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Model-Informed Precision Dosing Strategy for Sitagliptin and Duloxetine in Hepatic Cirrhosis: An Interventional Pilot Study

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Abstract

Purpose Liver cirrhosis can change antidiabetic and analgesic drug pharmacokinetics, mandating the need for dose modifications. Physiologically based pharmacokinetic PBPK modeling helps expect these pharmacokinetic alterations in cirrhotic patients and estimate dosage across various degrees of cirrhosis severities with subsequent evaluation of the recommended doses.

Methods PBPK models were first validated in healthy participants and then adapted to incorporate cirrhosis-related pathophysiological changes. Pharmacokinetic parameters such as area under the plasma concentration-time curve (AUC) and plasma maximum concentration (C_{max}) were predicted and compared with observed data. Dose adjustments were calculated to achieve unbound drug exposures comparable to those seen in healthy volunteers, and recommendations were made across Child–Pugh (CP) classes A, B, and C. Clinical evaluation was performed to assess the effectiveness and safety of PBPK-guided dosing.

Results Predicted AUC and C_{max} values showed good agreement with observed data (within 2-fold). The models were also used to predict unbound plasma AUC across various disease stages and to evaluate change in the dosing for untested cirrhotic populations. The latter results have been compared with the healthy population. The model-informed dose adjustment reduced duloxetine to 48.8%, 24.3%, and 11.6% and sitagliptin to 83.3%,71.4%, and 62.5% of their standard doses across CP classes A, B, and C, respectively. Clinical evaluation confirmed that PBPK-guided dosing improved glycemic control and pain reduction while maintaining safety across cirrhosis severities.

Conclusion Duloxetine kinetics are significantly affected by hepatic impairment, whereas sitagliptin shows modest pharmacokinetic changes. Integrating PBPK modeling with clinical evaluation provides reliable, evidence-based guidance for dose optimization of these drugs in cirrhotic patients.

Clinical Trial Registration

ClinicalTrials.gov (Identifier: NCT07439536), registered retrospectively on 17 February 2026.

Key words
PBPK, Sitagliptin, Duloxetine, Diabetes, Peripheral neuropathy, Cirrhosis

Introduction

Liver cirrhosis (LC) is a widespread disease marked by the development of fibrous tissue that replaces healthy functional liver tissue with regenerative liver nodules [1]. The majority of absorption, distribution, and elimination kinetics of drugs depend fundamentally on the liver[2]. Therefore, in some cirrhotic patients, the drug bioavailability might significantly increase due to a marked alteration in hepatic clearance [3]. Hepatic blood flow interferes with high hepatic extraction drugs.[3] However, cytochrome P450 (CYP450) activity, which is also decreased in cirrhosis patients, has an impact on low hepatic extraction drugs[2, 4, 5]. In addition to reduced hepatic metabolism and biliary clearance capacity, liver dysfunction is associated with altered synthesis of drug binding proteins, leading to increasing the unbound drug concentration, particularly for highly plasma-binding medication [2]. Consequently, dose adjustment is often required in cirrhotic to prevent excessive drug accumulation and toxicity[4].

The physiologically based pharmacokinetic (PBPK) modelling and simulations strategy , with its inherent capacity to reflect the pathophysiological alterations occurring in LC, is an extremely valuable tool when clinical evidence is lacking [6, 7]. In several disease populations, including cirrhosis, it can be used to assess changes in medication pharmacokinetics [8]. This PBPK method predicts how the pharmacokinetics of drugs will alter in response to changes in disease by combining drug-related factors with population-specific parameters (related to body physiology)[9]. As a result, it enables estimation of optimal dosing for patients with LC using healthy volunteers' dose as a reference[10]. The modified PBPK model accounts for alterations in cirrhosis-related pathophysiology based on disease severity classified by Child-Pugh (CP) classification (CP grades A, mild, B, moderate, and C, severe)[9]. Many commercial and open-access programs are used for PBPK modeling and simulations; one of the most commonly utilized in government, business, and academia is the Simcyp® simulator[11].

Diabetes mellitus (DM) and liver cirrhosis frequently coexist and share a complex bidirectional association[12]. Patients with liver cirrhosis typically have peripheral hyperinsulinemia, which can reduce the number of insulin receptors in muscle tissues leading to insulin resistance[13]. More than 80% of LC patients have glucose intolerance, while approximately 30% of them have type 2 diabetes[13, 14]. In hepatic impairment patients, the administration of antihyperglycemic medications that are extensively metabolized by liver may be clinically challenging[15]. Sitagliptin, a highly selective inhibitor of dipeptidyl peptidase-4 (DPP-4), is predominantly eliminated via renal excretion in its unchanged form, with only a minor contribution from hepatic metabolism mainly via cytochrome P450 (CYP3A4), and CYP2C8 to a lesser extent[16, 17]. Despite the low hepatic metabolism of sitagliptin, the effect of cirrhosis on sitagliptin pharmacokinetics requires verification as the available studies were limited, controversial, and are absent for severe hepatic impairment.

Diabetic nephropathy (DNP) is a common complication of diabetes and a major cause of chronic neuropathic pain. Duloxetine have received regulatory approval for diabetic neuropathic pain in multiple countries[18]. Duloxetine undergoes extensive metabolism primarily via cytochrome P450 (CYP) isozymes 1A2 and 2D6 to a lesser extent[19, 20]. Therefore, LC may significantly reduce duloxetine clearance and lead to increased systemic exposure[20]. therefore, the identification of relevant comorbidities such as LC that might require dosage modifications or additional monitoring of therapy, is required [21]. Consequently, patients with liver cirrhosis may experience substantial increases in duloxetine exposure, and preliminary studies suggest the need for dose reduction in moderate hepatic impairment[22].

Despite the availability of pharmacokinetic data derived from healthy populations **(Tables 1)**, optimal dosing recommendations for sitagliptin and duloxetine in liver cirrhotic patients across varying stages of disease remain poorly defined. Due to the scarcity of clinical trials in hepatic impairment patients, many of these medications are labeled as "use with caution" or "not recommended," resulting in restricted evidence-based therapeutic options for this vulnerable population. From a clinical perspective, the pharmacokinetic of drugs such as sitagliptin and duloxetine have not been adequately studied in varying degrees of cirrhosis severity. In this context, robust PBPK models offers a valuable tool to fill these gaps by enabling dose optimization for cirrhotic patients.

In order to verify PBPK-based dosing recommendations, a pilot clinical trial was conducted in this trial to investigate the efficacy, and safety of the proposed optimized doses of sitagliptin and duloxetine in patients with varying stages of liver cirrhosis. Accordingly, this study aimed to integrate PBPK modeling with clinical evaluation to validate dose optimization of sitagliptin and duloxetine across different stages of LC.

Methods

Validation of PBPK model for sitagliptin and duloxetine

Model Structure

The PBPK model for duloxetine was available in Simcyp® from the library of Simcyp® simulator (version 22, Certara, Sheffield, UK). While the model of sitagliptin was previously developed by Hsueh, C. H et al [23]. Furthermore, Drug-specific parameters for the two drugs are reported in Supporting information (**Tables S1 and S2)**.

The sitagliptin and duloxetine absorption was described with the first-order absorption model [24]. Developed sitagliptin model employed full PBPK distribution model, while the model for duloxetine utilized a minimal PBPK

strategy. The method 2 (Rodger's et al. method) was used to predict the steady state volume of distribution (Vss) [25, 26]. The predicted value of duloxetine and sitagliptin Vss was 3.19 and 2.27 L/kg respectively [27].

For these drugs, the prediction of hepatic clearance was employed via the well stirred liver model according to Eq (1) [28].

$$CL_H = \frac{Q_H \times fu_B \times CL_{u,H,int}}{Q_H + fu_B \times CL_{u,H,int}} \ldots\ldots\ldots\ldots\ldots\ldots\ldots (1)$$

Where Q_H indicates the hepatic blood flow, fu_B indicates the unbound fraction of the drug in blood, and $CL_{u,H,int}$ indicates the unbound intrinsic hepatic clearance.

Modeling approach, simulation condition and drug specific parameters.

