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ORIGINAL RESEARCH ARTICLE

Published Population Pharmacokinetic Models of Imatinib Perform Poorly on TDM Data from Pediatric Patients

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Abstract

Background Population pharmacokinetic models can potentially provide suggestions for an initial dose and the magnitude of dose adjustment during therapeutic drug monitoring procedures of imatinib. Several population pharmacokinetic models for imatinib have been developed over the last two decades. However, their predictive performance is still unknown when extrapolated to different populations, especially children.

Objective This study aimed to evaluate the predictive performance of these published models on an external real-world dataset containing data from both adults and children.

Methods A real-world dataset was collected, containing observations from adult and pediatric patients with Philadelphia chromosome-positive/Philadelphia chromosome-like acute lymphoblastic leukemia and chronic myeloid leukemia ($N = 39$) treated with imatinib. A systematic review through PubMed was conducted to identify qualified population-pharmacokinetic models for external evaluation (i.e., prediction-based, simulation-based, and Bayesian forecasting diagnostics). Standard allometric scaling was used for models that were developed based on data from adults only.

Results Fifteen published models were found for evaluation, of which only two were based on data from both children and adults. Prediction-based diagnostics showed that some models had an acceptable level of bias. The model by Shriyan et al. (with allometric scaling) performed best with a median prediction error of 1.24%. However, no models performed well on precision even when allometric scaling was used, where the lowest median absolute prediction error was 37.66% using the model by Schmidli et al. The models by Golabchifar et al. and Schmidli et al. (both with allometric scaling) performed the best of all tested models, with a median prediction error ≤ 15%, median absolute prediction error ≤ 40%, fraction of prediction error within ± 20% (F_{20}) ≥ 0.3, and within ± 30% (F_{30}) nearly 0.4. Simulation-based diagnostics showed that most of the observations outside the 90% prediction interval were from children. Bayesian forecasting showed that the model prediction could be improved using one prior sample, particularly in adults.

Conclusions Current models fail to accurately predict imatinib plasma concentrations in our real-world dataset, especially for children. Future pharmacokinetic studies should focus on developing better models for pediatric populations.

1 Introduction

Imatinib is a highly selective inhibitor of the BCR-ABL1 tyrosine kinase fusion protein generated by the genetically abnormal Philadelphia chromosome (Ph). As the first approved tyrosine kinase inhibitor, imatinib has revolutionized the survival rates in BCR-ABL1 leukemia over the last two decades [1]. Currently, in most cases, it is still used as the first-line treatment of patients with newly diagnosed Ph-positive (Ph+) acute lymphoblastic leukemia (ALL) and chronic myeloid leukemia (CML). For Ph-like (ABL-class) ALL, imatinib is added to first-line treatment in the prospective ALLTogether1 trial for patients aged 0–45 years.

The recommended total daily dose of imatinib is 400 mg orally for adult patients with CML (with a possible escalation to 600–800 mg to avoid the disease progressing to the accelerated or blast phase), 600 mg for adult patients with ALL, and a dosage range of 260–340 mg per square meter of body surface area for pediatric patients [2]. The pharmacokinetics of imatinib is characterized by high bioavailability (exceeding 95%) after oral administration [3] but high inter-individual variability in drug exposure and trough concentrations [2]. A significant pharmacokinetic (PK) and pharmacodynamic correlation is observed between imatinib through concentrations and clinical responses in both patients with CML [4–7] and patients with gastrointestinal

Key Points

Fifteen population pharmacokinetic models of imatinib were found in a systematic review, whereof only two included data from children.

In an evaluation of the 15 models using an external dataset containing both children and adults, it was shown that all the models had a lower prediction performance in children compared with adults, despite standard allometric scaling being used.

Although imatinib is utilized in the treatment of pediatric leukemia, there is a considerable deficiency of pharmacokinetic studies specifically addressing its use in children, and moreover, predictions derived from adult-based models lack precision.

stromal tumors [7–9]. Studies in adult patients with CML show that a trough concentration above 1000 ng/mL can give a significantly higher cytogenetic and major molecular response rate [10–12]. However, a meta-analysis shows that trough concentrations above 1500 ng/mL do not increase efficacy [13], whereas concentrations above 3000 ng/mL might lead to serious adverse events such as neutropenia [12]. Consequently, it is recommended that the trough concentration should be kept between 1000 and 3000 ng/mL [12–14]. Efficacy of the treatment with imatinib can be followed by measuring the BCR::ABL1 transcript level by real-time polymerase chain reaction, and therapeutic drug monitoring (TDM) is increasingly recommended as an additional method to optimize imatinib treatment within patients with CML to avoid toxicity and follow compliance [13, 15]. Pharmacokinetic/pharmacodynamic data regarding pediatric ALL are currently lacking [2] and thus there is no recommendation for dosing for pediatric patients with ALL. For pediatric patients with CML, the US Food and Drug Administration suggest the same exposure level of imatinib as in adults [16]. Therefore, this is also applied in ALL in our clinical practice.

Imatinib is a substrate of influx transporters (e.g., organic cation transporter 1 and organic anion transporting polypeptide 1A2) and efflux transporters (e.g., ATP-binding cassette transporters ABCB1 and ABCG2) [17]. The pharmacogenetic-based variations in activity and expression of these transporters probably contribute to the variability in imatinib pharmacokinetics [18]. Additionally, imatinib is metabolized by the cytochrome P450 (CYP) system (mainly CYP3A4 and CYP3A5), which shows high between-subject variability in hepatic expression and biological activity [19]. The parent imatinib compound is metabolized mostly by CYP3A4 to N-desmethyl imatinib, which has similar in vitro potency to imatinib [3]. Children might show a different PK profile of imatinib than adults because of their physiological and anatomical differences [20]. However, data on imatinib pharmacokinetics in children are still sparse [21].

Population pharmacokinetic (pop-PK) models are potentially useful in TDM for predicting both the initial dose for newly diagnosed patients and the magnitude of dose adjustments when needed [22, 23], especially combined with a Bayesian maximum a posteriori method to adjust the individual PK parameters [24]. Several pop-PK models for imatinib have been published. However, these models are mostly built on an entirely adult population and their predictive performance across different populations, especially in children, remains unclear. This study aims to evaluate the predictive performance of the published pop-PK models on imatinib, using an external real-world dataset from northern Europe consisting of data from both children and adults. The goal is to identify a clinically acceptable model for all age groups that can be used to suggest both the initial dose and dose adjustments in daily TDM practice.

2 Methods

2.1 Review of Relevant pop-PK Models

A systematic literature review was conducted in PubMed for pop-PK models published before 24 May, 2024. Moreover, additional publications identified from the reference list of selected publications were also screened if relevant. The models were included if they were (1) a pop-PK model study using a non-linear mixed-effect modeling approach, (2) based on a human patient population receiving oral imatinib, and (3) written in English. Papers were excluded if they were (1) with insufficient parameter information to reproduce the model fully, (2) models combining both free and total imatinib concentrations, (3) only modeling on the first-day pharmacokinetics of imatinib (no data on the steady state), and (4) not an original research paper of an imatinib pop-PK model (i.e., review, simulation study). A single study was reported if data were presented in multiple publications to avoid duplication. The search terms used are shown in Table S1.1 of the Electronic Supplementary Material (ESM).

2.2 Patient Data Collection

The data from the current study were collected from the hematology and pediatric departments of 11 Nordic and Baltic hospitals (Table S1.2 of the ESM). Patients were either included in a PK sub-study of the ALLTogether1

trial or the Danish ABL-class Inhibitor pharmacokinetics/-dynamics Monitoring (AIM) study (Fig. S1.1 of the ESM).

