

Pharmacokinetic optimization of valganciclovir and ganciclovir therapy in lung transplant recipients

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Introduction/objectives: Intravenous ganciclovir (GCV) and its oral prodrug valganciclovir (VGCV) are gold standard treatments for both prevention and treatment of cytomegalovirus (CMV) infections (1). Our understanding of the pharmacokinetics (PK) of GCV/VGCV in lung transplant recipients remains limited (1-3). The primary goal of this study was to evaluate the PK of GCV/VGCV in a large cohort of lung transplant recipients. The secondary goal was to determine the probability of target attainment (PTA) for dosing protocols to achieve PK/PD targets for CMV prophylaxis and therapy.

Methods: A population PK analysis was carried out using NONMEM version 7.4.0. In total, 379 GCV concentrations (194 and 185 concentrations sampled after VGCV and GCV administration, respectively) were obtained from 110 patients and were included in the analysis. eGFR and cotreatment with antimycotics were tested as covariates for CL, body weight was assessed as a covariate for clearance (CL) and central volume of distribution (V_1), while sex and cystic fibrosis diagnosis were tested as covariates for CL, V_1 and bioavailability (F). For internal validation of the final model, bootstrap with 1000 resampled datasets and Normalized Prediction Distribution Error (NPDE) based on 1000 simulations were used. For Monte Carlo simulations (MCS), 1000 replicates of each patient from the original dataset were generated in Simulx Version 2024R1. Standard dosing regimens, in accordance with published GCV and VGCV dosing protocols (1), were simulated based on the final GCV/VGCV pop PK model, to obtain AUC_{24h} at steady state for patients with different functional renal statuses. Probability of target attainment (PTA) was then calculated for $AUC_{24h} > 50$ mg·h/L and AUC_{24h} between 80 and 120 mg·h/L.

Results: Observed GCV plasma concentrations were best described by a two-compartment model with log-normally distributed interindividual variability (IIV) on CL, and V_1 (Table 1, Figure 1). For F, a logit transformation was applied and a normal distribution for IIV was incorporated in the logit domain. eGFR was found to be the only significant covariate for clearance of ganciclovir/valganciclovir. For every 1 mL/min/1.73 m² decrease in eGFR, there was a 0.06 L/h decrease in GCV/VGCV CL. eGFR was 85.2 (16.8 – 153), median (min-max), mL/min/1.73 m² in this cohort of patients. Differences in PTA across groups highlight that recommended dosing may not be adequate for all patient populations (Figures 2-5). Due to the significant variability in GCV/VGCV PK, the recommended dosing regimens may not ensure optimal treatment for all lung-transplant recipients. A significant number of patients may be underexposed, potentially reducing clinical efficacy, or overexposed, which can increase the risk of toxic effects. Therefore, therapeutic drug monitoring (TDM) should still be considered to ensure safe and effective individual exposure. To improve TMD, the developed model can be integrated into TDM software to support monitoring of GCV/VGCV exposure in lung transplant patients.

Conclusions: Standard prophylactic and therapeutic GCV/VGCV dosing regimen leads to underexposure in patients with low eGFR, but may be appropriate for patients with higher eGFR values. However, substantial variability in GCV/VGCV exposure makes it challenging to achieve efficacy targets in individuals. For this reason, TDM should be considered. Our model can be integrated into TDM software and, alongside a TDM sample, be used for dosing guidance.

Parameter [units]	Final model (RSE %)	Bootstrap (median (95% CI))
Fixed effects		
V_1 [L]	43.1 (19%)	42.5 (10.9-57.8)
$CL [L/h] = CL_p + 0eGFR * (eGFR/85.2)$		
CLp	2.05 (31%)	2.017 (0.760 -3.882)
$\theta eGFR$	4.96 (16%)	4.93 (2.70 – 6.78)
V_2 [L]	140 (37%)	118 (12 – 960)
k_a [1/h]	0.334 (27%)	0.337 (0.202 – 0.502)
Q [L/h]	2.1 (20%)	2.11 (0.77 – 4.17)
Tlag [h]	0.563 (34%)	0.615 (0.105 – 0.881)
θF	0.304 (48%)	0.334 (-0.438 – 1.111)
F*	0.575 (derived)	0.58 (0.39 – 0.75)
Inter-individual variability (variance)		
CL	0.165 (23%)	0.152 (0.076 – 0.233)
V_1	0.431 (48%)	0.391 (0.103 – 2.301)
F	2.63 (39%)	2.53 (0.70 – 4.85)
Residual unexplained variability (variance)		
Proportional error	0.236 (11%)	0.229 (0.172 – 0.297)

