Online Resource - Supplementary material 1

Targeted oncology

Published population pharmacokinetic models of imatinib perform poorly on TDM data from pediatric patients

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Supplementary information 1

Table S1.1. The search term used for systematic review

Number	Search term
1	“Population pharmacokinetic” OR “Population pharmacokinetics” OR pharmacometrics OR “pharmacokinetic model” OR “population model” OR popPK OR PPK OR “nonlinear mixed effect model” OR NONMEM OR NLME OR “mixed effect” OR “WinNonlin” OR “Monolix” OR “Quantitative pharmacology”
2	Pharmacokinetics OR Pharmacokinetic OR PK
3	imatinib OR "Gleevec" OR Imatinib Mesylate[Mesh]
4	“Pharmacokinetic-pharmacodynamic model” OR “Pharmacokinetic and pharmacodynamic model” OR “PK-PD model” OR “Pharmacokinetic/pharmacodynamic model” OR “PK/PD model” OR “PKPD model” OR “population PKPD”
Final search	(#1 OR #2 OR #4) AND #3 (1003 results was found)

Table S1.2. The external dataset was collected from the following hospitals' daily TDM routines at the Hematology and Pediatric departments.

Hospitals
Rigshospitalet, Copenhagen
Odense
Aarhus
Oslo
Umeå
Linköping
Trondheim
Tampere
Aalborg
Helsinki
Skåne
Vilnius