After obtaining written informed consent from patients and/or legal guardians, the study participants were enrolled in the ALLTogether1 Study Protocol (EudraCT 2018-001795-38), which is an international multicenter prospective study. The study includes patients with Ph-like ALL aged 0–45 years and has, on top of chemotherapy, a non-randomized addition of imatinib to patients carrying an ABL-class fusion gene in the leukemic clone. Oral imatinib 340 mg/m^2/day was introduced from day 15 of induction (< 25 years; maximum dose: 800 mg) or day 29 (≥ 25 years; maximum dose: 600 mg) throughout treatment. Dose adaptation of imatinib was allowed in the case of toxicity according to protocol guidelines. Patients diagnosed with BCR-ABL1-positive (Ph+) ALL are excluded from the study. However, if the treating physician deemed the ALLTogether1 protocol to be the best standard of care, these patients could still be treated according to the protocol. A full list of ALLTogether1 inclusion/exclusion criteria, details on stratification, antileukemic therapy, and guidelines of dose adaptation are available at ClinicalTrials.gov (NTC04307576). In an observational PK sub-study of ALLTogether1, blood samples from study patients were obtained at already scheduled sampling timepoints according to protocol guidelines. A requisition following every sample included information about the time for the latest intake of imatinib, sampling time, height, and weight.

Both pediatric and adult patients diagnosed with CML or Ph+ ALL were included in the Danish ABL-class Inhibitor pharmacokinetics/-dynamics Monitoring (AIM) study conducted at Copenhagen University Hospital Rigshospitalet. The Danish AIM study was approved by The Scientific Ethics Committees for the Capital Region, Denmark (H-22057870). Patients were eligible if they received imatinib and gave written informed consent. Blood samples were taken at already scheduled timepoints for sampling according to standard of care. Every sample was followed by a telephone call to the patient to gather information about the timing of imatinib intake.

Eligible patients for this current study were children or adults diagnosed with CML or Ph+/Ph-like ALL, included in the ALLTogether1 PK sub-study or the Danish AIM study, treated with imatinib, and having at least one measured imatinib sample. Patients were included between January 2022 and December 2023 with longitudinal sampling collection until January 2024.

For each valid TDM occasion (or visit) with a clear dose regimen, a single imatinib (sometimes combined with metabolite N-desmethyl imatinib) concentration at steady state was included in the external dataset. Therapeutic drug monitoring visits were removed if no clear information was available on imatinib intake and blood sample time or if the time after the dose was more than 48 hours. In case the total body weight or height of a patient was not measured at one TDM visit (missing value in weight or height), the body weight or height in the most recent TDM visit, no more than 6 months apart, was imputed (only 8 of 122 TDM visits were imputed by this method). The patient basic demographic information was collected from a central study registry (for ALLTogether1 patients) or electronic medical records (for Danish AIM patients), including age, sex, weight, height, and time after diagnosis. The TDM follow-up was performed every few months for each patient.

2.3 Bioanalytical Method

Sample preparation: samples of 1–5 mL of whole blood were collected in EDTA tubes at weekly or monthly intervals and sent with regular mail to the Pediatric Oncology Research Laboratory, Copenhagen, Denmark. Plasma was prepared by centrifugation of EDTA blood. The plasma sample was added to stable isotope-labeled internal standards and then the analytes are extracted with ethyl acetate. The organic fraction was transferred to a new vial. After evaporation of the organic fraction, the sample was redissolved and the concentrations of imatinib and N-desmethyl-imatinib were determined by reversed-phase liquid chromatography tandem mass spectrometry.

Liquid chromatography tandem mass spectrometry: the method used is a slightly modified version of the method developed by Bouchet et al. [25]. The mass spectrometer was a Sciex Qtrap 6500$^+$. This was connected to a Sciex ExionLC UHPLC system (Sciex, Framingham, MA, USA). The column used was an Acquity UPLC™ HSS T3 column (2.1×50 mm, 1.8 µm) protected by an Acquity UPLC™ HSS T3 VanGuard pre-column (2.1×5 mm, 1.8 µm) both obtained from Waters (Wexford, Ireland).

2.4 External Evaluation

All selected pop-PK models were coded and evaluated in NONMEM 7.5.0 (ICON Development Solutions, Ellicott City, MD, USA). Statistical analysis and visualization were programmed through R software (version 4.3.0) and Python (version 3.9.19). If covariates were unavailable in the external dataset, the typical population value from the originally developed model was used. The inter-occasion variability model was removed if contained in the published models. All parameters (including fixed and random effects) were set to the published values and steady-state conditions were used for each model.

Most of the published models were built on data from an entirely adult population, thus, to evaluate how they predict in a real-world population like our dataset consisting

of both children and adults, the standard allometric scaling on clearance and volume of distribution was used and their performance was examined. Thus, all models were evaluated both in their original form as published and with allometric scaling, if this was not included in the original model.

The equations for scaling clearance and volume were:

$$\mathrm{CL} = \mathrm{CL}_{\mathrm{adult}} \times \left(\frac{\mathrm{TBW}}{70}\right)^{0.75}, \quad (1)$$

$$V = V_{\mathrm{adult}} \times \left(\frac{\mathrm{TBW}}{70}\right), \quad (2)$$

where CL, V, $\mathrm{CL}_{\mathrm{adult}}$, and V_{adult} are the clearance and volume of distribution after and before allometric scaling, respectively, and TBW is the total body weight. The volume of the peripheral compartment and intercompartmental clearance were also scaled for the two-compartment model. The allometric scaling procedure would replace the total body weight covariate when allometric scaling was used on the published modes. The performance of the allometric scaling model and the original published model was compared.

2.4.1 Prediction-Based Diagnostics

To evaluate the prediction performance of selected models, the prediction error (PE) and absolute prediction error (APE) were calculated using population predictions (C_{PRED}) and corresponding observations (C_{OBS}) as outlined in Eqs. 3 and 4, respectively.

$$\mathrm{PE}(\%) = \left(\frac{C_{\mathrm{PRED}} - C_{\mathrm{OBS}}}{C_{\mathrm{OBS}}}\right) \times 100 \quad (3)$$

$$\mathrm{APE}(\%) = \left|\frac{C_{\mathrm{PRED}} - C_{\mathrm{OBS}}}{C_{\mathrm{OBS}}}\right| \times 100 \quad (4)$$

The root mean squared error (RMSE) was calculated as follows (Eq. 5):

$$\mathrm{RMSE} = \sqrt{\frac{1}{N}\sum_{i=1}^{N}(C_{\mathrm{PRED}} - C_{\mathrm{OBS}})^2}, \quad (5)$$

where N is the number of observations considered. The C_{PRED} and C_{OBS} were all transferred to mg/L before calculating RMSE. No variability is included in this evaluation.

The median prediction error (MDPE) represents the bias, and the median absolute prediction error (MDAPE) and RMSE represents the precision. Additionally, the fractions of PE% within ± 20% (F_{20}) and ± 30% (F_{30}) of observed values were calculated to evaluate the predictive performance of the selected models. According to previous reports, a satisfactory model should reach the standard of MDPE ≤ ± 15%, MDAPE ≤ 30%, $F_{20} \geq 35\%$, and $F_{30} \geq 50\%$, whereas RMSE should be as close to zero as possible [26–29].

2.4.2 Simulation-Based Diagnostics

Stochastic simulations were performed in NONMEM for 1000 subproblems or replicates to evaluate the predictive performance of candidate pop-PK models with inter-individual variability and residual unexplained variability. The simulation dataset used the same external dataset changing the value in the DV column to NA, which means that the dataset used for simulation has the same patient demographic information and corresponding dose as the external dataset. Additional timepoints (every 0.5 hours) were used to capture the entire concentration–time profile under steady state. The PK profile for metabolite N-desmethyl imatinib was also simulated for models with metabolite N-desmethyl imatinib. The patient population was stratified by dose for both simulation and observation data. The 5th, 10th, 25th, 50th, 75th, 90th, and 95th percentiles of simulated data at each timepoint were calculated and graphically represented for each selected model to compare with the observed concentrations at the same timepoints.

2.4.3 Bayesian Forecasting Diagnostics

A subgroup of patients (25 patients) having more than one TDM occasion with observed imatinib plasma concentrations was selected (Bayesian dataset) and used to evaluate the Bayesian forecasting performance of the 15 models when one prior TDM observation data point was included. If more than two TDM visits were available for a single patient, the most recent two occasions were used in this study.