Table 1. Estimated parameters of the final model
Abbreviations: RSE = relative standard error of the estimate; CI = confidence interval, V_1 = volume of distribution of central compartment; CL = clearance; CLp = population value of clearance; eGFR = estimated glomerular filtration rate in mL/min/1.73m² according to CKD-EPI equation, $\theta eGFR$ = increase in CL per mL/min/1.73m² eGFR; V_2 = volume of distribution of the peripheral compartment; k_a = constant of absorption rate; Q = intercompartmental clearance; Tlag = lag time; F = bioavailability
*derived from $F = e^{\theta F} / (1 + e^{\theta F})$

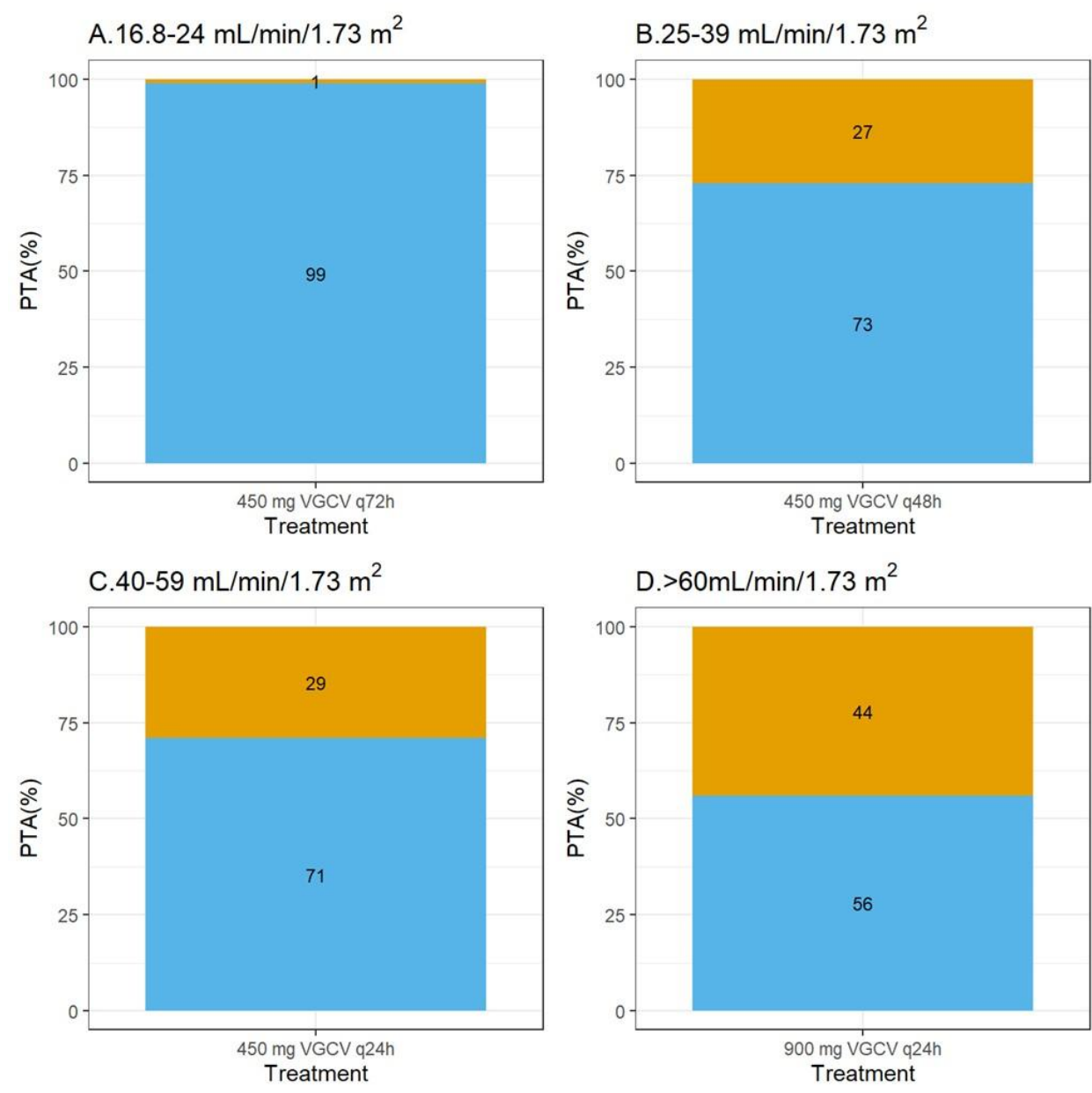


Figure 2. PTA for recommended VGCV standard dosing for CMV prophylaxis ($AUC > 50$ mg·h/L) in patients with various degrees of kidney function.

