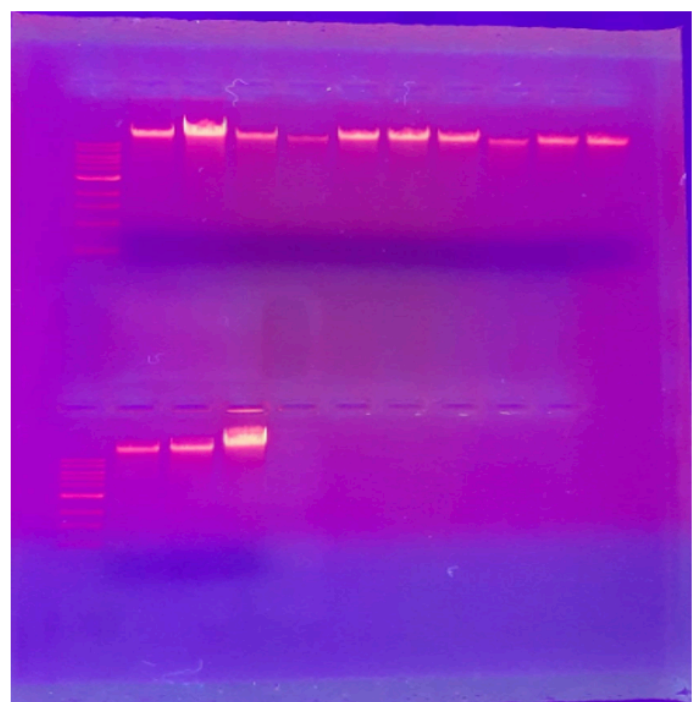
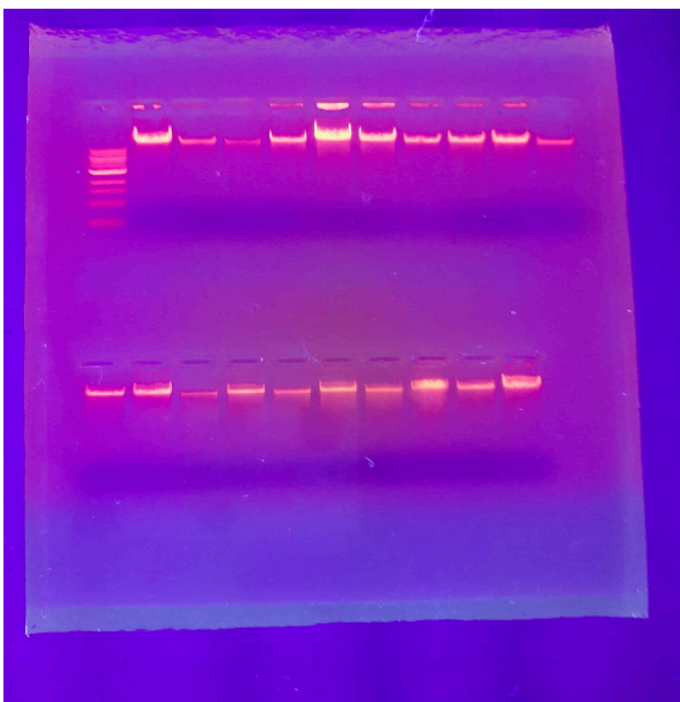


Figure 1

Genomic DNA on a 1% agarose gel.