The Bayesian forecasting was carried out sequentially on two TDM occasions. The a priori scenario (prediction performance with 0 previous observations) used only typical PK parameters and all available patient covariates and dose information to predict the imatinib concentration on the first TDM occasion and to calculate the prediction error through the C_{PRED} and C_{OBS} in Eq. 2, as previously described. The individual a posteriori scenario (with one previous observation) predicted the imatinib concentration at the second TDM occasion by including the first occasion and accounting for the inter-individual variability and residual unexplained variability of the models. The following equation calculated the individual prediction error (IPE%):

$$\mathrm{IPE}(\%) = \left(\frac{C_{\mathrm{IPRED}} - C_{\mathrm{OBS}}}{C_{\mathrm{OBS}}}\right) \times 100, \quad (6)$$

where C_{IPRED} is the individual prediction generated by NONMEM.

3 Results

3.1 Review of Relevant pop-PK Models

An overview of the selection strategy for including the published pop-PK models on imatinib is shown in Fig. S1.2 of the ESM. Several pop-PK models were excluded because the models were not built on steady-state plasma concentration data [30–32], contained subgroup patient populations [33] from another included model [34], were joint models on free and total imatinib concentrations [35], or there were missing stochastic parameters [36, 37]. The literature search identified 15 imatinib pop-PK models for further external evaluation, for which detailed information is summarized in Table 1. Among them, one was an international multicenter study [38], others were conducted in the USA and Europe (N = 8) [9, 34, 39–44], East Asia (N = 4) [45–48], South Asia (N = 1) [49], and West Asia (N = 1) [50]. Most patient populations for the selected models were either CML or GIST. Furthermore, ten models were developed based on a small population of fewer than 100 patients [9, 34, 39–42, 44, 46, 49, 50]. Three Chinese population models were based on populations with a size of 110–230 patients [45, 47, 48]. One model from the international phase III trial on imatinib was derived from a larger population (371 patients) [38], and one model founded on observation data collected from 2006 to 2010 contained the largest population in selected models with 2478 adult European patients [43]. Only two models included children. One model by Menon-Andersen et al. [40] was developed for children and young adults with Ph+ leukemia, the age group being 6–24 years, and another model by Petain et al. [34] included 33 patients with solid malignancies aged 2–22 years in a phase II study.

A one-compartment model was used in almost all the included models (N = 14), except one that used a two-compartment model [41]. The absorption phase was characterized by first-order (N = 7) [34, 39, 42, 45–48], zero-order (N = 7) [9, 38, 40, 43, 44, 49, 50], and a transit model (N = 1) [41]. One study found a lag time in imatinib absorption [50]. Two studies also included the PK profile of the main metabolite N-desmethyl imatinib in their model [34, 40]. The typical apparent clearance was estimated to be 7.29–17.3 L/h.

Total body weight was the most frequently identified covariate (N = 5). Hemoglobin (N = 2), white blood cell count (N = 2), plasma AGP (N = 2), and albumin (N = 2) were other covariates found more than once. Pharmacogenomic variances in the *ABCG2* and *SLC22A1* were identified as covariates influencing imatinib clearance in one model each (Table 1). More clinical information about the selected models is provided in Table S1.3 of the ESM.

3.2 Patient Demographic Information

The external dataset included 39 patients with 122 imatinib plasma concentration samples and 100 samples of N-desmethyl imatinib. There were 25 (64% of the total) patients who provided more than one sample for imatinib, which could be used for Bayesian forecasting evaluation. Children (patients aged ≤18 years) accounted for around 40% of the total population, and for 60% of imatinib or N-desmethyl imatinib observations, which led to high variability in age, weight, and height of this dataset. The age distribution of the external dataset is shown in Fig. S2.1 of the ESM. Additionally, 14 of 16 children were diagnosed with ALL, while 19 of 23 adults had CML in this dataset. The demographic information is summarized in Table 2. All patients received imatinib once daily, with doses of 100 mg, 150 mg, 200 mg, 250 mg, 270 mg, 300 mg, 350 mg, 400 mg, 450 mg, 550 mg, or 600 mg.

3.3 Prediction-Based Evaluation

The performance of the selected models based on prediction-based diagnostics is shown in Table 3. This aims to examine the model's performance at the population level and its ability to predict the initial dose for different subpopulations with given covariates. Because there are children in the external dataset, the standard allometric scaling was used for selected models building on adult data only. Allometric scaling was not used in the models by Menon-Andersen et al. and Petain et al. [34, 40], as their models were based on a population of both adults and children, and they used body weight scaling in their original models.

Only the original model of Demetri et al., He et al., Wang et al., and Yamakawa et al. fulfill the criteria of MDPE ≤ ± 15%. None of the original models met any of the criteria from MDAPE ≤ 30%, F_{20} ≥ 35%, and F_{30} ≥ 50%. The models by Menon-Andersen et al. and Petain et al. did not show superior performance compared to the other models, even though they included children and body weight scaling in their original models. After allometric scaling, Eechoute et al., Gdabchifar et al., Jiang et al., Judson et al., Schmidli et al., Shriyan et al., Wang et al., and Yamakawa et al. met the criteria of MDPE ≤ ± 15% (Table 3). However, none of the models met the MDAPE, F_{20}, and F_{30} criteria even after standard allometric scaling. The models by Golabchifar et al. and Schmidli et al., when using allometric scaling, showed better predictive performance compared with other models, as they achieved the MDPE ≤ ± 15% criteria, and

Table 1 Summary of published population PK models of imatinib in this external validation study

Study and publication year	Country or region	Number of patients/ samples	Total dose per day	Diagnosis	Imatinib structural model	Covariates included	Age range	Bioassay [LOQ (ng/mL)]	PK parameter and formula	BSV	RUV
Judson et al. (2005)	Europe and USA	43/517	400–1000 mg	GIST, STS	1-CMT, ZO	TBW[a]	NA	LC-MS/MS [4]	CL/*F*: $10.6 \times (\frac{TBW}{67.5})^{0.002}$ Vc/*F*: 182 D1: 1.51	$Var(\eta_{CL})$: 0.305 $Var(\eta_{Vc})$: 0.34 $Cov(\eta_{CL}, \eta_{Vc})$: 0.237	Prop: 34% Add: 273 ng/mL
Schmidli et al. (2005)	Multi-county	371/1930	400 mg	CML	1-CMT, ZO	TBW, HG, WBC	18–70	LC-MS/MS [25]	CL/*F*[b]: $(13.8 + (-3.18) \times OCC) \times \left(\frac{TBW}{80}\right)^{0.301} \times (\frac{HG}{13})^{0.897} \times (\frac{WBC}{16})^{-0.105}$ Vc/*F*[b]: $(252 + (-7.82) \times OCC) \times \left(\frac{TBW}{80}\right)^{0.405} \times (\frac{HG}{13})^{0.676} \times (\frac{WBC}{16})^{-0.07}$ D1: 1.5	CV%(CL): 31.9% CV%(Vc): 31.4% $Cov(\eta_{CL}, \eta_{Vc})$: 0.071	Prop: 26% Add: 0.249 mg/L
Widmer et al. (2006)	Switzerland	59/321	150–800 mg	GITS, CML, ALL (1 patient)	1-CMT, FO	None[c]	20–79	HPLC [50]	CL/*F*: 14.3 Vc/*F*: 347 Ka: 0.61	CV%(CL): 36% CV%(Vc): 63%	Prop: 31%
Petain et al. (2008)	France	67/505	340 mg/m^2 (children); 400 mg (adults)	Solid malignancies (children); GIST (adults)	1-CMT, FO	TBW, AGP, ALB	2–84	HPLC [imatinib: 10] [metabolite: 10]	Imatinib: CL/F: $7.29 \times (\frac{TBW}{54})^{0.56} \times (\frac{AGP}{1.13})^{-0.65} \times (\frac{ALB}{38})^{0.66}$ Vc/*F*: $202 \times (\frac{TBW}{54})^{0.79} \times (\frac{AGP}{1.13})^{-1.01}$ Ka: 1.03 Metabolite: CLm/fm[b]: $52.2 \times (\frac{TBW}{54})^{-0.62} \times (\frac{AGP}{1.13})^{-0.81} \times 0.7^{occ}$ V_1m/fm: 32.2	Imatinib: CV%(CL): 19% CV%(Ka): 82% Metabolite: CV%(CLm): 28% CV%(V_1m): 81%	Imatinib: Prop: 33.6% Metabolite: Prop: 34.8%
Demetri et al. (2009)	Europe and USA	73/NA	400 or 600 mg	GIST	1-CMT, ZO	ALB, WBC	25–79	LC-MS [4]	CL/*F*: $8.18 \times (\frac{ALB}{38.3})^{1.66} \times (\frac{WBC}{7})^{-0.418}$ Vc/*F*[b]: $(168 + 58.5 \times OCC) \times (\frac{ALB}{38.3})^{1.66} \times (\frac{WBC}{7})^{-0.418}$ D1: 1.69	CV%(CL): 34.6% CV%(Vc): 35.7% $Cov(\eta_{CL}, \eta_{Vc})$: 0.119	Prop: 34.9% Add: 0.004 mg/L
Menon-Andersen et al. (2009)	USA	41/842 (imatinib) + 424 (metabolite)	260–570 mg/m^2	Ph+ leukemia; solid tumor	1-CMT, ZO	TBW	6–24	HPLC [imatinib: 1 or 10] [metabolite: 2]	Imatinib: CL/F: $10.8 \times (\frac{TBW}{70})^{0.75}$ Vc/F: $284 \times (\frac{TBW}{70})$ D1: 1.67 Metabolite: CLm/fm: $9.65 \times (\frac{TBW}{70})^{0.75}$ V_1m/fm: $11.6 \times (\frac{TBW}{70})$ Qm/fm: $2.9 \times (\frac{TBW}{70})^{0.75}$ V_2m/fm: $256 \times (\frac{TBW}{70})$	Imatinib: CV%(CL): 31.5% CV%(D1): 92.6% Metabolite: CV%(CLm): 33.4%	Imatinib: Log-scale add: 40.8% Metabolite: Log-scale add: 34.7%
Yamakawa et al. (2011)	Japan	34/622	100–600 mg	CML	1-CMT, FO	None[d]	21–80	HPLC [NA]	CL/*F*: 8.7 Vc/*F*: 430 Ka: 2.06	ω_{CL}: 0.363 ω_{Vc}: 0.457 ω_{Ka}: 0.747	Add: 0.4 mg/L
Eechoute et al. (2012)	Europe	50/1743	400–800 mg	GIST	2-CMT, T5	LIVM, TAF	39–82	LC-MS/MS [NA]	CL: $9.12 \times (1 - 0.000381 \times LIVM)$ Vc: 128 *Q*: 24.9 Vp: 197 Ka: $0.699 \times (1 + 1.18 \times e^{(-0.0256 \times \frac{TAF}{24})})$ Ktr: 15.8 F: $1 + 0.482 \times e^{(-0.0256 \times \frac{TAF}{24})}$	CV%(CL): 49.5% CV%(Vc-Ka): 70.9% CV%(Ktr): 160% CV%(Vp): 65.9%	Log-scale add: 35%