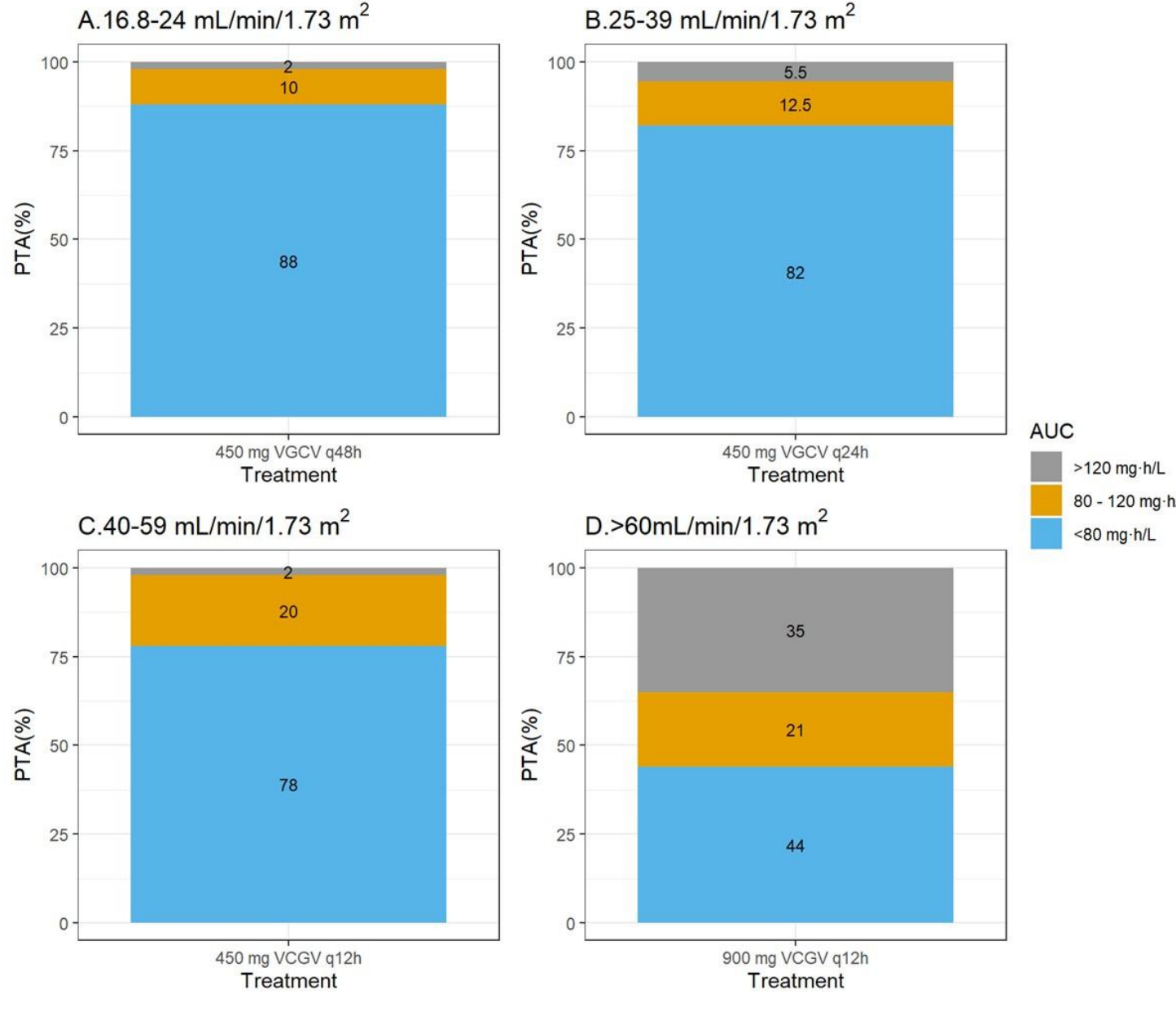


Figure 3. PTA for recommended VGCV standard dosing for CMV therapy ($AUC = 80-120$ mg·h/L) in patients with various degrees of kidney function

