Changes in liver volume II – a population-based approach to meta-analysis of paediatric, adult and geriatric populations - an update

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Objectives

- Liver volume (LV) is a critical parameter for both liver transplantation and as a scaling factor for predicting clearance (CL) in physiologically-based pharmacokinetic modelling (PBPK); therefore obtaining its accurate and precise estimation is essential.
- The objective of this study was to extend an existing meta-analysis for the estimation of LV to other race groups (e.g. Caucasian, Japanese, Chinese) and paediatric and geriatric populations using non-linear mixed effect modelling techniques.

Methods

The overall workflow (Fig 1) comprised the following steps:

- Development of a search string to ensure optimal retrieval of data.
- Extraction of data and simulation of missing variables to give a final dataset including both averaged study data as well as individual datum.
- Construction of a non-linear mixed effect model (NLME) of the data including covariates.
- Final covariate selection and model evaluation

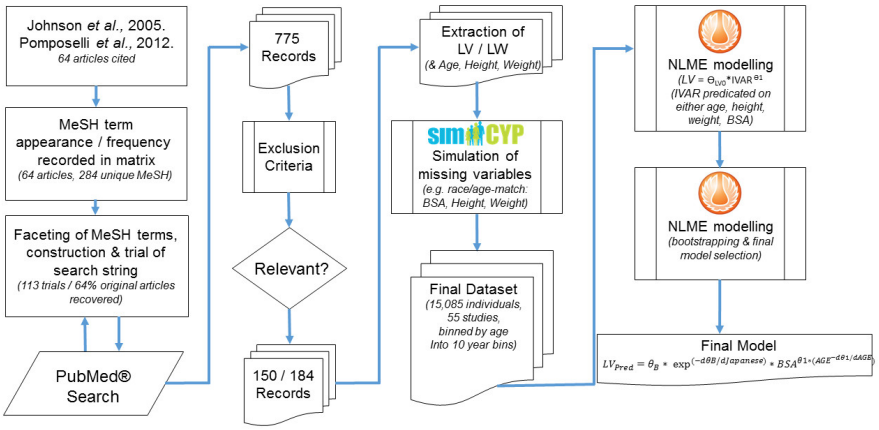

Figure 1. *A workflow describing the meta-analysis and NLME modelling of the acquired LV data*

Results

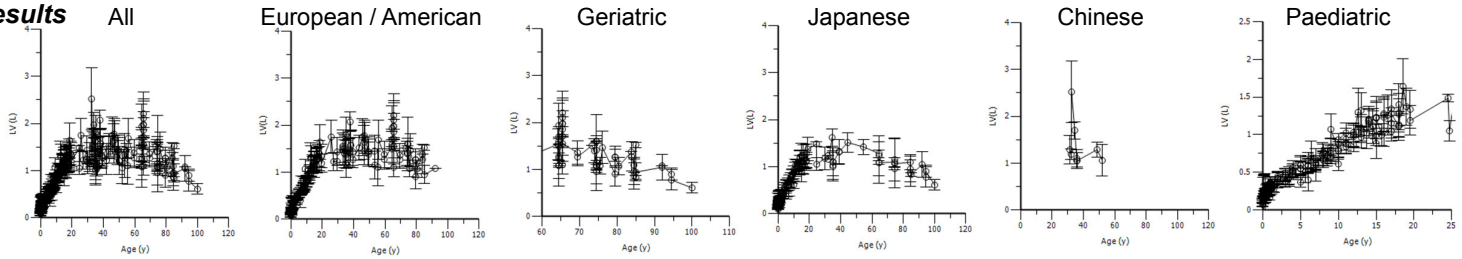

Figure 2. *Observed LV (L) data by age (y) for different population groups*

- Data collated from 55 studies included 2906 LV measurements from averaged data and 1787 from 'individuals'.
- In this context 'Individuals' are representative of the collated studies binned by age (i.e.10y bands; Fig 2) and therefore IPRED was reflective of a study rather than individual prediction *per se*. Evaluation of covariate models revealed well performing models predicated using bodyweight and body surface area (BSA) as independent variables (IVAR) (see Table 1).
- The BSA predicated model was chosen (Final model), due to its parsimony when compared against the Urata model and it was therefore less complex for a similar 'goodness of fit'.
- Predicted population estimates of LV as a function of BSA (left and middle) and conditionally weighted residuals (CWRES) (right) were well determined against observed values (Fig 3).