Table 1 (continued)

Study and publication year	Country or region	Number of patients/ samples	Total dose per day	Diagnosis	Imatinib structural model	Covariates included	Age range	Bioassay [LOQ (ng/mL)]	PK parameter and formula	BSV	RUV
Golabchifar et al. (2014)	Iran	61/533	300–800 mg	CML	1-CMT, ZO, LAG	None	17–67	HPLC [62.5]	CL/*F*: 10.8 Vc/*F*: 278 D1: 1.43 Tlag: 0.197	CV%(CL): 30.2% CV%(Vc): 53.5% CV%(D1): 36% CV%(Tlag): 68.3%	Prop: 8.1%
Gotta et al. (2014)	Europe	2478/4095	100–1200 mg	CML	1-CMT, ZO	Sex, Age	18–91	LC-MS/MS [25]	CL/*F*[e]: $17.3 \times (1 + (-0.152 \text{if Female})) \times (1 + (\text{Age} - 40) \times \theta_{\text{Age}})$ Vc: 430 D1: 3.1	CV%(CL): 37.6% CV%(Vc): 50.4% $\rho_{\text{CL-Vc}}$: 0.73 CV%(σ_{Prop}): 36.2%	Prop: 29.2% Add: 82.8 ng/mL
Di Paolo et al. (2014)	Italy	60/117	200, 400, or 600 mg	CML	1-CMT, FO	AGP, hOCT1	27–79	HPLC [25]	CL/*F*[f]: $13.093 \times (0.775 \text{if AGP} > 94 \frac{\text{mg}}{\text{dL}}) \times \theta_{\text{SLC22A1}}$ Vc/*F*: $359.238 \times (0.793 \text{if AGP} > 94 \frac{\text{mg}}{\text{dL}})$ Ka: 1.29	CV%(CL): 19.62%	Prop: 28.98%
Wang et al. (2019)	China	170/229	400 mg	CML	1-CMT, FO	TBW	16–82	UPLC-MS/MS [2.6]	CL/*F*: $9.25 \times (\frac{\text{TBW}}{70})^{0.228}$ Vc/*F*: 222 Ka: 0.329	CV%(CL): 18.2%	Prop: 40.6% Add: 3.137 ng/mL
Shriyan et al. (2022)	India	49/221	400–800 mg	CML	1-CMT, ZO	None	≥18	HPLC [NA]	CL/*F*: 10.2 Vc/*F*: 389 D1: 2.42	CV%(CL): 27.8%	Prop: 21%
Jiang et al. (2023)	China	110/NA	200–600 mg	GIST	1-CMT, FO	RBC, ABCG2	27–79	LC [6.72]	CL/*F*[g]: $9.72 \times (\frac{\text{RBC}}{3.7})^{0.49} \times \theta_{\text{ABCG2}}$ Vc/*F*: 229 Ka: 1.22	CV%(CL): 13.9%	Prop: 29.6%
He et al. (2023)	China	230/424	200, 300, or 400 mg	CML	1-CMT, FO	HG, eGFR	14–87	UPLC-MS [5]	CL/F[h]: $7.6 \times (\frac{\text{HG}}{13})^{0.671} \times \theta_{\text{eGFR}}$ Vc/*F*: 270 Ka: 0.329	CV%(CL): 23.6%	Prop: 18.5%

1-CMT one-compartment model, *2-CMT* two-compartment model, *AGP* plasma α1-acid glycoprotein level (g/L), *ALB* albumin (g/L), *ALL* acute lymphocytic leukemia, *AML* acute myeloid leukemia, *BSV* between-subject variability, *CL* clearance (L/h), *CL/F* apparent clearance (L/h), *CLm/fm* apparent clearance of metabolite N-desmethyl imatinib (L/h), *CML* chronic myeloid leukemia, *CV* coefficient of variation, *D1* duration of zero-order absorption (h), *eGFR* estimated glomerular filtration rate calculated by CKD-EPI equation (mL/min/1.73 m^2), *F* bioavailability, *FO* first-order absorption model, *GIST* gastrointestinal stromal tumors, *HG* hemoglobin (g/dL), *HPLC* high-performance liquid chromatography, *Ka* first-order absorption rate constant (h^{-1}), *Ktr* transit rate constant between the transit compartments (h^{-1}), *LAG* lag time absorption model, *LC* liquid chromatography, *LIVM* volume of liver metastasis (cm^3), *LOQ* limit of quantification, *MS* mass spectrum, *NA* not available, *OCC* , *Ph+* Philadelphia chromosome-positive, *PK* pharmacokinetic, *Q* intercompartmental clearance (L/h), *Qm/fm* apparent intercompartmental clearance of metabolite N-desmethyl imatinib (L/h), *RBC* red blood cell count (10^{12}/L), *RUV* residual unexplained variability, *SNPs* single neucleotide polymorphisms, *STS* soft-tissue sarcoma, *TAF* time from first dose administration (h), *TBW* total body weight (kg), *Tlag* absorption lag time (h), *T5* 5 transit compartment absorption model, *UPLC* ultra-performance liquid chromatography, *Vc* volume of distribution of central compartment (L), *Vc/F* apparent volume of distribution of central compartment (L), *Vp* volume of distribution of peripheral compartment (L), *V_1m/fm* apparent volume of distribution of central compartment of metabolite N-desmethyl imatinib (L), *V_2m/fm* apparent volume of distribution of peripheral compartment of metabolite N-desmethyl imatinib (L), *WBC* white blood cell count (10^9/L), *ZO* zero-order absorption model