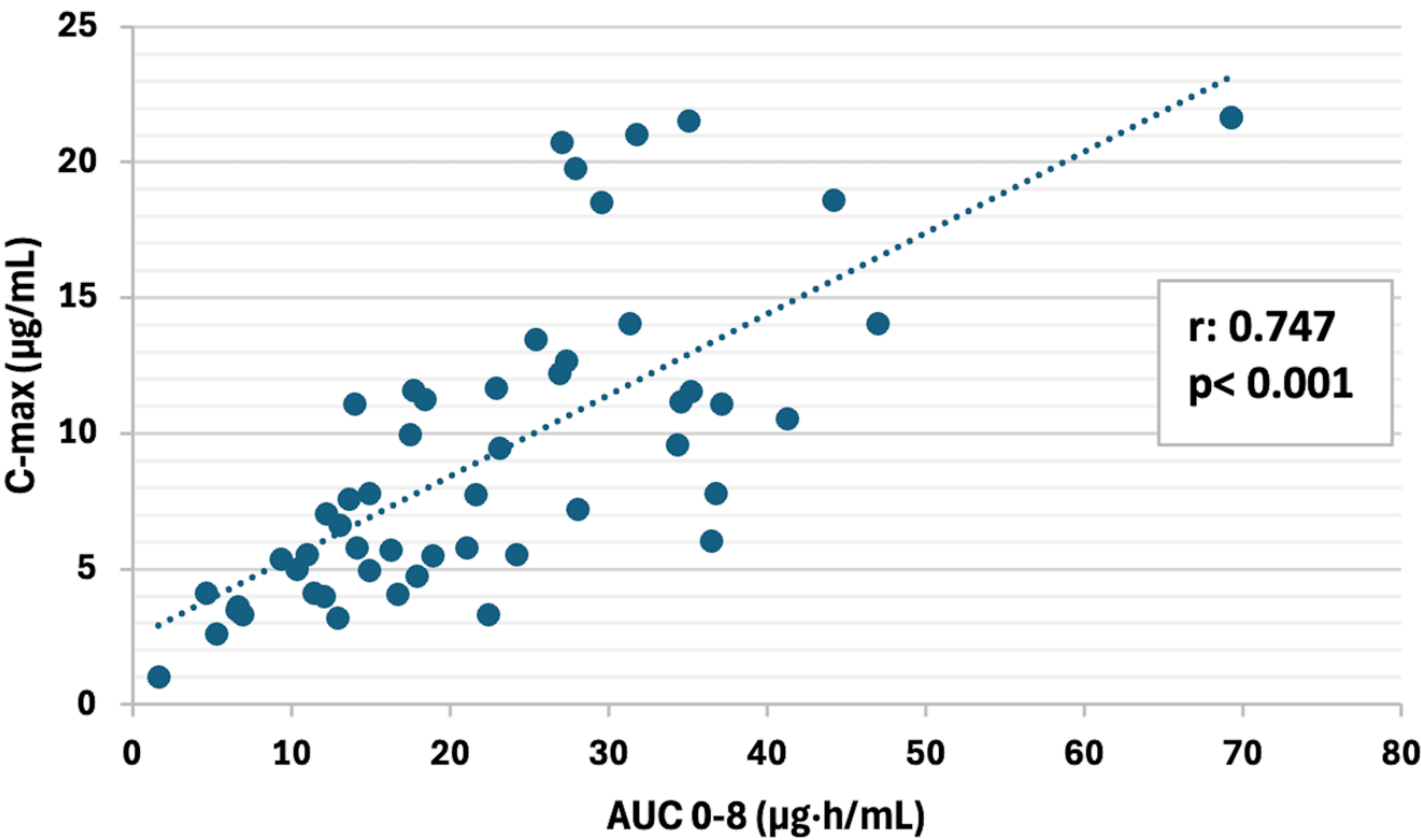


Figure 2

Significant positive correlation between MPA AUC₀₋₈ and C-max among lupus nephritis patients; Statistical test: Spearman correlation (r) Correlation coefficient. Among lupus nephritis patients, MPA AUC₀₋₈ correlated significantly and positively to MPA C-max among lupus nephritis patients (*r*: 0.747; *p* < 0.001).

MPA AUC 0-8 ($\mu\text{g}\cdot\text{h}/\text{mL}$)

