

A Physiologically-based Pharmacokinetic (PBPK) Approach to Evaluate Differences in Pharmacokinetics Between Healthy Subjects and Cancer Patients

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Background

- It is well-recognized that cancer patients are different from healthy volunteers (HV) with regards to age, plasma protein levels, concomitant medications etc [1-3].
- Various population characteristics of the patient population such as age, height, weight, protein and hematocrit levels can affect ADME and PK of drugs.
- Therefore, accurate representation of the distribution of these population characteristics and the correlation among them in the target patient population is critical to predict the effect of intrinsic and extrinsic factors on the PK of drugs using the PBPK approach.
- Simcyp® is one of the software platforms available for mechanistic modeling and simulation of the absorption, distribution, metabolism, and excretion (ADME) of drugs in virtual patient population.

Objectives

- To characterize the population characteristics and their relationships in cancer patients
- To establish a custom population profile for Simcyp that can better predict PK and the effect of intrinsic and extrinsic factors on drug exposure in oncology

Methods

Establishment of Custom Population Profile for Cancer Patients

Data collection:

An oncology population database was established based on demographic (gender, age, height, and body weight) and lab (albumin, AAG, and hematocrit) data from 21 historical Genentech clinical trials in 2597 cancer patients.

Correlation of Population Characteristics:

- Mathematical models describing the distribution and relationship among population characteristics were obtained from the Simcyp healthy volunteer (HV) population profile (Simcyp® version 10.0, Simcyp, Sheffield, UK) and fitted to the observed data in the oncology population database.
- SigmaPlot (version 10.0, Systat Software, Inc.) was used for model fitting using nonlinear regression and to generate graphs.

Prediction of Population Characteristics

- Simulations were conducted using 50 trials with 10 subjects per trial (total n=500) for the Simcyp HV and the oncology population profiles.
- The distribution of demographic and lab variables from the simulated trials were compared with observed data.
- All predictions and simulations were performed using Simcyp® version 10.0.

Prediction of PK

- PK of 7.5 mg midazolam and 1200 mg saquinavir in HV and cancer patients were predicted using the two population profiles.
- Simulations were conducted for 50 trials with 10 subjects per trial (total n=500).
- The plasma PK parameters (C_{max} and AUC) of midazolam and saquinavir from PBPK simulations were compared in the two populations.

Results

Establishment of Custom Population Profile for Cancer Patients

Data collection:

Table 1: Summary of Clinical Data in the Oncology Population Database

Variable Type	Variable	Number of patients	
		Male	Female
Demographic	Age	1279	1318
	Height	1279	1318
	Body Weight	1279	1318
	Albumin	1260	1304
	AAG	677	399
Lab	Hematocrit	309	409
	Phase I	388	359
	Phase II	224	549
Study Type	Phase III	667	410
	NSCLC	703	448
	MBC	-	352
Disease Type	Other	576	518

Footnote: AAG: Alpha-1-acid Glycoprotein, NSCLC: non-small cell lung cancer, MBC: metastatic breast cancer