[a]The population PK model was described differently on day 1, day 29, and the extension phase. The model on the extension phase was used in this current validation study

[b]Occasion (OCC) with OCC = 0 for day 1 and OCC = 1 (used in this current validation study) for day ≥ 29

[c]This current validation study used the demographic base model for imatinib in Widmer's paper

[d]The paper showed that single nucleotide polymorphisms in *SLCO1B3* and *ABCB1* were associated with imatinib clearance but did not build a covariate model on the population PK model

[e]When Age < 40 the $\theta_{\text{Age}} = 0.00475$, else $\theta_{\text{Age}} = -0.00566$ when Age > 40

[f]When *SLC22A1* CG or GG $\theta_{SLC22A1} = 0.882$, else $\theta_{SLC22A1} = 1$ when *SLC22A1* CC

[g]When *ABCG2* GG $\theta_{ABCG2} = 1$, ABCG2 GT $\theta_{ABCG2} = 0.879$, or ABCG2 TT$\theta_{ABCG2} = 0.976$

[h]When eGFR < 85 the$\theta_{\text{eGFR}} = (\frac{\text{eGFR}}{85})^{0.25}$

Table 2 Summary of patients' demographic information of the external dataset

Characteristics	Number or mean ± SD	Range or percentage
Number of patients	39	-
By (male/female)	26/13	66.7%/33.3%
By (children/adults)[a]	16/23	41%/59%
By (ALL/CML)	18/21	46.2%/53.8%
Number of patients provided imatinib samples	39	-
Have 1 sample	14	35.9%
Have 2 samples	10	25.6%
Have >2 samples	15	38.5%
Number of patients provided N-desmethyl imatinib samples	38	-
Have 1 sample	15	39.5%
Have 2 samples	9	23.7%
Have > 2 samples	14	36.8%
Number of imatinib observations	122	-
By (male/female)	97/25	79.5%/20.5%
By (children/adults)	71/51	58.2%/41.8%
By (ALL/CML)	88/34	72.1%/27.9%
Number of N-desmethyl imatinib observations	100	-
by (male/female)	77/23	77%/23%
by (children/adults)	63/37	63%/37%
by (ALL/CML)	66/34	66%/34%
Weight (kg) Children Adults	59.8 ± 23.7 35.9 ± 14.7 76.5 ± 10.8	9.3–103 9.3–62 55–103
Height (cm) Children Adults	161.3 ± 24.5 142 ± 26.4 175.3 ± 8.7	73–190 73–182 155–190
Age (years) Children Adults	37.6 ± 26.3 10.2 ± 4.2 56.6 ± 16.1	1–75 1–17 19–75
Time after diagnosed (years)	2.33 ± 4.17	0.05–20.95
Dose (mg/day)	± 118.9	100–600

ALL acute lymphoblastic leukemia, *CML* chronic myeloid leukemia, *SD* standard deviation

[a]Children are patients aged ≤ 18 years, and adults are patients aged older than 18 years

had MDAPE ≤ 40%, $F_{20} \geq 30\%$, and F_{30} almost at 40%. In general, the allometric scaling slightly improved the mean statistical error metrics of models (mean MDPE% − 1.43% for allometric scaling models vs − 24.53% for models without; mean MDAPE% 44.71% for allometric scaling models vs 47.03% for models without; mean F_{20} 25% for allometric scaling models vs 21% for models without; mean F_{30} 36% for allometric scaling models vs 32% for models without; the mean of statistical error metrics were calculated for the 13 models, where allometric scaling was performed, i.e., excluding Menon-Andersen et al. and Petain et al. models).

The predictive performance of the metabolite N-desmethyl imatinib model by Menon-Andersen et al. was superior to Petain et al., considering MDPE, MDAPE, F_{20}, F_{30}, and RMSE. However, neither model attained the previously stated requirements.

To evaluate which subgroup of patients influenced the precision of model prediction, the RMSE (Fig. 1) was calculated for different subgroups of patients, i.e., adult versus children and patients with CML versus ALL. Figure 1 shows that the RMSE of the subgroup of children was higher (lower precision performance) than the adult subgroup in all selected models. Based on RMSE, standard allometric scaling improved model prediction for selected models on children but was still not as good as predictions in adults. However, when calculating the relative RMSE, allometric scaling on children's data improved predictions to a level that corresponded to what was seen in the adult population (Fig. S2.2 of the ESM). When dividing patients based on their diagnosis, all models predicted patients with CML with a lower RMSE than patients with ALL (Fig. 1). The metabolite prediction showed a similar trend as imatinib,

Table 3 Summary of prediction-based metrics of selected models

Models	Original model					Allometric scaled model				
	MDPE%	MDAPE%	*F*20	*F*30	RMSE	MDPE%	MDAPE%	*F*20	*F*30	RMSE
Imatinib										
Demetri et al. (2009)	− 13.71[a]	47.36	0.2	0.27	2.63	16.31	50.46	0.16	0.34	2.26
Di Paolo et al. (2014)	− 42.14	48.82	0.24	0.32	2.9	− 22.67	40.62	0.32	0.41	2.61
Eechoute et al. (2012)	− 19.15	45.52	0.2	0.34	2.67	10.9[a]	44.34	0.2	0.34	2.3
Golabchifar et al. (2014)	− 31.6	44.9	0.22	0.34	2.78	− 7.68[a]	39.58	0.32	0.39	2.44
Gotta et al. (2014)	− 46.99	51.14	0.16	0.31	2.98	− 28.37	40.8	0.25	0.39	2.68
He et al. (2023)	6.42[a]	58.4	0.2	0.28	2.54	35	58.61	0.15	0.23	2.17
Jiang et al. (2023)	− 22.29	42.24	0.22	0.31	2.71	1.85[a]	41.95	0.27	0.37	2.36
Judson et al. (2005)	− 34.3	47.51	0.25	0.32	2.79	− 12.65[a]	41.02	0.27	0.39	2.49
Menon-Andersen et al. (2009)	− 28.75	41.06	0.26	0.4	2.66	–	–	–	–	–
Petain et al. (2008)	15.03	53.83	0.21	0.32	2.33	–	–	–	–	–
Schmidli et al. (2005)	− 22.91	37.66	0.22	0.37	2.64	− 8.82[a]	39.7	0.3	0.39	2.46
Shriyan et al. (2022)	− 23.67	44.31	0.2	0.37	2.73	1.24[a]	42.71	0.26	0.39	2.36
Wang et al. (2019)	− 12.65[a]	45.66	0.2	0.35	2.55	10.29[a]	46.88	0.23	0.34	2.28
Widmer et al. (2006)	− 47.32	51.35	0.2	0.31	2.96	− 28.57	38.52	0.25	0.43	2.68
Yamakawa et al. (2011)	− 8.59[a]	46.55	0.21	0.28	2.62	14.58[a]	56.02	0.24	0.3	2.25
Metabolite										
Menon-Andersen et al. (2009)	− 33.2	39.54	0.31	0.42	0.73	–	–	–	–	–
Petain et al. (2008)	− 36.79	59.81	0.17	0.23	0.83	–	–	–	–	–

MDAPE median absolute prediction error, *MDPE* median prediction error, *RMSE* root mean squared error (mg/L), F_{20} *and* F_{30} percentage of prediction error within 20% and 30%, respectively

[a]Indicates the fulfillment of the predefined criterion (MDPE ≤ ± 15%, MDAPE ≤ 30%, $F_{20} \geq 35\%$, and $F_{30} \geq 50\%$)

where adult and CML populations had a better prediction than children and patients with ALL (Fig. S2.3 of the ESM).