Regarding sitagliptin and duloxetine, simulations for healthy volunteers' population were conducted, and the results were evaluated in comparison with the available clinically observed data. After confirming that the model could be utilized for predicting the exposure of each drug to the healthy volunteers, the model was extended to estimate the drug exposure in cirrhosis CP-A, CP-B, and CP-C groups. Following the selection of the cirrhosis population, plenty of physiological changes linked to cirrhosis at varying stages of disease severity that may impact drug kinetics were taken into consideration, as presented in **(Table S5).** The study flowchart work is shown in (**Fig. 1).**

In the context of the number of individuals, percentage of females, age, weight, and medication dosage regimens, all simulations were conducted using the study design used in the clinical trials, as shown in (**Table 1**). For every clinical research, ten virtual trials were used. When there were no data from clinical trials for the cirrhosis population under evaluation, the simulations for each treatment were set to 10 individuals with age ranges of 18–65 years in healthy volunteers and 20–90 years in cirrhosis patients (CP-A, B, and C), with 50% of the participants being female.

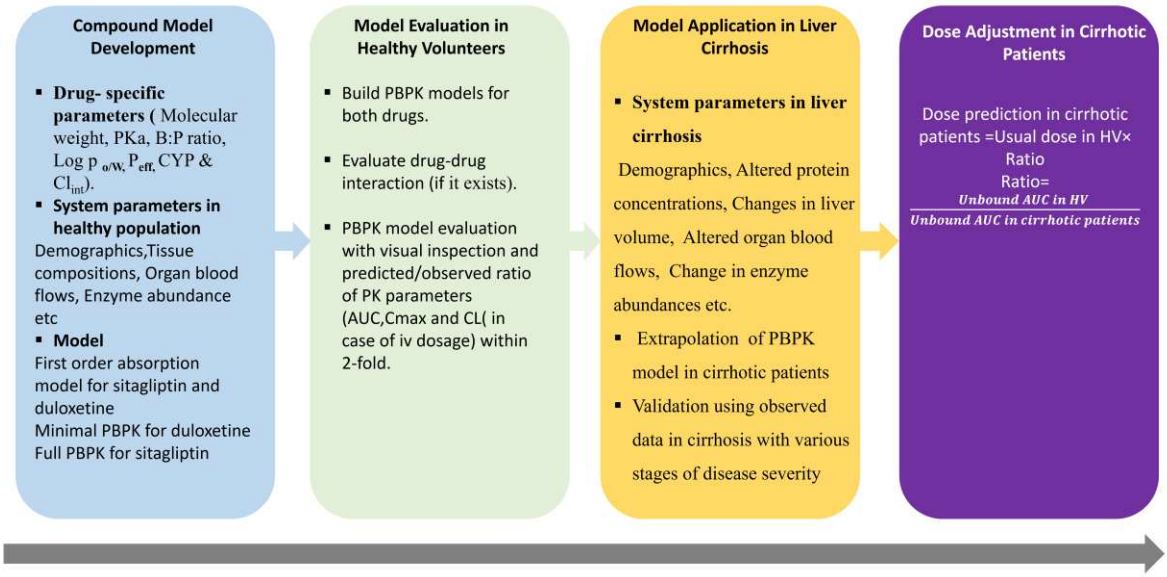


Fig. 1 A flowchart PBPK Modelling for sitagliptin and duloxetine drug. $LogP_{o:w}$; octonal-water partition coefficient, pKa; acid dissociation constant, B:P; blood to plasma, $fu_{,P}$; fraction of unbound drug in plasma, Clint; intrinsic clearance, Peff,man; human jejunum permeability, AUC; area under the concentration- time curve, PK pharmacokinetic, Cmax; maximum concentration, CL; renal clearance, PBPK; physiology based pharmacokinetic, CYP; cytochrome P450, HV; healthy volunteers.

Table 1 Clinical study characteristics, design, for published studies used in drug model validation.

Drug	Population	Number of subjects	Age years (range)	Proportion of females	Weight (kg) (range)	Dose	Route	Reference
Sitagliptin	Healthy (white, Non-Hispanic/Latino)	12	18-55	0.58	55-104.3	100 mg (SD)	Oral	[29]
	Healthy	17	20-50*	0	NR	100 mg once daily for 5 days	Oral	[30]
	Healthy	29	21-60	0	NR	100 mg (SD)	Oral	[31]
	Healthy (28 white, 4 Black African American)	32	18-55	0.5	NR	100 mg QD	Oral	[32]
	Healthy	24	45-65	0.5	NR	200 mg (MD) BID for 28 days	Oral	[33]
	Healthy	16	18-50	0	60-98	100 mg (q.d.) over 5 days	Oral	[34]
	Healthy	28	18-45	0.5	NR	100 mg (SD)	Oral	[35]
	Healthy (Caucasian)	18	25-42	0.33	NR	100 mg (SD)	Oral	[36]
	Healthy	8	18-45	0	63.4-97.7	On day 1, 25 mg QD for 10 days fast	Oral	[37]
		8				On day 1, 50 mg QD for 10 days		

		8				On day 1, 100 mg QD for 10 days		
		8				On day 1, 200 mg QD for 10 days		
		8				800 mg (SD) administered on day 1, followed by 300 mg BID for 10 days		
		8				On day 1, 400 mg QD for 10 days		
	Healthy	8	18-32	0	61.4-91.8	100 mg (SD)	Oral	[38]
	Healthy (Japanese)	6	20-46	0	48-95	5 mg (SD)	Oral	[39]
						12.5 mg (SD)		
						25 mg (SD)		
						25 mg Fed (SD)		
						50 mg (SD)		
						100 mg (SD)		
						200 mg (SD)		
						400 mg (SD)		
	Cirrhotic patients (CP-B)	10	18-75	0.5	NR	100 mg (SD)	Oral	[40]
Duloxetine	Healthy Chinese	12	22-25	0.5	46-72	22.4 mg (SD)	Oral	[41]
						44.8 mg (SD)		
						67.2 mg (SD)		
	Healthy	10	21–25	0.5	52–80	30 mg (SD)	Oral	[42]

		10				60 mg (SD)		
		10				90 mg (SD)		
		10				30 mg BID for 7 days.		
	Healthy Caucasian	24	20-47	0.54	55.2-86.2	20 mg (SD) 40 mg (SD) 60 mg (SD)	Oral	[43]
		16	19-48		59.8-85.2	20 mg BID for a total of nine doses over 5 days. 40 mg BID for a total of nine doses over 5 days.		
	Healthy Japanese	24	20-31	0.58	43.5-73.9	20 mg (SD) 40 mg (SD) 60 mg (SD)	Oral	[43]
		16	20-34		53.9-72.3	20 mg BID for a total of nine doses over 5 days. 40 mg BID for a total of nine doses over 5 days.		

	Cirrhotic patient (6 CP-B) (CYP2D6) EM	6	18-64	0.17	73.9-93	20 mg (SD)	Oral	[22]
	Healthy (6 EM,1 PM)	7	24-63	0.14	62.8-93.9	20 mg (SD)	Oral	[22]
	Healthy Chinese	23 (SD), then 21 (MD)	20-45	0.42	47-86	Day 1, 60 mg (SD), then on day 4 to 9, 60 mg QD for 9 days	Oral	[44]
	Healthy Caucasian	24	20-45	0.5	48.7-90.5	60 mg (SD)	Oral	[44]
	Healthy Caucasian	16	20-45	0.5	59.4-88.3	60 mg (MD)	Oral	
	Healthy Japanese	24	20-45	0.5	44.5-79.1	60 mg (SD)	Oral	
	Healthy Japanese	16	20-45	0.5	52.8-73	60 mg (MD)	Oral	
	Healthy	12	32-50	100	NR	40 mg (SD)	Oral	[45]
	Healthy	6	22-35	100	NR	40 mg was given every 12 hours for 3.5 days	Oral	[46]
	Healthy Chinese	12	20.9-27.2*	0.5	52.3-64.7	15 mg (SD)	Oral	[47]
		12	22.2-27.5*		50.1-65.7	30 mg (SD), then continued as 30 mg QD for 7 days		

		12	19.7-26.2*		53.1-65.1	60 mg (SD)		

CP-B; Child–Pugh B, SD; Single Dose, * Ranges used in simulations, CYP; Cytochrome, PM; Poor metabolizer of CYP2D6, EM; Extensive metabolizer of CYP2D6, NR; Not reported, QD; once daily, BID; twice daily.