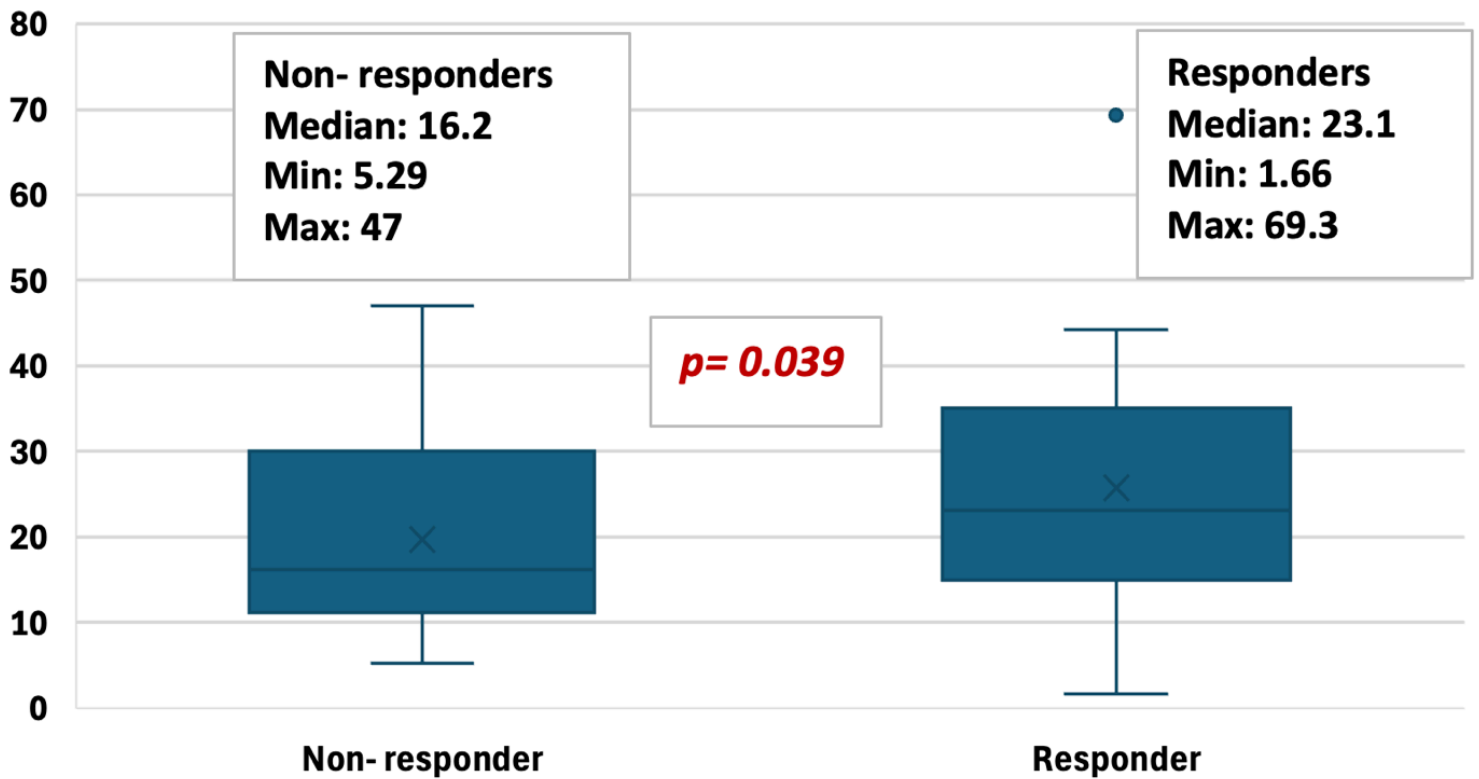


Figure 3

MPA Area under curve differences between non- responders and responders; MPA: Mycophenolic acid; AUC: Area under curve; Statistical test: Man Whitney test. The figure illustrated presence of significant differences in MPA AUC between LN patients who showed response to MMF and who did not achieve response to MMF with higher median value of AUC among responders of 23.1 $\mu\text{g}\cdot\text{h}/\text{mL}$ than non-responders of 16.2 $\mu\text{g}\cdot\text{h}/\text{mL}$; $p= 0.039$.