3.4 Simulation-Based Evaluation

The virtual patients in the simulation dataset had the same demographic properties as the external dataset. Except for Menon-Andersen et al. and Petain et al., the other original models were developed mainly on adult data. Figure S2.4 of the ESM shows the simulation performance of all selected models on imatinib. The simulation-based evaluation aims to examine whether the published models could capture the true PK variability of our real patients. This relates to the performance of using these models for model-informed precision dosing. The model by Eechoute et al. with allometric scaling (Fig. 2) captured most of the observations and performed better than the other models. The 90% prediction interval (PI, range between the 5th and 95th percentiles) of this model captured around 85% of the entire observations and around 90% of adult observations (Fig. S2.5 of the ESM). For most of the models, the standard allometric scaling provided more variability and made their 90% PI capture more observations than the original models. This improvement is more significant in the children (Fig. S2.5 of the ESM). Regardless of allometric scaling, most of the observation points outside the 5th–95th percentile range for all selected models were from children, especially in the lower dose group where most patients were children. This is also the case for the model by Menon-Andersen et al. and Petain et al., although children and weight scaling were included in their original models. A similar trend was also observed in the two metabolite (N-desmethyl imatinib) models (Figs. S2.6 and S2.7 of the ESM), i.e., that they did not capture 90% of the observations in their 90% PI and most of the observations of metabolite outside the PI were from children.

3.5 Bayesian Forecasting Evaluation

The Bayesian forecasting performance was evaluated on a subset of the dataset with 25 patients (12 children and 13 adults) with at least two TDM occasions. Bayesian forecasting is the key procedure when using pop-PK models for model-informed precision dosing, and this evaluation aims to examine the performance of these models when individualizing the dose in the clinic. The box plots of IPE distribution are shown in Fig. 3. For adults, with one more prior imatinib information, the individual prediction was improved (median of IPE closer to zero), and the variability of IPE was decreased in most of the selected models, especially in the models by Golabchifar et al.,

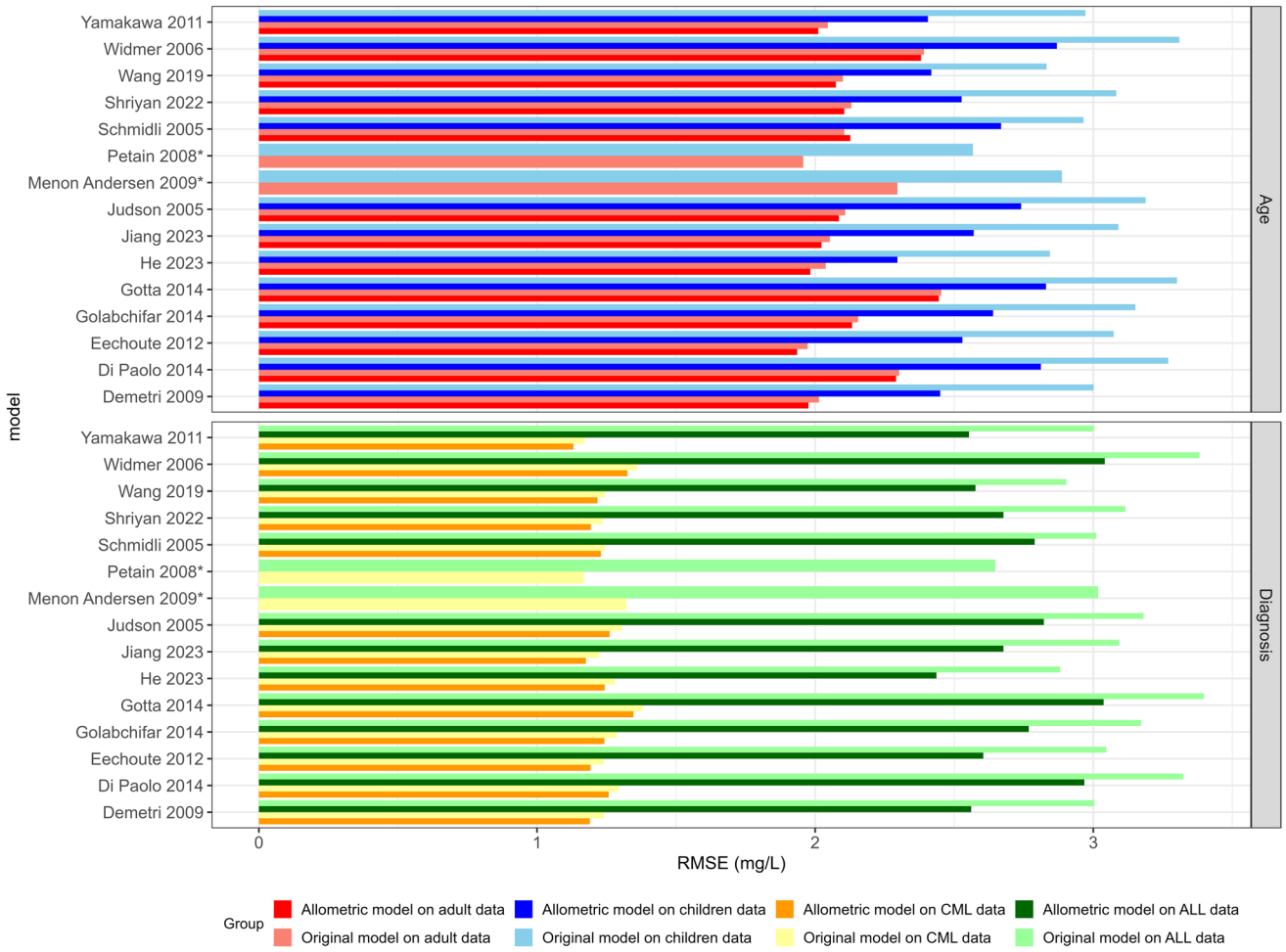

Fig. 1 Root mean squared error (RMSE) of selected models with different subgroups of patients. The upper subplot divided subgroups of patients based on children (≤ 18 years of age) or adults (> 18 years of age). The lower subplot divided patients into subgroups based on their chronic myeloid leukemia (CML) or acute lymphocytic leukemia (ALL) diagnosis. Standard allometric scaling was not tried on the models with a star (*) as they were developed on a population also containing children and used scaling in the original model. The unit of RMSE is mg/L and lower RMSE means better prediction

Gotta et al., and Widmer et al. For children, when no prior imatinib information was available, the model with allometric scaling showed better prediction than the original model for all the models except He et al. However, the median of IPE for the original model on children was closer to zero when one prior imatinib sample was available, especially in the models by Golabchifar et al., Schmidli et al., and Yamakawa et al. All selected models showed a larger variability of IPE in children after one occasion was included.

4 Discussion

Recent studies have increasingly focused on using pop-PK models to optimize dose selection in TDM. These models are employed in TDM to optimize drug therapy, ensuring that patients receive the appropriate dose to achieve therapeutic efficacy while minimizing adverse effects, which is particularly important for drugs with narrow therapeutic windows (e.g., tacrolimus [51], vancomycin [52]) and significant PK variability (e.g., imatinib, methotrexate [53]). However, most of these pop-PK studies are single center based or conducted in a small group of patients with specific population demographics. Thus, external validation of these models is essential to ensure their predictive accuracy and precision in another population before implementing them in a daily clinical setting. This is to our knowledge the