System parameters

The pharmacokinetics of sitagliptin and duloxetine in healthy volunteers were simulated in Simcyp using the "Sim-Healthy Volunteers" population, whereas the pharmacokinetics of these medications in cirrhosis patients classified according to the Child-Pugh scoring system were simulated using the "Sim-cirrhosis CP-A, B, or C populations[48]. CYP enzyme expression, liver weight, liver blood flow, villous blood flow, hematocrit, cardiac output scalar, mean gastric resistance time, and plasma protein concentrations were among the demographic, anatomical, and physiological data that were altered in Sim-Healthy Volunteers in relation to changes occurring in cirrhosis. Based on the degree of change in those parameters, three cirrhosis population files (CP-A, B, and C) were created in the simulator, as indicated in **(Table S5).**

These variables can influence the pharmacokinetics of sitagliptin and duloxetine. Eq. 2, which is used in Simcyp, shows how changes in plasma albumin concentration affect the unbound fraction of duloxetine and sitagliptin in cirrhotic patients.

$$fu_{cirrhosis} = \frac{1}{1+\left[\frac{[P]_{cirrhosis}}{[P]_{HV}} \times \frac{(1-f_{uHV})}{f_{uHV}}\right]} \quad \text{..... (2)}$$

Where $f_{u_{cirrhosis}}$ and f_{uHV} are the unbound fractions of drugs in cirrhosis patients and healthy volunteers, respectively, where $[P]_{cirrhosis}$ and $[P]_{HV}$ are the plasma protein (e.g., albumin) concentrations in cirrhosis patients and healthy volunteers, respectively. Healthy volunteers (*HV)* values correspond to the typical physiological parameters of 25-year-old individuals.

Clinical data

The sitagliptin and duloxetine pharmacokinetic data were extracted from published plasma concentration-time profile utilizing the Plot digitizer online application (rohatgi2025plotdigitizer, Ankit Rohatgi, 2025, Version 3.1.6, https://plotdigitizer.com). (**Table 1)** summarizes reference studies reporting pharmacokinetics details for sitagliptin and duloxetine in cirrhotic patients and healthy volunteers. Regarding drug-drug interaction (DDI) studies involving duloxetine, in a single-center, open-label study, healthy Chinese male subjects aged 21–27 years were enrolled to evaluate the pharmacokinetic interaction between duloxetine and paroxetine (CYP2D6 inhibitor). Duloxetine 40 mg was administered orally alone (n = 10) or concurrently with paroxetine 20 mg once daily (n = 9)[19]. In sitagliptin and duloxetine clinical study, 10 and 6 cirrhotic patients were categorized as Child–Pugh B according to the CP score (7-9), respectively[22, 40].

Model evaluation

The model is evaluated by visual inspection of the predicted and observed plasma concentration-time curve, ensuring that observed data were adequately captured within the 5th and 95th percentiles of the simulations. Quantitative assessment was conducted by calculating the ratios of predicted / observed pharmacokinetic parameters such as AUC and/ or C_{max} and sometimes clearance (CL) for intravenously administered drugs. The acceptable range for ratios was within a twofold [49, 50]. For the DDI study, the predicted-to-observed ratio for the impact of DDI on pharmacokinetic parameters was assessed, with values within a two-fold range considered acceptable [49, 50].

Dose adjustment recommendation

Clinical pharmacokinetic studies of sitagliptin and duloxetine in moderate hepatic impairment patients were used to verify the performance of the developed cirrhosis model. According to this validation, the predicted unbound area under the plasma concentration–time curve ($AUC_{unbound}$) for each drug has been compared between cirrhotic populations and healthy volunteers to determine the need for dose adjustment. The exposure-response relationship in both populations was assumed to be the same for these comparisons. To assess any alteration in exposure associated with each cirrhotic class in comparison to healthy volunteers, the unbound AUCs for sitagliptin and duloxetine drugs in healthy populations and cirrhotic patients were displayed in boxplots (**Fig. 4**) using GraphPad Prism [Version 10.2.3 [403], 2024, (Computer software), GraphPad Software, LLC, California, USA. (https://www.graphpad.com/)], and based on these relative changes, optimized doses for each CP class were subsequently evaluated.

The following equation (Eq. 3) can be used to calculate the predicted optimal dose in cirrhotic individuals.

$$Predicted\ dose\ in\ cirrhosis = \frac{AUC_{unbound,last}\ in\ Healthy\ Volunteers}{AUC_{unbound,last}\ in\ Cirrhotic\ patients} \times Dose\ in\ Healthy\ volunteers \quad \ldots\ldots\ldots (3)$$

Clinical Evaluation of dose recommendation for sitagliptin and duloxetine

Study design

This study was a prospective, interventional, pilot clinical study conducted at the Gastroenterology, Hepatology, and Infectious Diseases Department, Kafrelsheikh University Hospital, and its outpatient clinic between 1 July 2024 and 1 July 2025. All procedures were performed in accordance with the ethical standards of the Scientific Research Ethics Committee/Institutional Review Board of Kafrelsheikh University, Egypt (Approval No. KFSIRB200-211; approved on 29 April 2024). The study was retrospectively registered at https://clinicaltrials.gov (Identifier: NCT07439536) on 17 February 2026. The study evaluated the clinical applicability of simulation-guided dosing predictions for commonly

prescribed medications in patients with liver cirrhosis, addressing metabolic and diabetic neuropathic complications separately. Control group for each drug received the standard therapeutic doses sitagliptin (JANUVIA 100 mg) once daily and duloxetine (CYMBATEX 60 mg) once daily, whereas cirrhotic patients for each drug received dose-adjusted regimens based on the recommended doses required to achieve AUC at steady state comparable to those observed in healthy subjects.

Diabetes mellites management with sitagliptin

A total of thirty-five Egyptian patients diagnosed with cirrhosis complicated by type 2 diabetes mellitus were invited for a screening visit to assess eligibility. Participants were enrolled in the study if they are $\geq$ 18 years old and had evidence of chronic hepatic injury, including dull liver edge, irregular liver surface, and rough echoic levels in liver based on computed tomography CT and/ or ultrasound findings, in addition to blood tests, which showed thrombocytopenia, and impaired hepatic biosynthetic function (reduced prothrombin activity, serum albumin, and total cholesterol) and were also required to meet the American Diabetes Association (ADA) diagnostic criteria for T2DM, with HbA1c levels ranging from 7% to 10% [51]. Patients who had acute illness episodes associated with deterioration in liver function within two months of the screening, renal impairment, or malignancy were excluded. Both male and female patients, who fulfilled the established criteria for hepatic function-based subcategorization were included. Hepatic function was assessed using the Child-Pugh classification scoring system, which incorporates scores for ascites, encephalopathy, serum albumin, serum bilirubin, and prothrombin time[48]. Three patients were excluded prior to enrollment due to not meeting inclusion criteria, while two patients were lost during the follow-up period. Patients were classified into the following: control (n =12); mild hepatic impairment (n =12), moderate hepatic impairment (n = 12), or severe hepatic impairment (n = 6).

Diabetic neuropathic pain management by duloxetine

A total of fifteen subjects with diabetic neuropathic pain caused by type 2 diabetes mellitus were enrolled in the clinical study. Participants were enrolled in the study if they were $\geq$ 18 years old, had evidence of chronic hepatic injury, and had a mean 24-hour average pain score of at least 4 on the 11-point numeric rating scale (NRS). The Brief Pain Inventory (BPI), which consists of two domains pain severity and pain interference, was used to assess pain[52]. The mean of four items assessing worst, least, average, and pain right now was used to calculate the pain severity score[52]. The mean of seven variables measuring how much pain affects general activity, mood, walking ability, regular work, relationships with others, sleep, and enjoyment of life was used to generate the pain interference score[52]. All items were rated on an 11-point numeric rating scale ranging from 0 (no pain/no interference) to 10 (worst imaginable pain/complete interference), with higher scores indicating greater pain intensity or functional impairment [52].

Patients who had acute illness episodes associated with deterioration in liver function within two months of the screening and disease complications that were regarded to affect the DPNP assessment, like neurological disorders irrelevant to diabetic neuropathy (e.g., phantom limb pain following amputation) and peripheral vascular disease (ischemic pain) were excluded. Three patients withdrew during follow-up period, and one patient was excluded due to non-compliance. Both male and female patients, who fulfilled the established criteria for hepatic function-based sub-categorization were included. Patients were classified into control (n = 11) and mild hepatic impairment (n = 11) groups. While recruitment of patients with moderate and severe hepatic impairment (CP-B and C) was initially planned, these groups could not be included because of low prevalence of eligible patients meeting all inclusion/exclusion criteria and logistical challenges for this more clinically complex population. in ensuring adequate follow-up.