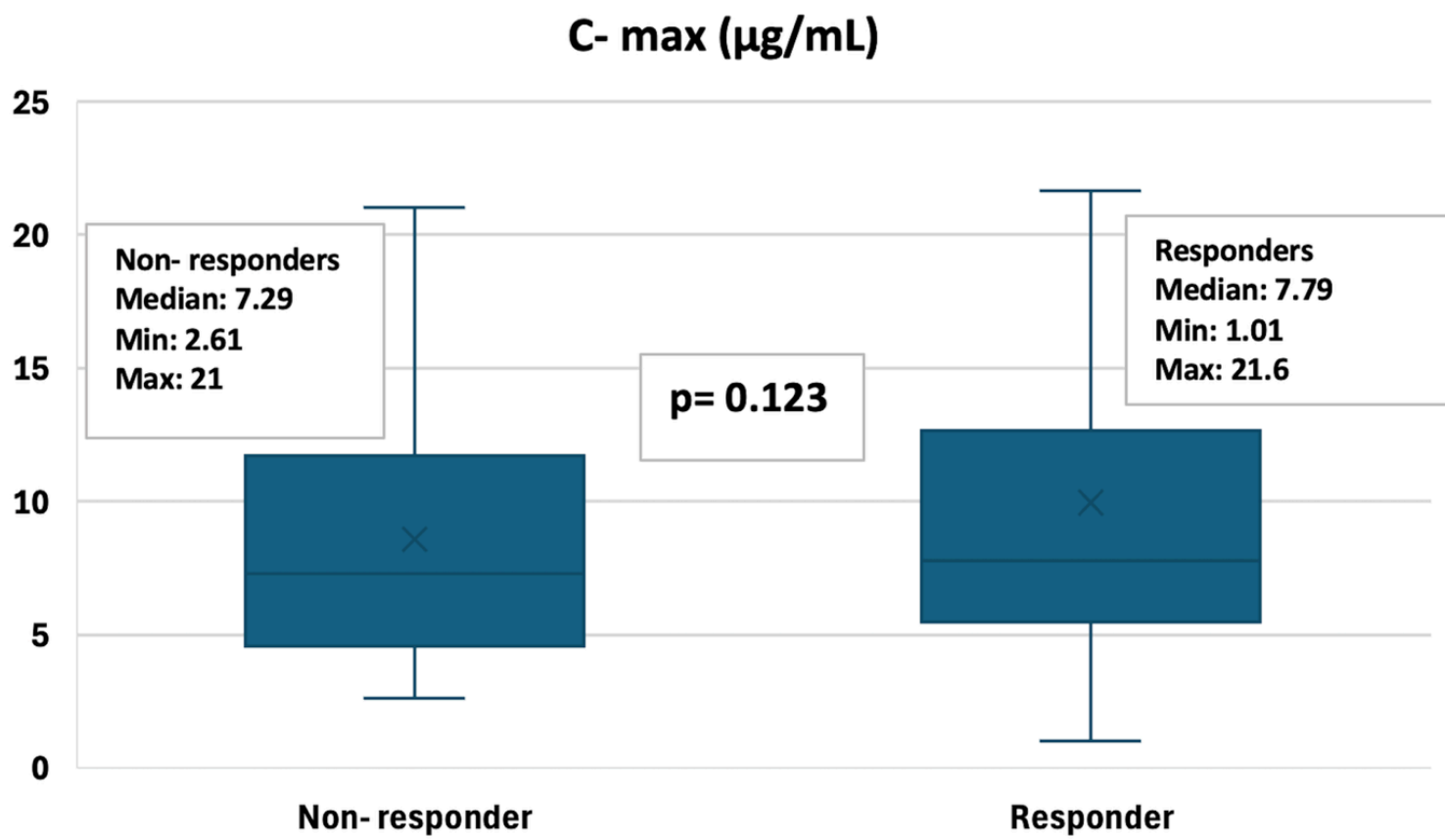


Figure 4

C- Max differences between non- responders and responders; MPA: Mycophenolic acid; Statistical test: Man Whitney test. The figure illustrated absence of significant differences in MPA C- max between LN patients who showed response to MMF and who did not achieve response to MMF; $p = 0.123$.