Figure S1.1. Flow chart of the patient collection process

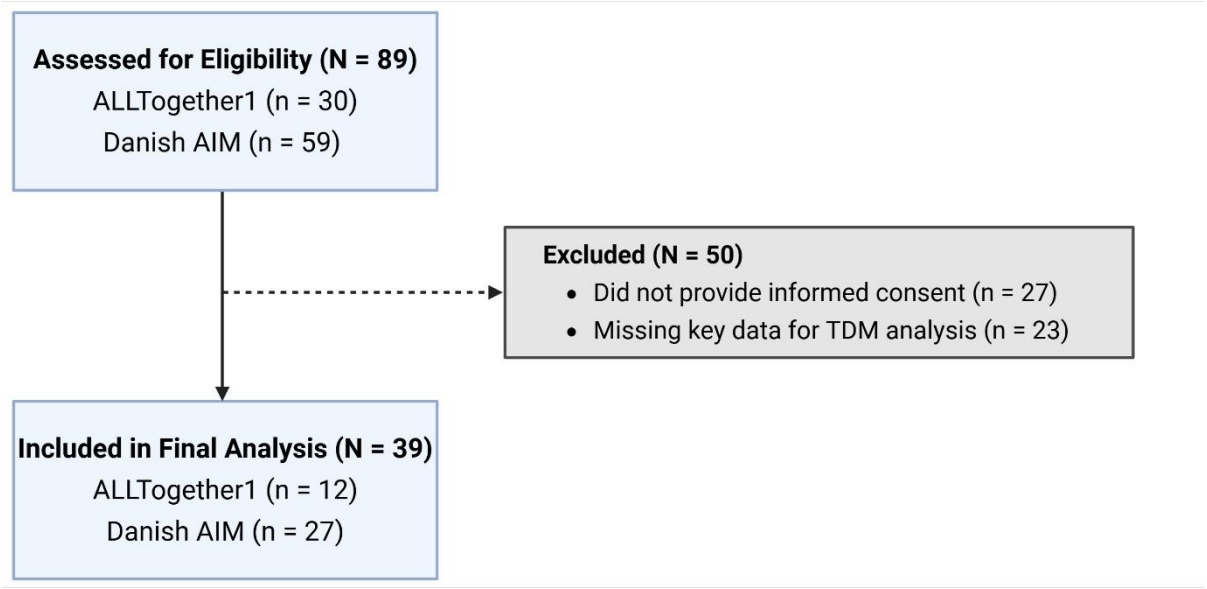
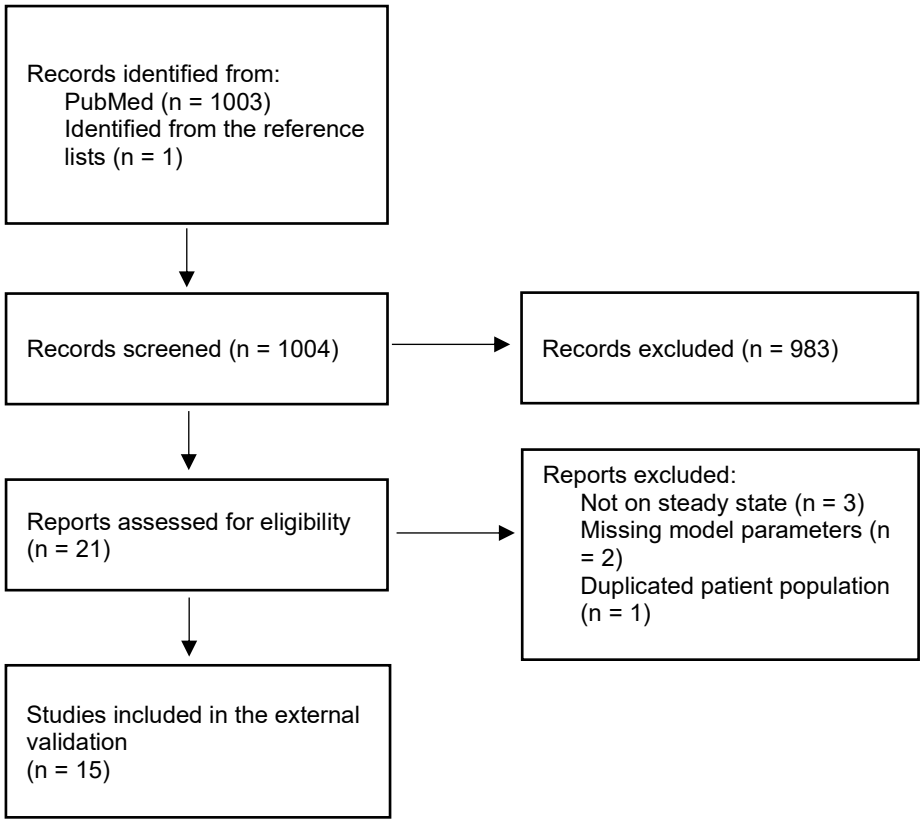


Figure S1.2. Screen process of population pharmacokinetic models



More information about the selected published models

Table S1.3.