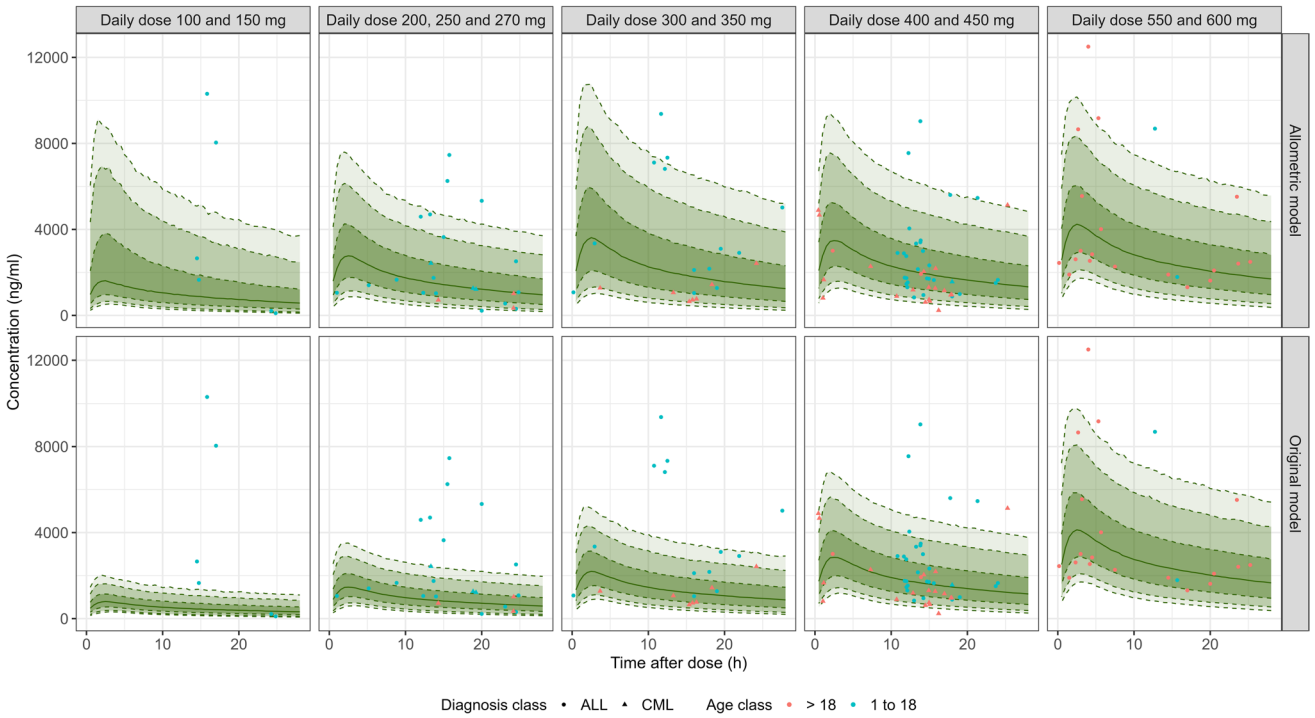

Fig. 2 Simulation-based visual predictive check plots of an external evaluation dataset for imatinib prediction through models by Eechoute et al. Patients were stratified on their daily imatinib dose. For simplicity doses within intervals of 50–70 mg were combined, for example, 100 mg and 150 mg were one group. The dotted lines are the 5th, 10th, 25th, 75th, 90th, and 95th percentile at each timepoint of the simulated data and the solid lines are the median. Blue marks are children (≤ 18 years of age), red marks are adults (> 18 years of age), circles are patients with acute lymphocytic leukemia (ALL), and triangles are patients with chronic myeloid leukemia (CML). *h* hours

first systematic study to evaluate published imatinib pop-PK models in an external dataset containing children's data.

In the last 20 years, more than 15 pop-PK studies of imatinib have been conducted. These studies were mostly based on data from adult patients with CML or GIST and very few included data from children. This highlights the limited PK research conducted on the pediatric population in treatment with imatinib; however, the lack of pediatric data is also an issue for many other drugs. The limited number of pediatric patients with Ph+ leukemia receiving imatinib makes it difficult to accumulate data for a pop-PK study in this population. Moreover, blood sampling in children, especially younger (toddlers and preschool) children, is another challenge for performing a PK study. Therefore, collaborations between multiple hospitals and countries may be necessary to gather PK sample data in this special population [21]. Our review found that no model focused on investigating the PK profile of imatinib in patients with ALL. Although there is no physiological reason for ALL to have a different PK profile from patients with CML, patients with ALL usually receive multiple anti-cancer agents and supportive care drugs that may affect the PK profile of imatinib [2]. Of the investigated models in our study, only the model by Menon-Andersen et al. [40] and Widmer et al. [39] included patients with ALL in their modeling population, the former only a few children with ALL and the latter only one adult with ALL. The data in the Menon-Andersen study were based on a clinical trial, and drugs that may affect imatinib pharmacokinetics were avoided [40]. Future studies are needed to focus more on the imatinib PK profile in patients with ALL and investigate whether there are potential drug interactions in this specific population. Moreover, unlike adult patients with CML, the relationship between imatinib plasma concentration and response for pediatric patients and patients with ALL of any age is still unclear [2].

The level of α1-acid glycoprotein (AGP) is frequently identified as a covariate in published imatinib models. Imatinib shows a high protein binding to AGP, and the impact of AGP in imatinib pharmacokinetics has been reported [39]. An increased level of AGP may reduce the unbound fraction of imatinib leading to a decrease in total clearance [35]. A previous study [54] showed a better prediction performance in pop-PK models with the AGP covariate model than without. Other covariates such as albumin, white blood cell count, and hemoglobin are included in some selected models. The relationship between them and imatinib pharmacokinetics is unclear but may be related to their correlation with patient health status and disease progression [9, 39]. The polymorphisms in *SLC22A1* and *ABCG2* are pharmacogenetic covariates found in some

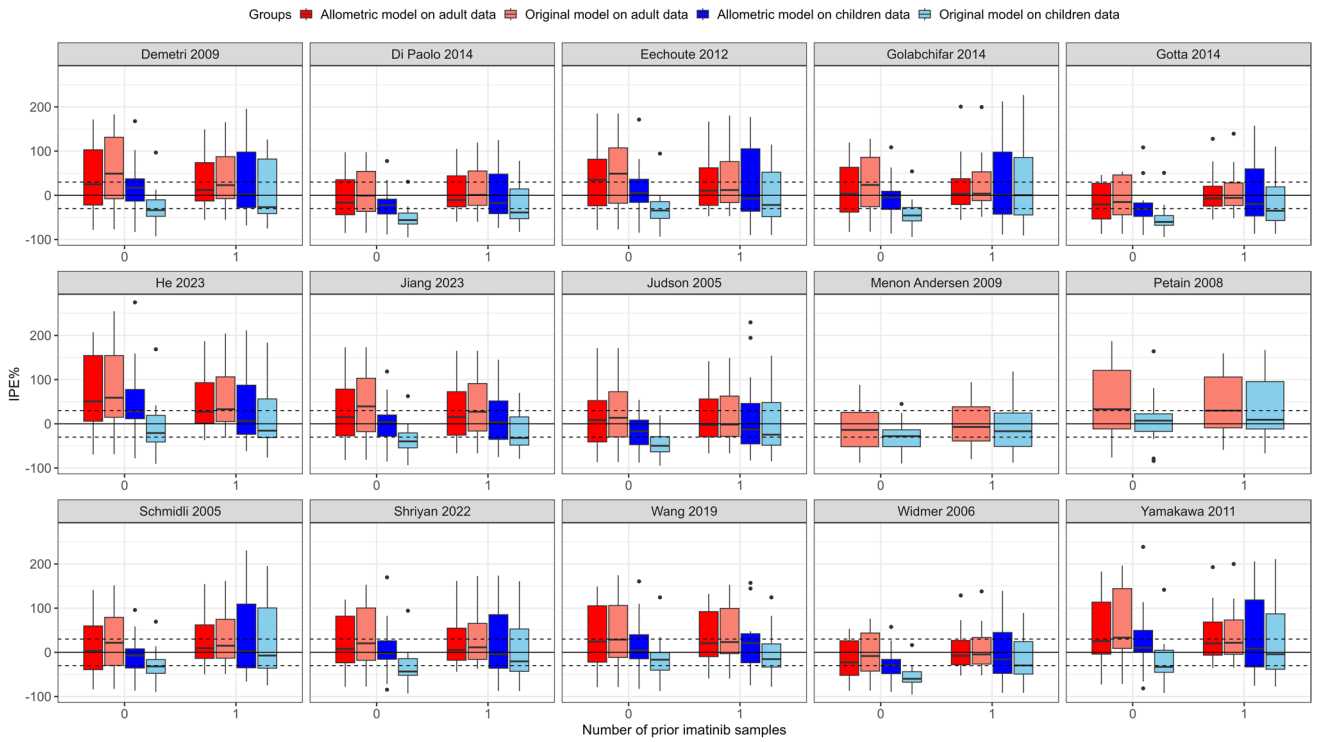

Fig. 3 Box plots of individual prediction error (IPE) for selected models in different scenarios (0 represents predictions without prior imatinib samples, and 1 represents with one prior imatinib sample concentration, respectively). Solid black horizontal lines, unbiased perfect prediction (IPE% = 0); dashed horizontal lines, IPE equal to ± 30% (acceptable bias)

models [42, 48]. The study by Yamakawa et al. found that individual estimated clearance was significantly affected by the polymorphism in the genes *SLCO1B3* and *ABCB1* [46]. However, they did not test them as covariates in their pop-PK model. The polymorphism of these transporters and CYP system enzymes for which imatinib is a substrate might in principle contribute to the PK variability of imatinib. However, several studies, for example [45, 49] tested a group of pharmacogenetic covariates, but found no significant covariates. Thus, further studies investigating the relationship between pharmacogenetics and the pharmacokinetics and pharmacodynamics of imatinib are needed.

