Modeling Age-related Changes in Kidney Function Using Aminoglycoside Clearance as a Surrogate: Can Body Composition Help?

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Introduction

- Drug dose modification for aging often relies on estimates of kidney function.
- Current kidney function equations estimate different rates of age-related decline in kidney function but it is not clear how best to model this trajectory.
- Body size is used to estimate kidney function but we presently do not incorporate body composition, which also changes with age.
- We hypothesized radiomic-based models of aging as covariates of kidney function.

Methods

- The study population retrospectively reviewed patients who were treated with tobramycin or gentamicin.
- Patients with at least 3 measured drug concentrations and available CT imaging were included.
- A population pharmacokinetic (Pop-PK) model for aminoglycoside was constructed to compute the volume (V) and clearance (Cl) estimates with Monolix V2024R1.
- Various combinations of CT-based biomarkers were developed as a BA_{Mor} index and tested against amino-glycoside Cl to improve kidney function.

BA_{Mor_1}	$(Psoasexpmuscarea * BMD)/Fasciaarea$
BA_{Mor_2}	$Psoasexpmuscarea * PsoasexpmuscHU * Vbslabheight$
BA_{Mor_3}	$(Dmgexpmuscarea * BMD)/Visceralfatarea$

Results

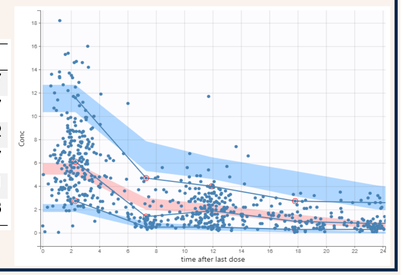
- The final sample included 156 unique patients, 89 (58%) of which had tobramycin administered (n=89).
- The median (minimum, maximum) age, height, and weight of patients were 58 (21, 93) years, 170 (147, 203) cm, and 80 (43.8, 139.3) Kg.
- The PK of aminoglycosides was best described using a one-compartment structure with an additive and proportional error model.
- Estimated PK parameters: 45.89 L for V and 2.62 L/h for Cl.

Model number	19.1 BA_{Mor_1}-based		25.1 BA_{Mor_2}-based		29.2 BA_{Mor_3}-based		6.1 CA-based	
	Value (SE)	RSE%	Value (SE)	RSE%	Value (SE)	RSE%	Value (SE)	RSE%
Fixed effects								
V_pop	49.09 (3.27)	6.66	45.87 (3.39)	7.39	45.89 (3.23)	7.03	49.2 (3.46)	7.04
Beta_V_drug_tobramycin	0.24 (0.083)	34.5	0.29 (0.087)	29.5	0.28 (0.085)	30.2	0.25 (0.086)	33.8
Cl_pop	5.8 (0.26)	4.48	5.72 (0.27)	4.65	2.62 (1.02)	38.9	5.82 (0.26)	4.55
Beta_Cl_(BA_{Mor}/creat)	0.15 (0.047)	30.5	0.12 (0.046)	38.2	0.11	29.4		
Beta_Cl_(subcutfathu)					-0.93 (0.38)	40.5		
Beta_Cl_(CA^{-1}/creat)							0.19 (0.062)	32.7
Fixed effects by category								
V_drug_Gentamicin	49.09 (3.27)	6.66	45.87 (3.39)	7.39	45.89 (3.23)	7.03	49.2 (3.46)	7.04
V_drug_Tobramycin	62.38 (3.23)	5.17	61.61 (3.21)	5.21	60.75 (3.22)	5.31	63.42 (3.34)	5.26
Standard deviation of the random effects								
Omega_V	0.37 (0.038)	10.5	0.37 (0.043)	11.6	0.36 (0.039)	10.7	0.38 (0.04)	10.7
Omega_Cl	0.49 (52.63)	6.43	0.51 (0.034)	6.61	0.49 (0.032)	6.53	0.49 (0.032)	6.41
Error model parameters								
a	0.049 (0.023)	46.7	0.12 (0.043)	34.9	0.13 (0.038)	30.5	0.069 (0.037)	53.5
b	0.4 (0.013)	3.38	0.38 (0.014)	3.59	0.39 (0.014)	3.67	0.4 (0.014)	3.51

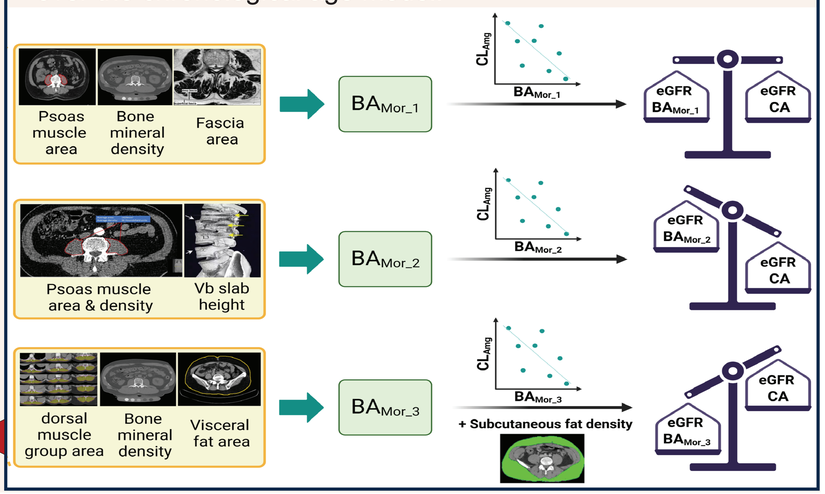
Discussion

- Radiomic biomarkers can be aggregated to develop biological indices representing aging and body composition in patients.
- BA_{Mor}-based Pop-PK models of aminoglycoside clearance had significantly lower AIC than the CA-based model.
- Future research is encouraged to incorporate biomarkers such as kidney-specific imaging metrics or genetic factors to refine the BA indices.

Model	AIC
Base (1-compartment combined-2)	2617.07
Base + CA/creat_CL + drug_V	2608.97
Base + 1/(CA*creat)_CL + drug_V	2602.12
Base + BA_{Mor_1}/creat_CL^1 + drug_V	2601.57
Base + BA_{Mor_2}/creat_CL^2 + drug_V	2601.71
Base + BA_{Mor_3}/creat_CL^3 + subcutfathu[4]_CL + drug_V	2598.33



- The radiomic biological age model offers a small improvement over the chronological age model.



Conclusion

References

1. Alikhani R & Pai MP. (2023) Clin. Trans. Sci. 16(11), 2095-2105.
2. Alikhani R, Horbal S, Rothberg A, Pai MP. (2024). Clin. Trans. Sci. (Under Revision)