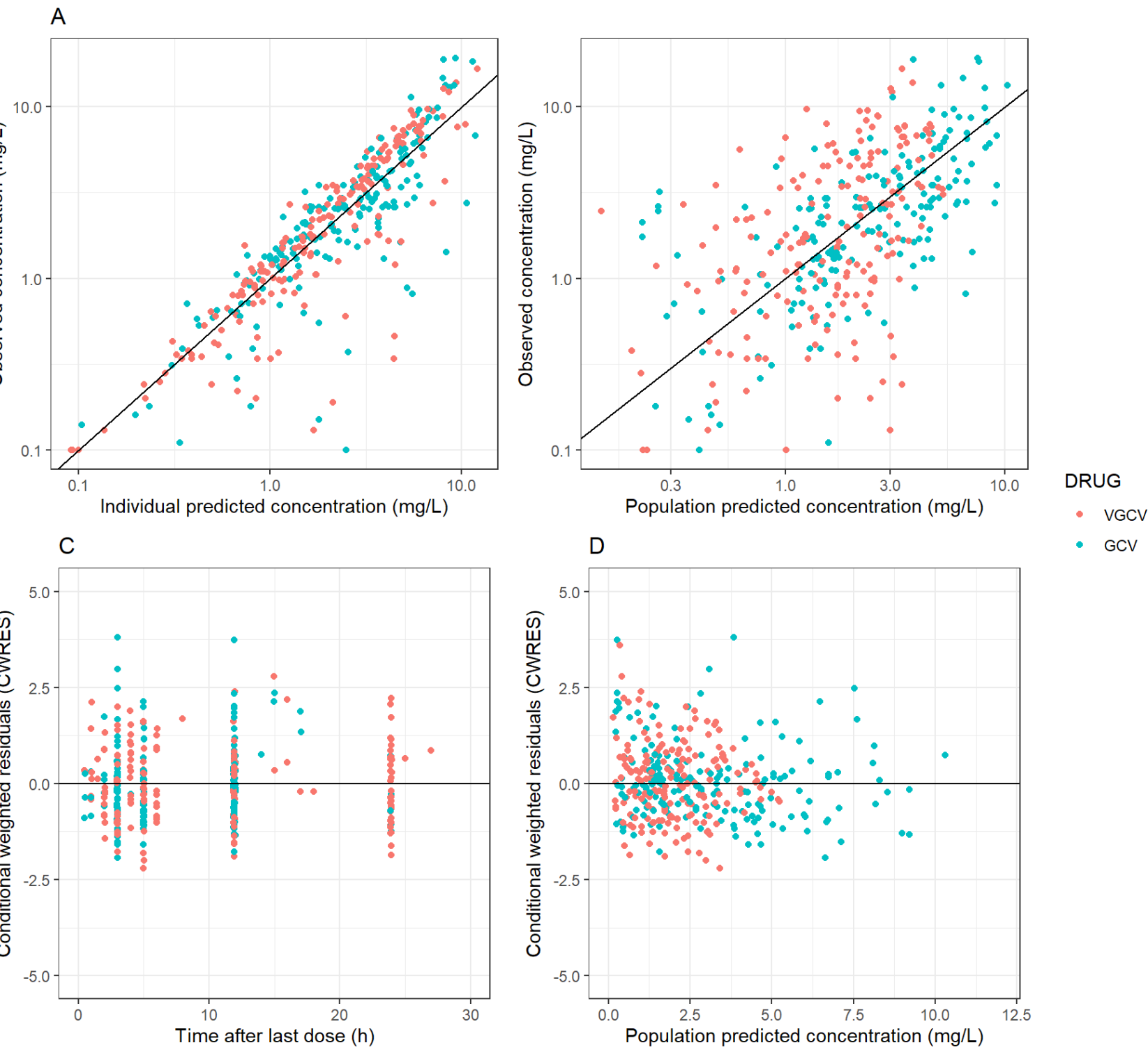


Figure 1. Basic goodness of fit plots of ganciclovir (GCV)/valganciclovir (VGCV) in patients with lung transplants. A. Population predicted GCV/VGCV concentration vs. observed GCV/VGCV concentration. B. Individual predicted GCV/VGCV concentration vs. observed GCV/VGCV concentration. C. conditional weighted residuals (CWRES) vs. time after dose. D. Conditional weighted residuals (CWRES) vs. population predicted concentrations.