Studies	Liver Function	Renal Function	Concomitant medication information	Pharmacogenetic-related covariates tested [included in the final model]	Other information about the patient and sample
Judson et al. (2005)	NA	Creatinine (μmol/L): <80 (N = 12), 80-100 (N = 16), >100 (N = 14)	The use of potential cytochrome P450-interactive drugs was restricted, and major interactions were not expected by the authors.	None	Patients with GIST or STS were from a phase I or a phase II trial. Samples were taken on day 1 and day 29. Some samples were after 12 months
Schmidli et al. (2005)	AST (U/L) median (range): 22 (5 - 65) on day 1 and 21 (7 – 100) on day 29, ALT (U/L) median (range): 21 (3 – 105) on day 1 and 19.2 (3 – 166) on day 29, Total bilirubin (μmol/L) median (range): 8.6 (1.7 – 49.6) on day 1 and 8.6 (1.7 – 39.3) on day 29	Creatine clearance (mL/min) median (range): 103.6 (48.2 – 270) on day 1 and 98.6 (45.2 – 300.4) on day 29	Comedication was investigated (group by different classes), but no clinically relevant differences were observed. It must be stressed that this study is not designed to investigate drug-drug interactions.	None	Patients were from the phase III trial of the International Randomized Study of Interferon and STI571 (IRIS) for the treatment of newly diagnosed chronic phase CML. Samples were taken on day 1 and day 29.
Widmer et al. (2006)	NA	NA	Comedication was investigated (grouped by different classes), but no clinically relevant differences were observed. It must be stressed that this study is not designed to investigate drug-drug interactions.	*ABCB1* genotype, CYP3A4 activity	Patient data were collected over 3 years, including 38 patients with GIST, 20 with CML, and one with ALL. All patients were pooled in the analysis, regardless of their medical history. All samples were collected under steady-state conditions. (Here defined as after unchanged dosage for at least 1 month).
Petain et al. (2008)	Total bilirubin level < 1.5 × the upper limit of normal, AST and ALT < 2.5 × the upper limit of normal (or < 5× if has hepatic metastases or disease)	Serum creatine value < 1.5 × the upper limit of normal	No concomitant anticancer or investigational drug in children.	Genotypes of: *ABCB1, ABCG2, CYP3A4, CYP3A5, AGP1*	Adult patients (n = 34) with metastatic and/or unresectable malignant gastrointestinal stromal tumors were from a Phase III trial, conducted by the French Sarcoma Group BFR 14. Children, adolescents, and young adult patients (ages <21 years; n = 33) with malignant solid tumors were from an open-label, exploratory phase II study (CSTI 571BFR10) of the Innovative Therapies with Children with Cancer European consortium. Samples were taken on day 1, day 30 and day 60.
Demetri et al. (2009)	Adequate hepatic, renal, and cardiac function was one of the inclusion criteria	Adequate hepatic, renal, and cardiac function was one of the inclusion criteria	Patients could receive prior chemotherapeutic regimens, but the last dose must be administered at least four weeks before entering the study.	None	Patients with unresectable or metastatic CD117-positive GIST from a phase II trial. Samples were taken on day 1 and day 29.
Menon-Andersen et al. (2009)	Adequate hepatic function	Adequate renal function	Concomitant medications that significantly affect the pharmacokinetics of imatinib were avoided	None	One part of patients (age 7 – 24, N = 26) with Ph+ leukemia were from a phase I trial, while another part of patients (age 6 – 22, N = 15) with refractory or relapsed solid tumors were from a phase II trial. The former phase I trial contained 31 patients with recurrent or refractory Ph+ leukemia (CML, ALL, AML(N=1)), and then data from 26 patients were used in this popPK model. Samples were both taken on day 1 and day 8.
Yamakawa et al. (2011)	AST (U/L) median (range): 22 (9 - 61), ALT (U/L) median (range): 18 (7 - 220)	Creatinine clearance (mL/min) median (range): 83 (24 - 133)	Concomitant medication was recorded, and medications such as ketoconazole or acetaminophen, which may affect the pharmacokinetics of imatinib, were not administered.	Association of genetic polymorphisms in (*SLC22A1, SLCO1B1, SLCO1B3, ABCB1, ABCG2, CYP2C9, CYP2C19, CYP2D6, and CYP3A5*) with individual clearance were evaluated. However, they do not test these genotypes as a potential covariate model.	This study includes 34 Japanese patients, including 32 chronic phase CML and 2 accelerated phase CML Samples were collected at the steady state (day ≥ 30 of imatinib treatment)
Eechoute et al. (2012)	AST (U/L) median (range): 24 (12 - 145), ALT (U/L) median (range): 22 (5 - 274), Total bilirubin (μmol/L): 9 (3 - 39),	NA	Patients took no medications that showed major interactions with CYP3A4 and CYP3A5.	None	Patients with histologically confirmed GIST were from a randomized controlled trial at two Dutch and two Italian medical centers. Samples were collected on day 1 and after 1, 6, and 12 months.