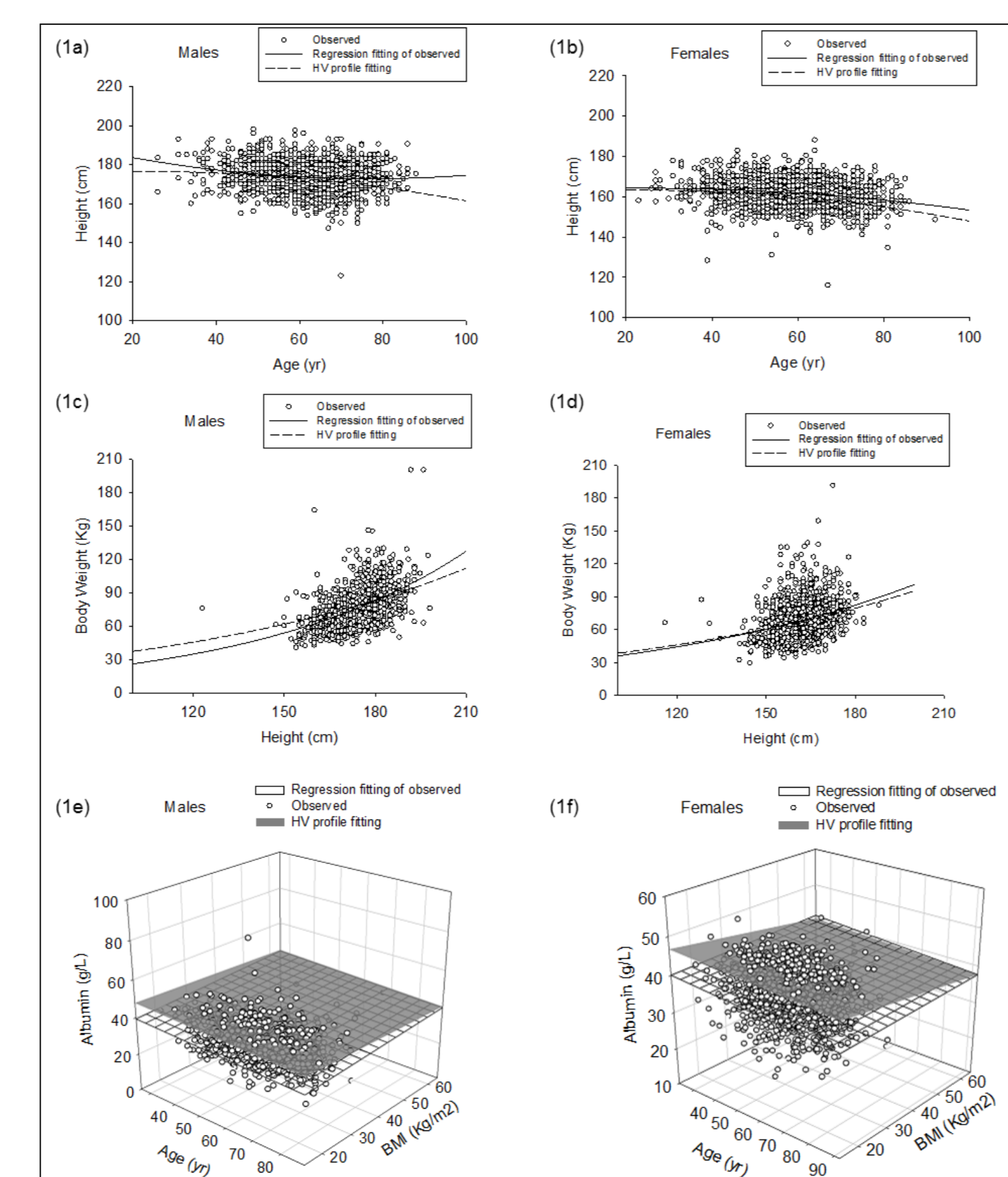
Correlation of Population Characteristics:

- Summary of parameters used in the custom oncology population profile are shown in Table 2 and correlations of population characteristics in the patient population are shown in Figure 1.