Outcomes: The primary outcomes were the PBPK model-predicted unbound plasma exposure ($AUC_{unbound}$) and the model-informed dose adjustment of sitagliptin and duloxetine across Child-Pugh classes aiming to achieve drug exposure comparable to that observed in control group in addition to clinical outcomes including glycemic control improvement and pain reduction. Secondary outcomes included safety outcomes including the incidence of adverse events such as headache, diarrhea, dizziness, muscle pain, nasopharyngitis, constipation, somnolence, and dry mouth.

Statistical analysis

The mean ± standard deviation (Mean± SD) is used to depict all data. IBM SPSS® Statistics (Version 31.0; IBM Corp., Armonk, NY, USA) was used for statistical analysis. The Shapiro–Wilk test was utilized to test the normal distribution of continuous variables. A comparison of mean values within groups was performed using a paired *t*-test. An unpaired (two-sample) t-test was used to compare groups at baseline, post-treatment, and the change from baseline. $P < 0.05$ with a 95% confidence interval was considered a significant statistical difference. Frequencies (%) were used to evaluate adverse effects.

Result

Healthy volunteers model evaluation

First, The PBPK model was tested for its capacity to represent the pharmacokinetics of sitagliptin and duloxetine in healthy volunteers prior to applying these models to liver cirrhosis. As shown in (**Fig. S1 and S2),** visual inspection revealed a strong agreement between the observed and predicted data in healthy volunteers. Additionally, as shown in **(Fig. 2 and 3)** (Excel 2019) and **(Tables S3 and S4)**, the computed predicted/observed AUC, C_{max}, and CL ratios (where available) were within (0.5-2) folds. The predicted/observed AUC and C_{max} ratios for duloxetine DDIs were computed using the following equations (Eqs. 4-6), and the ratio was within 2 folds, as **(Table 2**) illustrates.

$$\textit{Predicted}\ \text{AUC or Cmax ratios} = \frac{\text{Predicted AUC or Cmax with inhibitor}}{\text{Predicted AUC or Cmax without inhibitor}} \quad \text{……..(4)}$$

$$\textit{Observed}\ \text{AUC or Cmax ratios} = \frac{\text{Observed AUC or Cmax with inhibitor}}{\text{Observed AUC or Cmax without inhibitor}} \quad \text{……. (5)}$$

According to equations (4) and (5)

$$\textit{Predicted}/\textit{Observed}\ \text{AUC or Cmax ratios} = \frac{\textit{Predicted}\ \text{AUC or Cmax ratios}}{\textit{Observed}\ \text{AUC or Cmax ratios}} \quad \text{…..…… (6)}$$

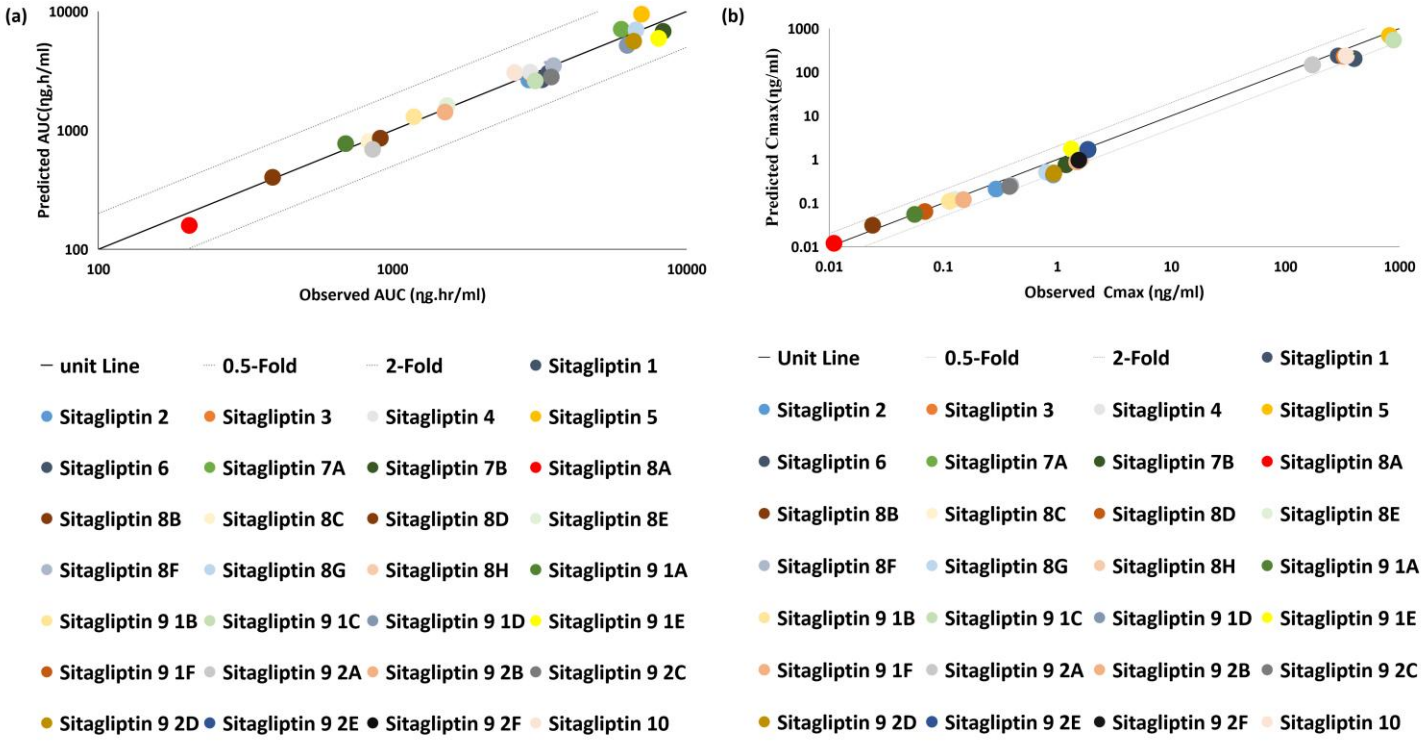


Fig. 2 a) Predicted versus observed area under the plasma concentration–time curve (AUC). b) Predicted versus observed maximum plasma concentration (C_{max}). The observed data were extracted from clinical studies of sitagliptin 1 from Kasichayanula[36], sitagliptin 2 from Krishna[38], sitagliptin 3 from He L et al 2014[35] , sitagliptin 4 from Moon SJ et al 2020[30], sitagliptin 5 from Dawra VK et al 2019[29], sitagliptin 6 from Aquilante CL et al 2013[31], sitagliptin (7A-7B) from Herman GA et al 2006[33] ,sitagliptin (8A-8H) from Herman GA et al 2011[39], sitagliptin 9(1A-1F) from Bergman AJ et al 2006[37], sitagliptin 9(2A-2F) from Bergman AJ et al 2006[37], sitagliptin 10 from Brand T et al 2012 [34].