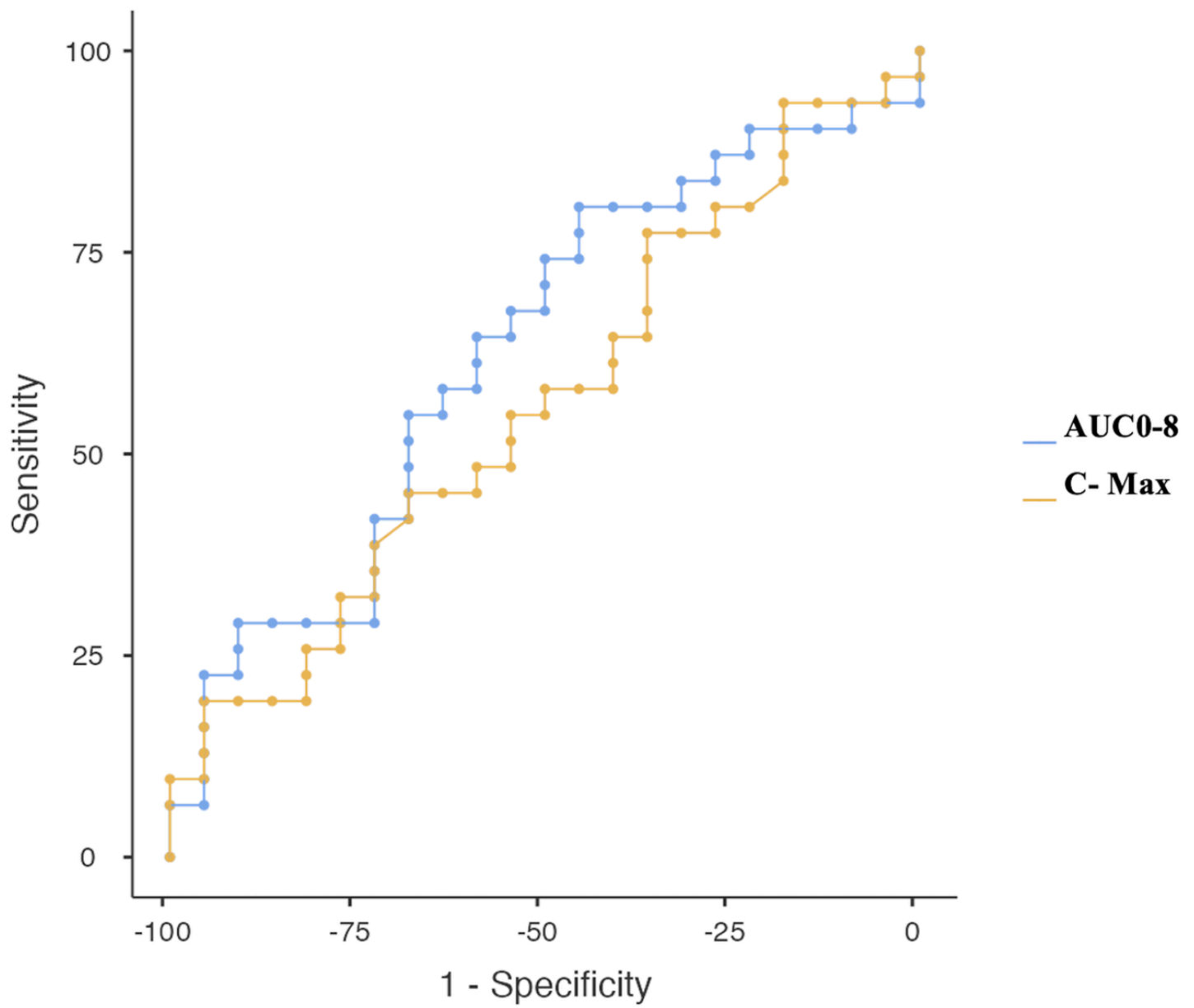


Figure 5

Receiver operator characteristics curve illustrating the predictive accuracy of MPA AUC₀₋₈ and MPA C-max in prediction of response to MMF among LN patients. An AUC₀₋₈ cut-off value of 14.18 µg·h/mL yielded a sensitivity of 80.65% and a specificity of 45.45%, with a positive predictive value of 62.5% and a negative predictive value of 67.57% (area under the curve = 0.63). A Cmax cut-off value of 5.51 µg/mL showed a sensitivity of 74.19% and a specificity of 36.36%, with a positive predictive value of 62.16% and a negative predictive value of 50% (area under the curve = 0.562).