Table 2: Custom Oncology Population Profile

Population Characteristics (unit)	Parameter	Value	Source	
Gender	Proportion of Female	0.51	Observed	
Age (year)	Maximum	92	Observed	
	Minimum	23		
Age Distribution	Male: Distribution parameter - σ	9.63	Fitting of observed	
	Male: Distribution parameter - β	65.1		
	Female: Distribution parameter - σ	8.22		
	Female: Distribution parameter - β	62.3		
Height (cm)	Male: height vs. age (intercept)	193	Fitting of observed	
	Male: height vs. age (slope 1)	-0.512		
	Male: height vs. age (slope 2)	0.00333		
	Male: height vs. age (CV)	3.9		
Ref Body Weight (Kg)	Female: height vs. age (intercept)	163	Fitting of observed	
	Female: height vs. age (slope 1)	0.0915		
	Female: height vs. age (slope 2)	-0.0019		
	Female: height vs. age (CV)	3.9		
Body Weight (Kg)	CI	70	Observed	
	Male: w: height vs. height (intercept)	1.86		Fitting of observed
	Male: w: height vs. height (slope)	0.0142		
	Male: w: height vs. height (CV)	15		
Body Surface Area (m ²)	Female: w: height vs. height (intercept)	2.55	Fitting of observed	
	Female: w: height vs. height (slope)	0.0104		
	Female: w: height vs. height (CV)	18.8		
	CI	0.00718		
Albumin (g/L)	Weight power	0.425	Published relationship [43]	
	Height power	0.725		
	Male: C0	39.5		Fitting of observed
	Female: C1	-0.0568		
Male: C2	0.0846			
Alpha-1-acid Glycoprotein (g/L)	Female: C0	40.9	Fitting of observed	
	Female: C1	-0.0469		
	Female: C2	0.0219		
	Male: Mean	1.47		
Hematocrit (%)	Male: %CV	34	Observed	
	Female: Mean	1.38		
	Female: %CV	38		
	Male: Mean	37.7		
Hematocrit (%)	Male: %CV	13	Observed	
	Female: Mean	35.8		
	Female: %CV	11		

Figure 1: Correlation of Population Characteristics



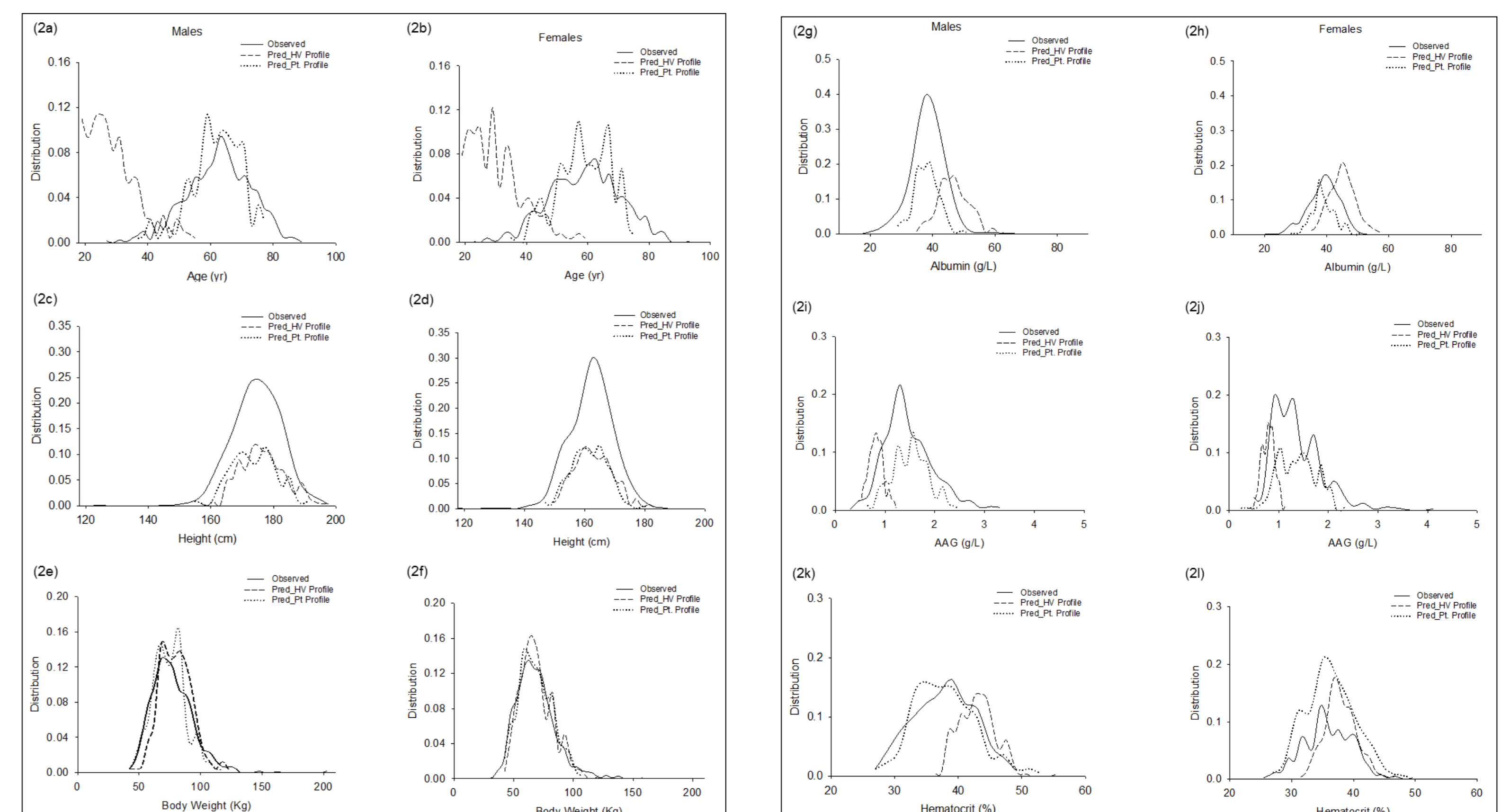
Results (cont'd)