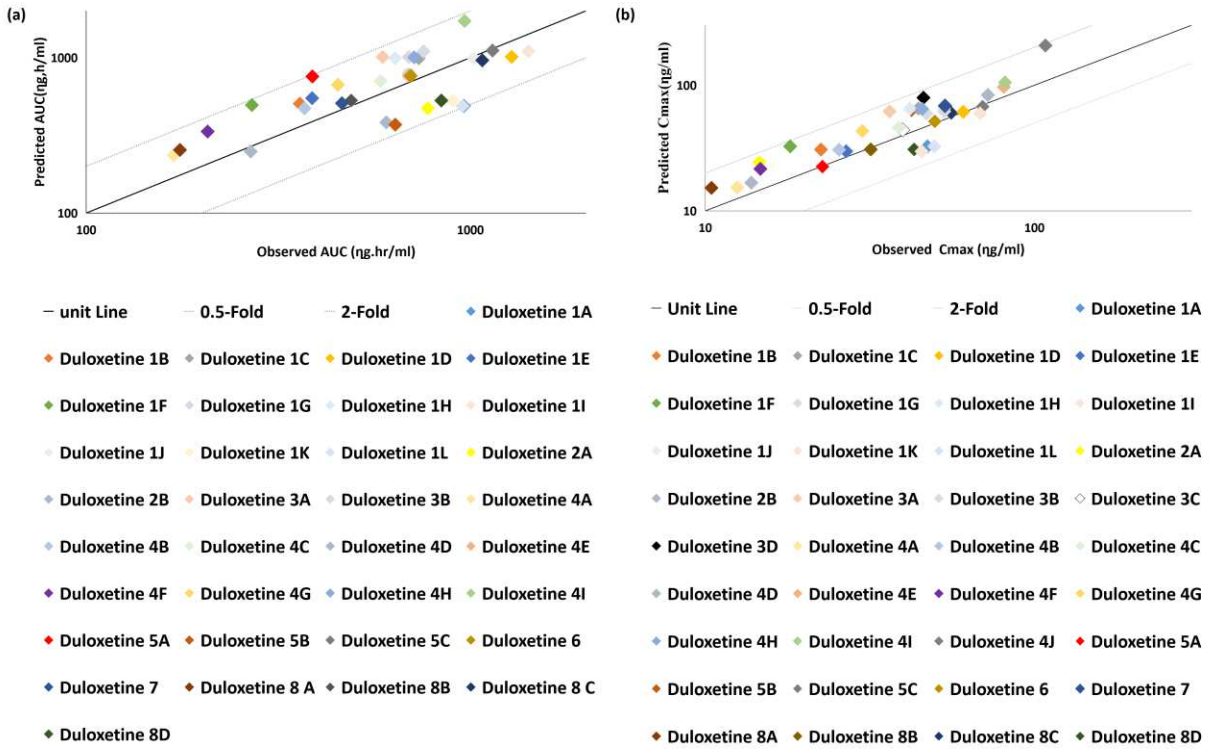


Fig. 3 a) Predicted versus observed area under the plasma concentration–time curve (AUC). b) Predicted versus observed maximum plasma concentration (C_{max}). The observed data were extracted from clinical studies of duloxetine (1A-1L) from Zhao R-k et al 2009[42], duloxetine (2A-2B) from Suri A et al 2005[22], duloxetine(3A-3D) from Tianmei S et al 2007[44], duloxetine (4A-4J) from Chan C et al 2007[43], duloxetine (5A-5C) from Ma N et al 2007[41], duloxetine 6 from Skinner M.H et al 2004[45], duloxetine 7 from Lobo E.D et al 2008[46], duloxetine (8A-8D) from Li H et al 2013[47].

Table 2 Predictive performance of the duloxetine model in a drug interaction study in healthy volunteers.

Drug	Interacting drug	Predicted without interaction		Predicted with interaction		Observed without interaction		Observed with interaction		Predicted with/without interaction		Observed with/without interaction		**Predicted/ observed ratios**		Reference
		AUC	C_{max}	AUC	C_{max}	AUC	C_{max}	AUC	C_{max}	AUC ratio	C_{max} ratio	AUC ratio	C_{max} ratio	AUC ratio	C_{max} ratio	
Duloxetine	paroxetine	753.73	60.02	987.98	71.82	797	35.2	780	55.7	1.31	1.2	1.57	1.58	**0.84**	**0.75**	[19]

Model assessment in cirrhotic patients

Model evaluation has been conducted for both sitagliptin and duloxetine in moderate disease populations (CP-B) after considering the changes in physiological parameters linked to cirrhosis in the three stages of cirrhosis. Visual inspection demonstrated that all measured data were within the range between the 5^{th} and 95^{th} percentiles in the drug concentration–time profile. Furthermore, the predicted/observed AUC ratios for sitagliptin and duloxetine were 0.83 and 0.7, and C_{max} ratios were 0.84 and 1.4, respectively, as indicated in (**Table 3)**.

Table 3 Predicted pharmacokinetic parameters of duloxetine and sitagliptin in cirrhotic patients.

Drug	Predicted (healthy)		Predicted (cirrhotic patients)		Observed (healthy volunteers)		Observed (cirrhotic patients)		Predicted ratio (cirrhotic to healthy)		Observed ratio (cirrhotic to healthy)		**Predicted/observed Disease impact**		Reference
	AUC	C_{max}	AUC	C_{max}	AUC	C_{max}	AUC	C_{max}	AUC ratio	C_{max} ratio	AUC Ratio	C_{max} ratio	**AUC ratio**	**C_{max} ratio**	[22]
Duloxetine	249.01	15.76	476.36	24.35	370	13.8	1027	14.6	1.9	1.5	2.7	1.1	**0.70**	**1.4**	
Sitagliptin	3654.4	290.8	3690	268	3869.4	426	4684.1	483	1	0.92	1.21	1.13	**0.83**	**0.84**	[40]

Model simulations in patients with cirrhosis

The CP-A and CP-C populations lack clinical pharmacokinetic data for sitagliptin and duloxetine, which have recommended dosages for moderate stages of cirrhosis[22, 40]. Model simulations can be employed to bridge this gap.

The relative AUC of cirrhotic patients compared to healthy volunteers was estimated by model simulations. The usual doses of sitagliptin tablets (100 mg once daily) and duloxetine (60 mg once daily) in the control group. After the simulations were run on Child-Pugh classes using the doses previously mentioned, the unbound $AUC_{0\text{-last t}}$ for each medication was considered. The predicted unbound $AUC_{0\text{-last}}$ for sitagliptin 60 mg once daily elevated from 2804.42 ŋg.h/mL in healthy volunteers to 3576.15 ŋg.h/mL in CP-A, 4105.79 ŋg.h/mL in CP-B, and 4673.58 ŋg.h/mL in CP-C. This means that the AUC increased by 1.2-, 1.4-, and 1.6-fold in the CP-A, CP-B, and CP-C populations, respectively, relative to that in the healthy volunteers' population.

Considering duloxetine, the predicted unbound $AUC_{0\text{-last}}$ for duloxetine increased from 48.65 ŋg.h/mL in healthy volunteers to 99.80 ŋg.h/mL in CP-A, 200.43 ŋg.h/mL in CP-B, and 417.53 ŋg.h/ml in CP-C. This means that the AUC increased by 2.05-, 4.12-, and 8.58-folds in the CP-A, CP-B, and CP-C populations, respectively, relative to that in the healthy volunteers' population. Dosage modification is required to achieve an unbound AUC of cirrhotic patients at values very close to the unbound AUC of healthy volunteers, as illustrated in **(Fig. 4)**.

Simcyb simulation showed that CP-B hepatic impairment patients exhibited approximately a 2.1-fold increase in unbound exposure compared with healthy volunteers. Evaluation of different dosing intervals (24-96 h) indicated that administration of 20 mg of duloxetine every 48h produced an unbound C_{aver} comparable to that observed with the standard 60 mg once-daily regimen in healthy volunteers. The predicted unbound $C_{ss,aver}$ values remained within approximately 1.1-fold of the reference exposure, as shown in **(Fig. S3).**