	26 patients had evaluable liver metastases				
Golabchifar et al. (2014)	NA	NA	Patients received imatinib as monotherapy	None	Outpatients with CML in the chronic phase were involved in this study. Blood samples were collected at a steady state, here defined as after unchanged dosage and schedule of administration for at least one month.
Gotta et al. (2014)	NA	NA	Comedication was investigated (grouped by different classes) but was insignificant when evaluated as a covariate model.	None	Data was collected from 2478 adult European patients (4095 samples) between 2006 and 2010. The samples included patients in the chronic phase (N = 2819), accelerated phase (N = 82), and some unreported (N = 1194). Samples were collected at the steady state.
Di Paolo et al. (2014)	NA	Creatinine clearance (mL/min) mean ± SD: 86.8 ± 30.2	Comedication was allowed and recorded.	Polymorphisms in genes *SLC22A1, ABCB1, ABCG2 [SLC22A1 included in the final model]*	Patients with CML in this study were enrolled up to July 2012. The median time interval between diagnosis and enrollment was 64 months (range 3 – 176 months).
Wang et al. (2019)	NA	NA	Patients taking comedications that significantly affect imatinib pharmacokinetics, such as ketoconazole and phenytoin, were excluded.	Polymorphisms in genes *SLC22A4, SLC22A5, SLCO1A2, SLCO1B3, ABCG2*	Patients with CML were enrolled in this study from June 2016 to July 2017. The patients were in the chronic phase (N = 169) and accelerated phase (N = 1). Samples were taken at steady state (≥ 7 days of imatinib treatment).
Shriyan et al. (2022)	AST (U/L) mean ± SD: 31.93 ± 10.01 ALT (U/L) mean ± SD: 37.67 ± 15.73	Creatinine (mg/dL) mean ± SD: 1.09 ± 0.19	Patients taking any cytochrome inhibitor or inducer 14 days before the sampling were excluded.	Polymorphisms in genes *CYP3A4, ABCB1, ABCG2*	The adult CML patients were required to have strict adherence to imatinib for one month before being enrolled. The final popPK model is based on steady-state data.
Jiang et al. (2023)	AST (U/L) mean (range): 23.9 (11 – 724.8) ALT (U/L) mean (range): 16.9 (2 – 645)	Creatinine clearance rate (mL/min) mean (range): 69.7 (28.5 – 118.8)	NA	Polymorphisms in gene *CYP1A2, SLC22A1, SLCO1A2, ABCG2*	Patients included were surgery-treated GIST patients from March 2021 to June 2022. Samples were taken at a steady state (treatment with imatinib ≥ 30 days)
He et al. (2023)	AST (U/L) mean ± SD (range): 23 ± 6.19 (7 – 66) ALT (U/L) mean ± SD (range): 20 ± 10.8 (3 – 95) Total bilirubin (μmol/L) mean ± SD (range): 11.9 ± 3.66 (4.05 – 26)	Creatinine clearance (mL/min) mean ± SD (range): 88.4 ± 26.6 (23 – 173) eGFR (mL/min/1.73m^2) mean ± SD (range): 85.1 ± 20.3 (22 – 130)	Concomitant medications that significantly affect imatinib's pharmacokinetics were set as an exclusion criterion. However, four patients took weak CYP3A4 inhibitors, 33 patients had comedications that did not affect imatinib pharmacokinetics, and 193 patients comedications information was unavailable.	Polymorphisms in gene *CYP3A4, CYP3A5, ABCB1, ABCG2, SLC22A1, POR*	Data from patients diagnosed with CML and undergoing TDM from January 2021 to March 2021 were collected. The patients were in the chronic phase (N = 196), accelerated phase (N = 12), blast phase (N = 1), and unrecorded (N = 21). Samples were taken at a steady state.

ALL, Acute lymphocytic leukemia; ALT, Alanine transaminase; AST, Aspartate aminotransferase; CML, Chronic myeloid leukemia; GIST, Gastrointestinal stromal tumor; STS, Soft tissue sarcoma; TDM, Therapeutic drug monitoring.