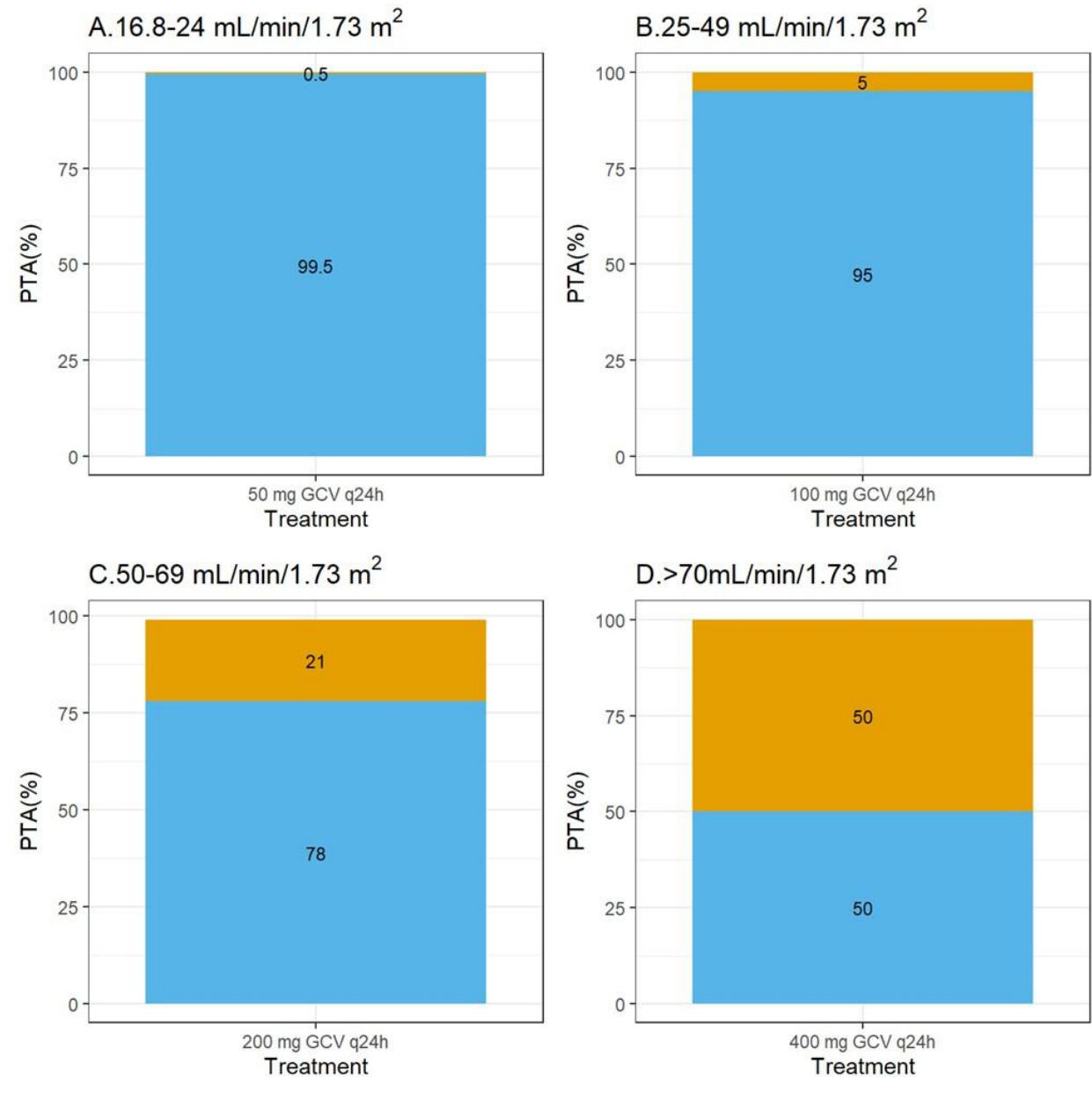


Figure 4. PTA for recommended GCV standard dosing for CMV prophylaxis ($AUC > 50$ mg·h/L) in patients with various degrees of kidney function