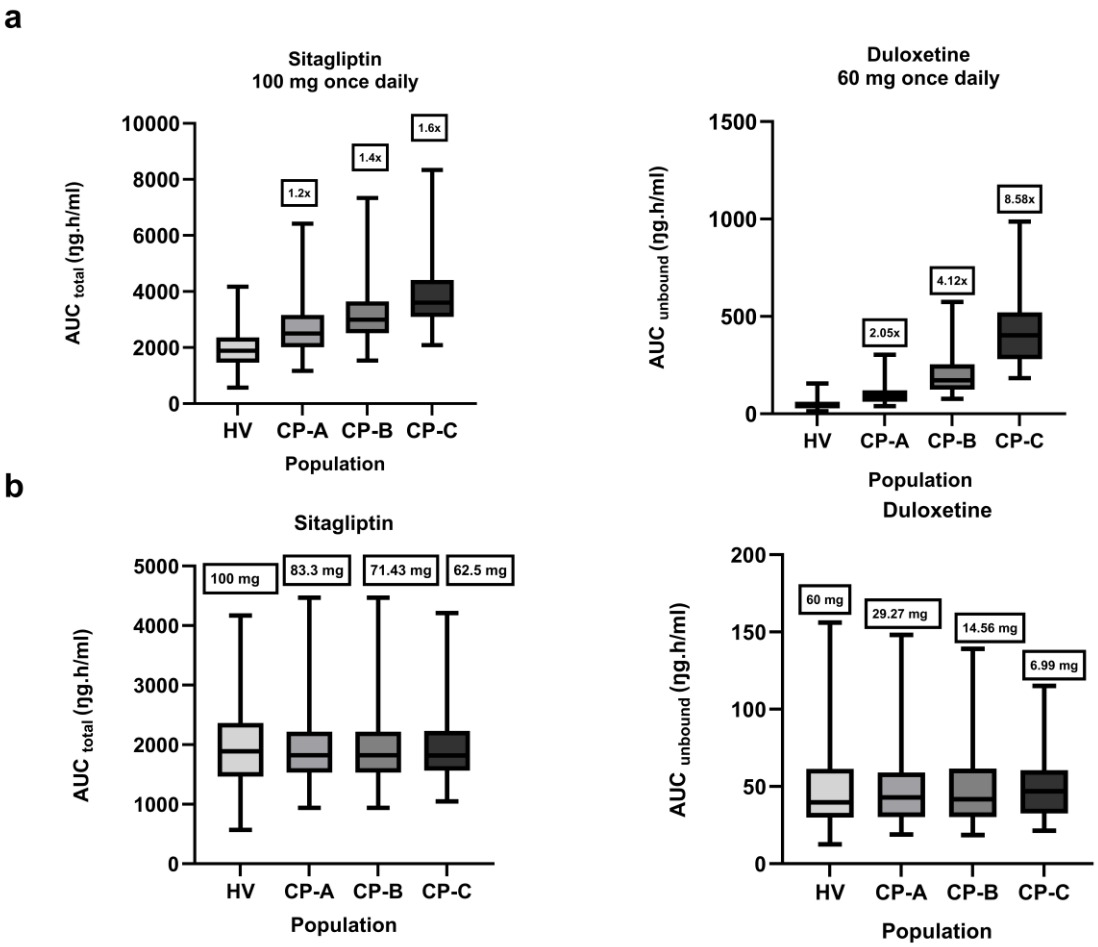

a
Sitagliptin
100 mg once daily
AUC total (ηg.h/ml)
10000
8000
6000
4000
2000
0
1.2x
1.4x
1.6x
HV
CP-A
CP-B
CP-C
Population
Duloxetine
60 mg once daily
AUC unbound (ηg.h/ml)
1500
1000
500
0
2.05x
4.12x
8.58x
HV
CP-A
CP-B
CP-C
Population
b
Sitagliptin
AUC total (ηg.h/ml)
5000
4000
3000
2000
1000
0
100 mg
83.3 mg
71.43 mg
62.5 mg
HV
CP-A
CP-B
CP-C
Population
Duloxetine
AUC unbound (ηg.h/ml)
200
150
100
50
0
60 mg
29.27 mg
14.56 mg
6.99 mg
HV
CP-A
CP-B
CP-C
Population

Fig. 4 Boxplots illustrating the predicted area under the curve ($AUC_{0\text{-}last}$) with median lines as well as 5^{th} – 95^{th} percentiles in healthy and cirrhotic patients. Panel (a) refers to the predicted $AUC_{unbound}$ before applying dose reduction of duloxetine (60 mg once daily) and AUC_{total} sitagliptin (100 mg once daily) to healthy and cirrhosis patients Panel (b) refers to the predicted $AUC_{unbound}$ after a reduction in the administered doses of duloxetine and AUC_{total} sitagliptin to cirrhotic patients to doses calculated from PBPK simulation results. CP-A: Child-Pugh -A; CP-B: Child-Pugh -B; CP-C: Child-Pugh -C.

Regarding clinical evaluation of sitagliptin and duloxetine dose recommendations in cirrhotic patients, Participants' demographics are presented in **Table (S6 and S9).** The results of the duloxetine study showed that baseline demographic and biochemical characteristics were comparable between the 60 mg control group and the 30 mg Child-Pugh A group, with no significant differences observed before treatment. After 12 weeks of therapy, liver function markers—including albumin, total bilirubin, INR, ALT, and AST—did not show any statistically significant changes within either group, nor were there significant differences in the change from baseline between groups, indicating that duloxetine did not adversely affect hepatic function in patients with mild liver impairment. Glycemic parameters (HbA1c, fasting blood glucose, and postprandial glucose), renal markers, and hematologic indices also remained stable throughout the study period. Pain outcomes measured by the Brief Pain Inventory improved in both groups; however, the degree of improvement did not differ significantly between the 30 mg and 60 mg doses, suggesting that both doses provided similar analgesic benefits without dose-dependent safety concerns. Importantly, duloxetine produced marked improvements in pain severity and interference score, with average pain reduced by 50% and 43.3%, worst pain by 51.4% and 45.9%, least pain by 60.5% and 52.6%, pain right now by 52.7% and 47.5%, and pain interference scores reduced by 53% and 63%, respectively, in the control and CP-A groups, as shown in (**Fig. 6)**.

In the sitagliptin study, baseline values reflected the expected progression of hepatic dysfunction -across CP classes A, B, and C, but these differences were related to disease severity rather than treatment. Following sitagliptin therapy, liver function tests remained stable in all groups, with no significant worsening in albumin, bilirubin, INR, or liver enzymes, even in patients with moderate or severe cirrhosis. In contrast, sitagliptin produced significant improvements in glycemic control, with marked reductions in HbA1c, fasting glucose, and postprandial glucose across all Child-Pugh classes by approximately 10–15%, fasting blood glucose by 20 to 25%, and postprandial glucose by 15-18% ($p < 0.001$), respectively, as shown in **(Fig. 5).** The extent of glycemic improvement did not differ significantly between groups, indicating preserved therapeutic efficacy regardless of the degree of liver impairment. Renal, hematologic, and lipid profiles showed no clinically meaningful changes after treatment. Overall, these results demonstrate that both duloxetine and sitagliptin were safe in patients with liver disease, with sitagliptin maintaining robust glucose-lowering efficacy and duloxetine providing effective pain relief without hepatic deterioration. Adverse effects were generally mild for both drugs, though sitagliptin showed a higher incidence of headache and gastrointestinal symptoms in CP-C patients, as presented in (**Table 4 and 5).** Neurological adverse events (dizziness) were not attributed to hepatic encephalopathy, as it was absent at baseline and during the study period. To sum up, these results suggest that sitagliptin is still tolerable and effective option for glycemic control in cirrhotic diabetics, while duloxetine provides substantial relief from neuropathic pain without compromising metabolic or hepatic stability.

Table 4 Reported adverse drug effects of duloxetine

Side Effect	**Control (n = 11) (n%) Dose =60 mg**	**CP-A (n = 11) (n%) Dose = 30 mg**
Nausea	0 (0%)	1 (9.1%)
Dizziness	1 (9.1%)	2 (18.2%)
Somnolence	1 (9.1%)	1 (9.1%)
Dry Mouth	1 (9.1%)	2 (18.2%)
Sweeting	0 (0%)	0 (0%)
Constipation	0 (0%)	1 (9.1%)

CP-A; Child-Pugh-A, n (%); number (percentage)

Table 5 Reported adverse drug effects of sitagliptin

Side Effect	**Control (n = 12) (n%) Dose =100mg**	**CP-A (n=12) (n %) Dose=100 mg**	**CP-B (n =12) (n %) Dose = 50 mg**	**CP-C (n = 6) (n %) Dose = 50 mg**
Headache	0 (0%)	1 (8.3%)	1 (8.3%)	2 (33.3%)
Nose & Throat irritation	0 (0%)	2 (16.6%)	2 (16.6%)	1 (16.6%)
Dry Mouth	1 (8.3%)	2 (16.6%)	1 (8.3%)	2 (33.3%)
Nasopharyngitis	0 (0%)	1 (8.3%)	0 (0%)	1 (16.6%)
Muscle pain	0 (0%)	1 (8.3%)	1 (8.3%)	2 (33.3%)
Diarrhea	1 (8.3%)	1 (8.3%)	1 (8.3%)	2 (33.3%)

CP-A; Child-Pugh -A, CP-B; Child-Pugh -B, CP-C; Child-Pugh -C;n (%); number (percentage)