Table 1. *Comparison and evaluation of optimal models (predicated using different IVAR)*
*NB. * additional constants in the Urata model are not considered within #Parms*

Model*(IVAR)	Model #	Covariates retained	-2(LL)	AIC	BIC	#Parms	#Obs	#Subj	*p*-value
BSA simple run	1	dθ1/dAGE, dLV0/dJapanese	-631.03	-617.03	-591.51	7	283	55	3.80E-15
WT simple run	2	dLV0/dCaucasian, dθ1/dCaucasian, dLV0/dJapanese, dθ1/dJapanese, dLV0/dAGE	-633.61	-613.61	-577.15	10	283	55	5.20E-33
HT simple run	3	dLV0/dMETHODS, dθ1/dMETHODS, dθ1/dJapanese	-514.11	-496.11	-463.3	9	283	55	3.70E-76
Age simple run	4	dLV0/dMETHODS, dθ1/dMETHODS, dLV0/dJapanese	-338.7	-324.7	-299.19	7	283	55	1.10E-45
Yu simple run (WT & HT)	5	dθ1/dJapanese, dLV0/dChinese	-632.98	-612.98	-576.53	10	283	55	1.20E-08
Urata simple run (BSA)	6	dθ1/dMETHODS, dLV0/dJapanese	-631.11	-617.11	-591.59	7*	283	55	1.20E-15

Final model: $LV_{Pred} = \theta_B \quad exp^{(-d\theta B/dJapanese)} \quad BSA^{\theta 1\ (AGE^{-d\theta 1/dAGE})}$

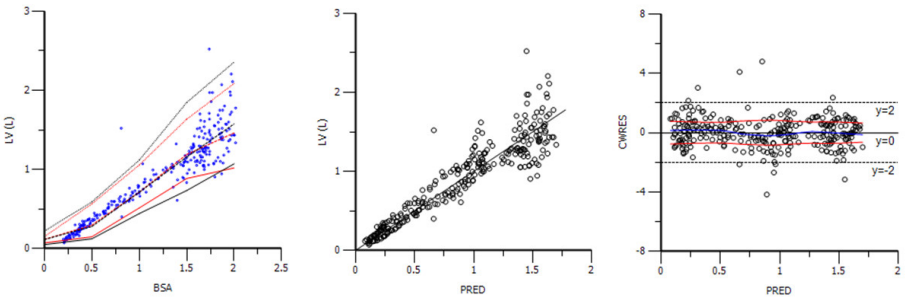

Figure 3. *Bootstrapped predicted population estimates of liver volume as a function of BSA predicated model (left and middle panels) and CWRES (right panel) from this same model respectively. The bulk of observed quantiles (red) fall within the 5 – 95 % range of predicted quantiles (grey) for the prediction intervals*

Conclusion

- Age and BSA are used here as important predictors of LV.
- Traceable model-based meta-analysis is important for arriving at accurate values for clinical parameters.
- The final model corrects some of the deficiencies of a previous model[1] and may be applied both clinically and to PBPK modelling.

References

1. Johnson TN et al. Liver transplantation. 2005;11:1481-93.
2. Urata K et al. Hepatology1995;21:1317-21.
3. Yu HC et al. Liver Transplantation. 2004;10:779-83.
4. Pomposelli JJ et al. Liver Transplantation. 2012; 18:1083 – 1092.