Our results showed that none of the original pop-PK models fully met the predefined criteria for satisfactory predictive performance (MDPE ≤ ± 15%, MDAPE ≤ 30%, $F_{20} \geq 35\%$, and $F_{30} \geq 50\%$) across the entire external dataset, which included both adults and children. After applying standard allometric scaling to adjust for body size differences between adults and children, some models demonstrated improved predictive performance in both prediction- and simulation-based diagnostics. Some models showed an acceptable bias (indicated by MDPE), where the best-performing models with allometric scaling could achieve an MDPE of < 2% [48, 49]. However, none of these models showed an acceptable MDAPE% and RMSE, which means these predictions may not be precise enough, and the prediction performance may be highly varied in real clinical settings. Additionally, none of the models achieved the critical F30 value of 50%. The best-performed models could achieve an F30 of around 40%, which means around 60% of predicted concentrations are over ± 30% biased from the true value, and therefore would lead to a high possibility of dosing outside the therapeutic range. Models developed in populations similar to the evaluation dataset are expected to have better predictive performance because of comparable racial backgrounds. However, in our study, no model (including both models developed based on European or Asian populations) showed satisfactory predictive performance on our data even with allometric scaling. This finding underscores the complexity of accurately predicting imatinib pharmacokinetics across different patient demographics.

The Bayesian analysis with one prior sample could improve model prediction, especially in adults. Although no models showed satisfactory results in prediction- and simulation-based diagnostics, the model by Gotta et al. [43] and Widmer et al. [39] showed an acceptable IPE when combined with one TDM sample and used in the adult population. This indicates that these two models might have the potential to predict individual imatinib concentrations for

adults when one TDM sample is available in clinical settings. In contrast, the improvement by one prior sample was minor in children. All diagnostics indicated that the models predicted worse in children and patients with ALL than in adults and patients with CML, respectively. However, the lower predictive performance in pediatric patients might be due to the inherent bias in our dataset, as most of the children were diagnosed with ALL and only two with CML while adults were primarily diagnosed with CML. This is consistent with the fact that pediatric CML constitutes only 3% of all pediatric leukemia while ALL is the most common childhood cancer [2]. With the general lack of clinical studies performed in pediatric patients, it is not surprising that most studies on imatinib are conducted in adult patients with CML. As aforementioned, the comedication usually used in patients with ALL may affect imatinib pharmacokinetics. The patients with ALL in our data also received chemotherapy and supportive drugs according to the clinical protocol, which is a limitation of this study. We presume that the low prediction performance may be attributable to pediatric patients as allometric scaling improved the prediction of ALL populations in our dataset (Fig. 1) and it is unlikely that allometric scaling will improve the low prediction precision because of comedication. Additionally, several selected models test comedications (including CYP3A4 inducers and inhibitors) as covariates when modeling, but no clinically significant covariates were found (Table S1.3 of the ESM). However, further study needs to be done.

Previous studies [54, 55] found acceptable models for their external population. This might be because their external populations were all adults with CML. Furthermore, all patients in the study by Corral Alaejos et al. received the standard dose of 400 mg. In contrast, the patients in our external data set received multiple different doses (see Sect. 3.1). The more similarity between the populations used for model development and external evaluation, the more robustness will be found for model predictions. The models by Menon-Andersen et al. [40] and Petain et al. [34] showed the highest similarity with the population in our dataset as they also included pediatric data. However, the 33 children included in the study by Petain et al. had solid malignancies and in the study by Menon-Andersen et al. only seven children below the age of 12 years but above 6 years had Ph+ leukemia [34, 40]. Thus, there are very limited data on imatinib in the pediatric population with Ph+ leukemia and no data on children under 6 years of age. Furthermore, the models from the two studies did not perform well in predicting either imatinib or the metabolite plasma concentrations using our external data set. This may be because of the high variability and complexity of pharmacokinetics in pediatrics, resulting from the physiological and anatomical changes that occur during childhood [20]. Age-related changes in the gastrointestinal environment, body composition (such as body water and fat), plasma protein levels, the expression of enzymes and transporters, and maturation of the liver and kidney may all contribute to PK variability in children [20, 56]. This highlights the need for more PK studies of imatinib in pediatric populations and preferably with separate models for different pediatric age groups. There is a special need for studies in the younger age groups, where we currently have no data and where it is known that maturation of metabolic pathways and kidney function affects the pharmacokinetics.

One limitation of this study is that it relied on retrospectively collected, routine imatinib TDM data and missed information on some covariates (e.g., AGP, hemoglobin, genetic information) included in seven published pop-PK models [9, 34, 38, 41, 42, 47, 48]. Their poor prediction performance may be due to the bias when inputting key covariates using typical values. For example, missing AGP information in the external dataset may affect the performance of the model by Petain et al. and Di Paolo et al., as a previous study suggested AGP might improve the model prediction when reusing imatinib models in an external dataset [54]. Ignoring inter-occasion variability may lead to overestimating shrinkage and compromising the accuracy of empirical Bayes estimates [57]. However, like this study, it remains a challenge to incorporate inter-occasion variability when using a previously published model, as the defined occasions in these models do not apply to the new dataset. Moreover, patient compliance in this study could not be ascertained. Studies showed that less adherence to routine medication is a clinical challenge to imatinib treatment, especially in adolescents and young adults [2]. A small number of patients ($N = 39$) and observations for imatinib ($N = 122$) and its metabolite ($N = 100$) might also limit the robustness of the current results. Finally, all subjects were from Nordic and Baltic countries, and the impact of population, region, or race could not be determined.

5 Conclusions

Previously published pop-PK models for imatinib were systematically reviewed and only two models were found that included children. Their external predictive performance was evaluated using a dataset containing both children and adults from Nordic and Baltic centers. The standard allometric scaling was used and evaluated for models developed on data from only an adult population. Although allometric scaling improved the model prediction in children, none of the 15 models fulfilled all predefined criteria satisfactorily. However, the maximum a posteriori method improved the model prediction in adults. All selected models showed a lower prediction performance in children than in adults based on all diagnostics. These results indicate that further

PK research still needs to be done, especially in the pediatric population.

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Declarations

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Conflicts of interest/competing interests Tianwu Yang, Anna Sofie Buhl Rasmussen, Allan Weimann, Maria Thastrup, Cecilie Utke Rank, Bodil Als-Nielsen, Johan Malmros, Hilde Skuterud Wik, Olli Lohi, Overgaard, Inga Maria Rinvoll Johannsdottir, Goda Vaitkeviciene, Kim Dalhoff, Kjeld Schmiegelow, and Trine Meldgaard Lund have no conflicts of interest that are directly relevant to the content of this article.

Ethics approval This study has received approval from the local ethics committee. All procedures involving human subjects were performed following the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Consent to participate All participants provided written informed consent.

Consent for publication Not applicable.

Availability of data and material The data of this study are available from the corresponding author upon reasonable request.

Code availability Not applicable.

Authors' contributions TY: conceptualization; data curation; formal analysis; investigation; methodology; software; validation; visualization; writing (original draft); writing (review and editing). ASBR: conceptualization; data curation; investigation; resources; writing (review and editing). AW and MT: data curation; resources; writing (review and editing). CUR, BA-N, JM, HSW, OL, UO, IMRJ, and KD: resources; writing (review and editing). KS: funding acquisition; project administration; resources; supervision; writing (review and editing). TML: conceptualization; funding acquisition; project administration; resources; supervision; writing (review and editing).

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