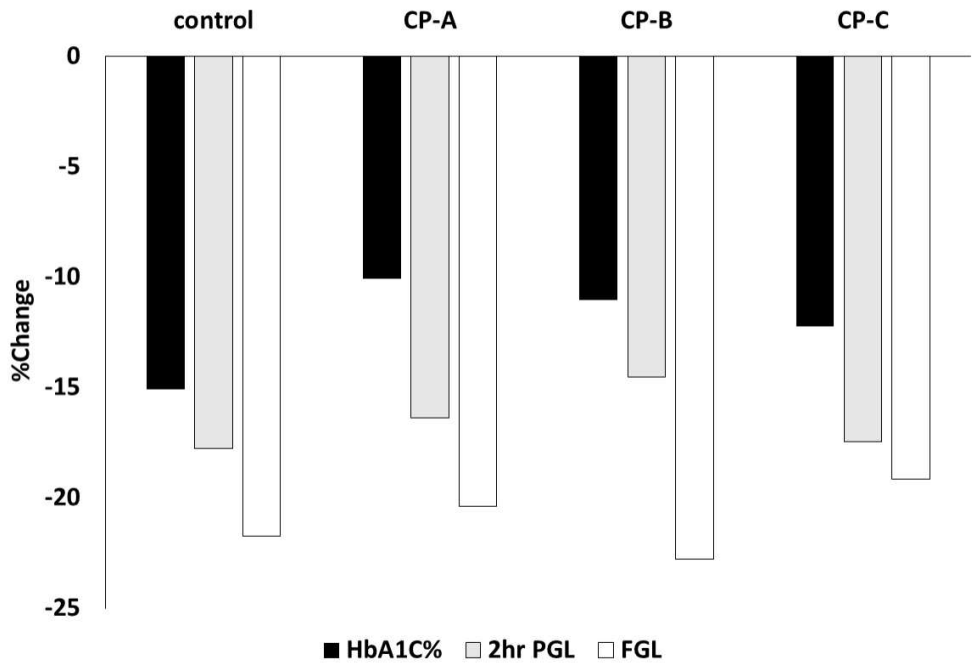


Fig. 5 Percent changes in glycemic parameters after treatment with sitagliptin compared to before treatment in control group and CP (A, B, and C) cirrhotic patients. Hb A1C: hemoglobin A1C; 2hr PGL: 2hr postprandial glucose level; FBG: fasting blood glucose; CP-A: Child-Pugh A; CP-B: Child-Pugh B; CP-C: Child-Pugh C. No significant difference between control and cirrhosis groups.

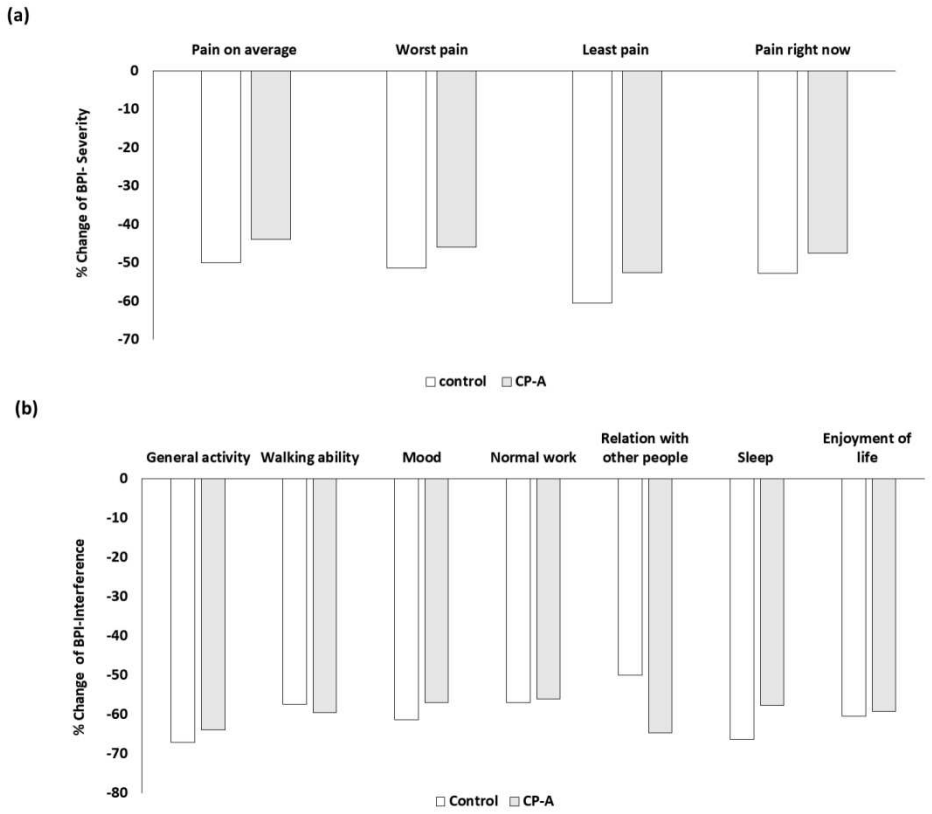


Fig. 6 Percent changes in (a) BPI-severity scores and (b) BPI interference scores after duloxetine treatment compared to before treatment in control subjects and Child-Pugh A (CP-A) cirrhotic patients.

Discussion

Management of type 2 diabetes and DNP in patients with liver cirrhosis poses significant clinical challenges due to underlying hepatic impairment and portal hypertension, which increases the risk of drug toxicity [53]. Progressive hepatic dysfunction alters drug disposition limiting the use of several glucose-lowering agents. Consequently, there is a growing need for antidiabetic therapies that provide effective glycemic control with minimal hepatic burden. To the best of our knowledge, this is the initial study that compares cirrhotic populations to healthy volunteers using PBPK modeling to predict dose modification of sitagliptin and duloxetine medications. It also conducts clinical evaluation to evaluate the safety and effectiveness of the recommended doses in those patients. When there is a lack of clinical data, PBPK models as well as simulations have been used in clinical pharmacology and drug development to provide some insight on alterations to drug exposure[6, 7]. Even though the use of PBPK dose recommendations in certain patient populations is still ongoing, a few studies have demonstrated a reasonable validity of this method of evaluation in populations with hepatic and renal impairment. Although the anticipated exposure changes in severe stages of hepatic impairment reflect the worst-case scenarios, the predicted results of these population models have been shown to be more reliable in initial stages of hepatic impairment[54, 55]. Therefore, to achieve the necessary therapeutic outcomes, adhering to the recommendations from PBPK simulations in CP-B and CP-C attempts to prevent toxicities in those patients who are at risk while keeping the exposure very close to that of healthy liver populations as possible[54, 55]. To increase the number of therapeutic options available to clinicians treating cirrhotic patients with type 2 diabetes and neuropathy, PBPK modeling along with simulations were employed here to provide evidence that can be used in line with expert guidance to recommend safe doses for sitagliptin and duloxetine drugs in cirrhotic patients.

In accordance with regulatory guidelines (e.g., EMA 2018, FDA 2018) supporting PBPK modeling to fill evidence gaps in specific populations, we mainly focused on medications having previously validated PBPK models that had been assessed in healthy participants [56]. When there is a scarcity of clinical data, this approach assists in establishing mechanistic hypotheses and mandates early dose modifications to prevent reliance on clinician's "educated guesses" alone. According to the QI consortium, 70% and 90% of the PBPK for hepatic impairment and renal impairment, respectively, agree with the observed data; whereas the remaining discrepancies point to cautious worst-case circumstances that can be detrimental [55]. Therefore, these models minimize patient risk by offering a safe, evidence-based framework for clinical research design and dose recommendations.

As seen in (**Fig. 2 and 3),** the PBPK model predicts kinetic processes in healthy volunteers following administering both sitagliptin and duloxetine medications, with predictions falling within a twofold range of observed measurements. Concerning the hepatic extraction ratio (E_R), drugs with a low E_R are mostly based on CL_{int}, while those with an intermediate E_R are impacted by fu, CL_{in}, and liver enzyme abundance changes[57]. In this research, in healthy volunteers, E_R for duloxetine and sitagliptin are about 0.54 and 0.07 which are regarded as intermediate and low E_R, respectively[22, 40]. CYP enzyme abundance and liver volume gradually decrease in cirrhosis patients with varying Child-Pugh classifications. Patients with cirrhosis have lower CYP450 enzymes levels, for instance CYP2D6, CYP3A4, and CYP1A2, although CYP2C8 levels are consistent in both the healthy population and all Simcyp cirrhotic populations, as shown in **(Table S5**)[58].