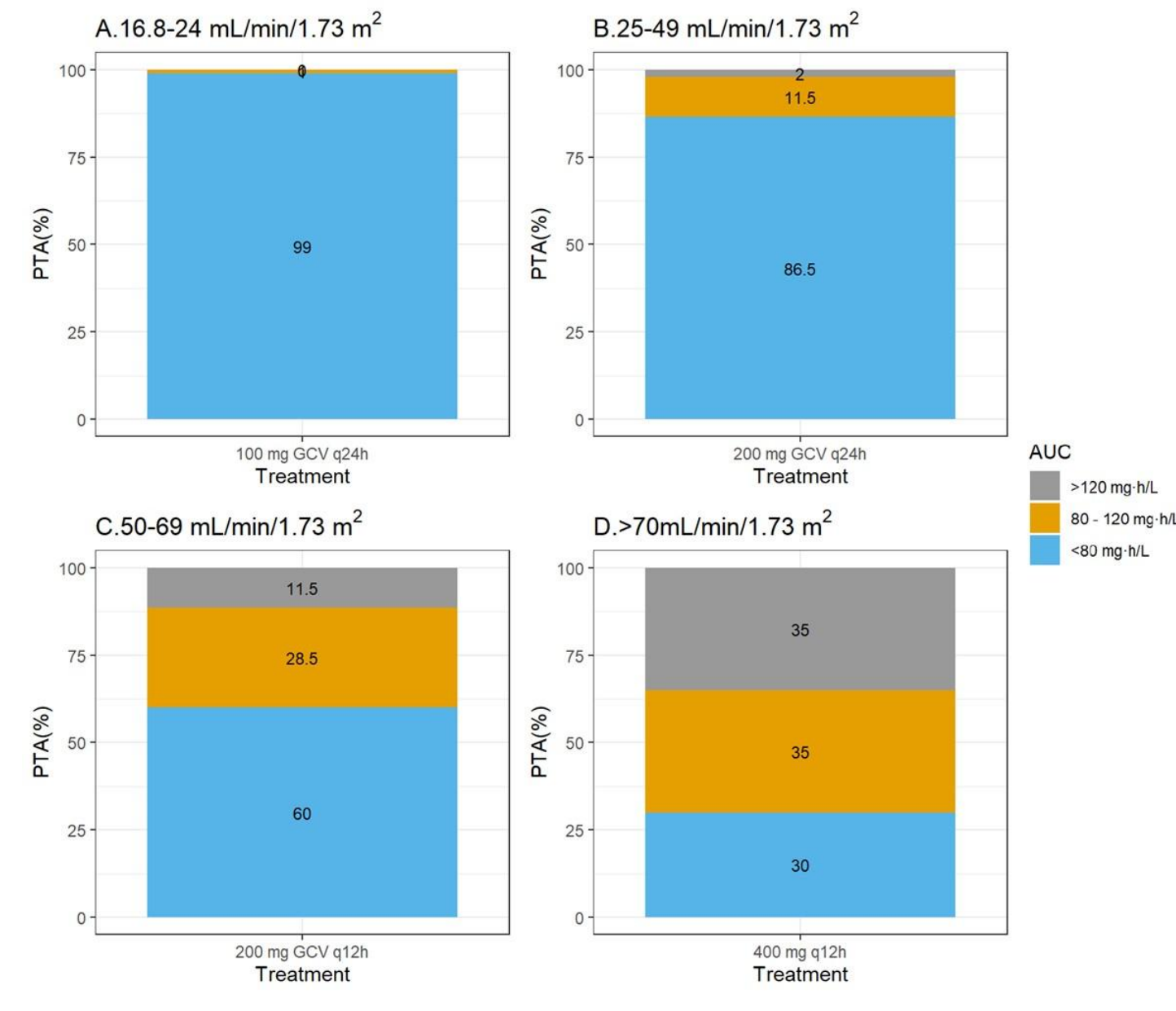


Figure 5. PTA for recommended GCV standard dosing for CMV therapy ($AUC = 80-120$ mg·h/L) in patients with various degrees of kidney function

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3. Kiser TH, Fish DN, Zamora MR. J Heart Lung Transplant. 2012;31(2): 159–166.