- Correlation between height and age, and body weight and height in male and female cancer patients are similar to the corresponding relationships published in HV [4].
- Albumin levels appear to increase with increasing BMI in cancer patients, while decreased with BMI in healthy subjects.
- Albumin levels decreased with increasing age in cancer patients, consistent with published trend in healthy subjects [5].

Prediction of Population Characteristics:

- The oncology population profile accurately predicted the observed age distribution in patients (peak at ~63yrs; range: 23-92 yrs) whereas Simcyp HV population profile under-predicted the age distribution (peak at ~22 yrs) (Figures 2a & 2b).
- The height and body weight distributions in the virtual populations generated using both the population profiles were similar to those observed in patients (Figures 2c, 2d, 2e, & 2f).
- HV population profile over-predicted albumin concentration with the distribution peaks at ~45 g/L. However, custom oncology population profile predicted albumin distribution similar to that observed in patients (peak at ~38 g/L; range: 15-80 g/L) (Figures 2g & 2h).
- Simcyp HV population profile under-predicted AAG concentration with distribution peak at ~0.8 g/L. However, AAG distribution predicted using the custom oncology population profile was similar to that observed in patients (peak at ~1.3 g/L; range: 0.3-4 g/L) (Figures 2i and 2j).
- Simcyp HV population profile over-predicted hematocrit concentration with distribution peaks at 44 % and 38 % in males and females, respectively. Oncology population profile predictions were similar to that observed in patients (peak at ~35 %; range: 25-50 %) (Figures 2k and 2l).

Figure 2: Observed and Predicted Population Characteristics



Prediction of Midazolam PK:

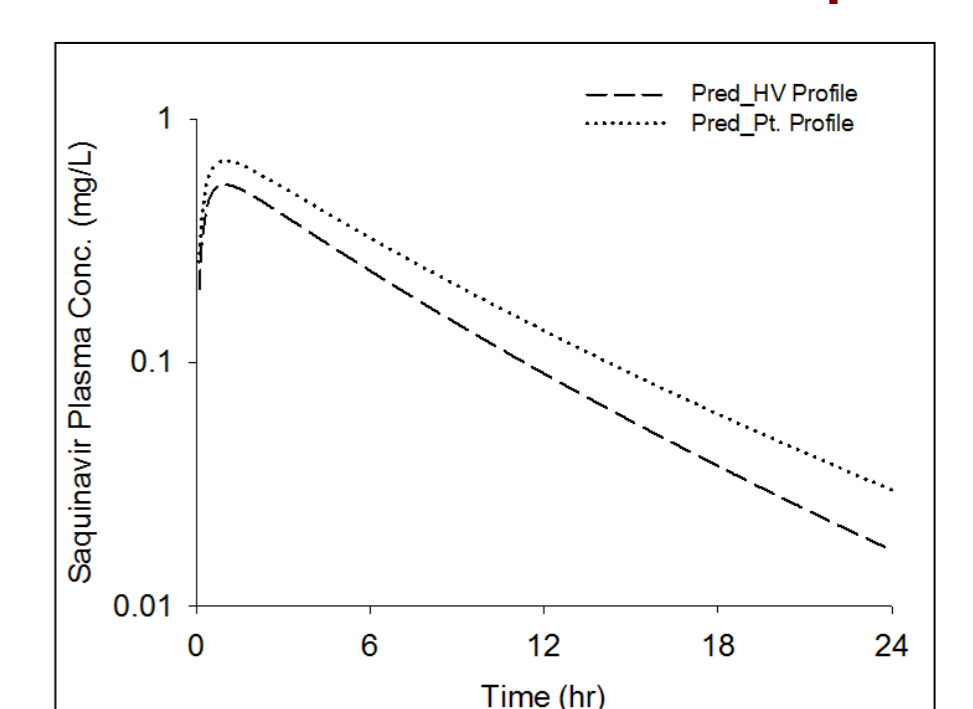
- The PBPK simulations suggested that PK of midazolam (which is extensively metabolized by CYP3A4) is not different in cancer patients compared to healthy subjects, consistent with the literature (Table 3).
- It has been shown in the literature that CYP3A activity did not change with age, sex, and body size measurements in 134 patients with advanced cancer [6], which supports the lack of difference in midazolam PK between the two populations.

Table 3: PK Parameters of Midazolam (7.5 mg)

Population	Reference	n	Type	Observed		Predicted	
				C_{max} (ng/ml)	AUC ₀₋₂₄ (ng·hr/ml)	C_{max} (ng/ml)	AUC ₀₋₂₄ (ng·hr/ml)
Healthy	[7]	12	Healthy	37.5 (50.3) ^a	31.5 (50.3) ^a	27.8	157
	[8]	16	Healthy	59.7 (36.4) ^a	196.4 (30.3) ^a	(26.3-29.3) ^d	(144-171) ^d
	[9]	20	Healthy	35.4	102		
	[10]	18	Prostate cancer	(29.7-42.3) ^b	(81.9-128) ^b		
Patients	[11]	20	Breast cancer	39.8 (43.3) ^a	187 (68) ^a	28.6	174
	[12]	8	Metastatic renal cell carcinoma/gastrointestinal stromal tumor	24 ± 6.9 ^c	96 ± 35 ^c	(27.4-29.8) ^d	(159-188) ^d

Footnote: ^a Geometric mean (%CV); ^b Geometric mean (95% CI); ^c Mean ± SD; ^d Mean (SE); Mean (95%CI)

Figure 3: Predicted Mean PK Profiles of Saquinavir



Prediction of Saquinavir PK:

The oncology population profile predicted higher plasma exposure for saquinavir compared to the HV population profile (Figure 3).

- The predicted mean C_{max} (95% CI) in HV and cancer patients were 0.537 (0.492 - 0.582) mg/L and 0.674 (0.619 - 0.73) mg/L, respectively, following a 1200 mg single oral dose of saquinavir.
- Similarly, the predicted mean AUC (95% CI) in the two populations were 3.72 (3.35 - 4.1) mg/L*hr and 5.09 (4.56 - 5.61) mg/L*hr, respectively.

Possible reasons for higher exposure of saquinavir in patients compared to HV:

- Differences in age distribution of patient population versus healthy subjects:
 - MPPGL (microsomal protein per gram of liver) gradually decrease with age resulting in reduced clearance (CL) of drugs that are eliminated via hepatic metabolism [13].
- Differences in plasma protein levels between the two populations:
 - Plasma levels of AAG are higher in cancer patients. Saquinavir PK could have been affected due reduced free fraction.

Conclusions

- In summary, this work demonstrates the importance of a population profile specific for oncology due to various pathophysiological differences in cancer patients compared to healthy subjects.
- The custom oncology population profile is a valuable addition to the scientific toolbox given its ability to accurately generate virtual oncology population to better predict PK using Simcyp.

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