Sitagliptin has low protein binding, while duloxetine is highly bound to plasma proteins with free fractions (f_u, p) of 0.62 and 0.1, respectively[59, 60]. Cirrhosis frequently increases with protein-bound medications affinity like duloxetine, which might initially enhance total CL. Yet, cirrhosis also lowers intrinsic clearance (CL_{int}), typically because of reduced liver enzyme activity, which decreases total CL. Because of the conflicting effects on CL, changes in plasma protein binding may obscure changes in AUC or total CL. In contrast, unbound AUC, which more accurately represents pharmacologically active drugs, is not as impacted by binding alterations and is therefore recommended when making dosage modification decisions.

The selected drugs were sitagliptin and duloxetine. For sitagliptin, Simcyp predicted doses of approximately 83.3 mg for CP-A, which is closest to the commercially available 100 mg tablet; 71.4 mg for CP-B, with 50 mg being the nearest available strength; and 62.5 mg for CP-C, which is closest to the commercially available 50 mg tablet. For duloxetine, the predicted doses were 29.3 mg for CP-A (closest available strength: 30 mg), while 14.6 mg for CP-B (nearest available: 20 mg), and 6.9 mg for CP-C, which was considered not applicable.

The result of sitagliptin clinical study agree with a retrospective cohort study involving patients with diabetes and chronic liver disease (including 19 patients with cirrhosis), sitagliptin significantly reduced glycemic parameters without worsening liver transaminases, suggesting that it can be administered safely over long-term treatment in this population [61]**.** Even though sitagliptin is minimally metabolized by the liver, the simulation results showed that the systemic concentration of sitagliptin was increased with liver impairment (1.6-fold in patients with CP class C) compared to the normal condition. Concerning these simulation results, it is presumed that the impact of hepatic impairment on sitagliptin pharmacokinetics primarily comes from the correlation between the severity of cirrhosis and renal function due to the hepatorenal syndrome, which is involved into the PBPK model[62].

Although previous pharmacokinetic studies reported that no sitagliptin dose adjustment is required in moderate hepatic impairment and this was well captured by simulations, this conclusion was primarily based on the assessment of total drug exposure (AUC for the first dose).[29] However, reliance on the AUC for the last dose is recommended for more reliable dosage adjustment to ensure that the drug has reached steady-state conditions, supporting the need for dose reduction according to hepatic severity. Furthermore, our model provides further information on the potential exposure to AUC about mild and severe stages. A standard dose of 100 mg was administered to healthy controls and patients with CP-A, while reduced doses of 50 mg were optimized for patients with CP-B and CP-C. Despite these adjustments, the optimized regimens achieved effects comparable to the standard regimen, supporting dose individualization in hepatic impairment to preserve efficacy and potentially minimize unnecessary drug exposure and adverse events, as presented in **(Table S10)**.

Regarding duloxetine, a previous study evaluated duloxetine 20 mg once daily in moderate cirrhotic patients (CP-B) and recommended dose reduction based on total AUC that was in line with simulation results within 1.5 folds [22].However, reliance on total exposure alone may not fully reflect the pharmacologically relevant changes in cirrhotic patients. In liver cirrhosis, alterations in plasma protein binding are common, potentially leading to an increased unbound (free) fraction of drugs. Therefore, evaluation of unbound AUC rather than total AUC may provide a more accurate assessment of duloxetine disposition and clinical response in cirrhotic patients. This consideration is particularly relevant in advanced liver disease, where changes in protein binding may occur independently of total systemic exposure. Our PBPK simulations assessed unbound exposure, revealing greater increases in pharmacologically active drug levels. Consequently, an optimized dose of ~15 mg is suggested, where there is no clinically accessible dosage form with the appropriate dose strength to ensure safe dosing in patients with cirrhosis. Lastly, the current trial filled a gap in the research pool by reporting the pharmacokinetics of duloxetine in patients with cirrhosis across varying stages.

The result of this pilot study indicates that duloxetine showed consistent reductions in pain severity and pain-interference scores across both the standard-dose (SD) control group (60 mg) and the optimized-dose (OD) CP-A group (30 mg), as shown in **(Table S8).** Despite the dose reduction in CP-A patients, the magnitude of pain improvement did not significantly differ between groups, indicating that duloxetine maintains therapeutic efficacy even at a lower dose in mild hepatic impairment patients, as illustrated in (**Table S7)**.

Furthermore, duloxetine showed the highest reduction in exposure with deteriorating severity of cirrhosis, whereas sitagliptin exhibited the lowest change and a substantial need for medications dose reduction that is gradual with increasing disease severity. It is necessary to round some of these dosages to the closet available commercial dosage form, which limits the use of the recommended doses in clinical implementation in Child Pugh score C patients with duloxetine.

As seen in **(Fig. S3)**, given the increased unbound exposure observed in patients with CP-B hepatic impairment, extension of the dosing interval was explored as a potential strategy to optimize therapy and minimize drug accumulation. Simulation results suggested that administering 20 mg of duloxetine every 48 hours could achieve unbound $C_{ss,aver}$ comparable to that produced by the standard 60 mg once-daily regimen in healthy volunteers. However, despite the favorable pharmacokinetic predictions, implementation of such a regimen in clinical practice may be limited due to potential patient compliance challenges associated with a 48-hour dosing schedule and the lack of regulatory recommendations for this dosing strategy.

Limitations

This study relied on PBPK modeling to predict dose adjustments for sitagliptin and duloxetine in cirrhotic patients. While PBPK simulations provide mechanistic insights and align reasonably with observed data, the absence of large-scale clinical trials in this population remains a major limitation. Additionally, the recommended dose reductions for duloxetine (~15 mg and 7 mg) for CP-B and CP-C cirrhotic patients, respectively, are not supported by commercially available formulations, which may restrict clinical implementation. The absence of liver biopsy represents a limitation, as cirrhotic patients were classified solely by clinical and biochemical parameters, which may not fully capture the histological status of the liver. In addition, the relatively small sample size represents a potential limitation that may affect the external validity and generalizability of the outcomes. Accordingly, larger, multicenter studies with extended follow-up periods are warranted to validate these findings and assess their long-term clinical implications.

Conclusions

PBPK modeling as well as simulation offer a beneficial framework for expecting the pharmacokinetics of sitagliptin and duloxetine drugs in patients with cirrhosis across Child-Pugh classes, especially when clinical data are lacking. Because these agents are metabolized by CYP450 enzymes, hepatic impairment can change drug exposure, increasing the risk of toxicity. Dose adjustments should be informed by changes in unbound AUC, which reflects the pharmacologically active fraction. By integrating disease-specific physiological changes, PBPK models estimate optimal dosing for each severity degree, assuming comparable exposure and pharmacological effects to healthy individuals without increasing adverse events. This approach provides clinicians with evidence-based guidance for safe prescribing and expands therapeutic options in the absence of clinical trial data. Nevertheless, practical implementation requires more precise dosage and clearer dosing recommendations. In the current gap of clinical evidence, PBPK modeling demonstrates a data-driven strategy to support safer dosing decisions alongside clinical judgment.

Declarations

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Conflict of interest Eman El-Khateeb is an employee of Certara Predictive Technologies and may hold shares in Certara. All other authors declare no conflicts of interest.

Ethics Approval. All procedures were performed in compliance with the ethical standards of the Scientific Research Ethics Committee (Institutional Review Board) of Kafrelsheikh University, Egypt (Approval No. KFSIRB200-211) and the Declaration of Helsinki. Each patient gave his written informed consent for participation in these trials. The trial was registered at ClinicalTrials.gov retrospectively (https://clinicaltrials.gov/study/NCT07439536) on 17 February 2026.

Consent to Participate All authors provided consent for publication.

Availability of Data and Material

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions

Khaled Abdelkawy, Eman El-Khateeb and Noha M El-Khodary conceived and designed the study; Aya Fouda, Mohammed Hussien Ahmed Hussien and Eman El-Khateeb performed the practical work; Eman El-Khateeb, Noha M El-Khodary, Mohammed Hussien Ahmed Hussien and Khaled Abdelkawy collected and organized the resources; Aya Fouda, Eman El-Khateeb, Noha M El-Khodary, Mohammed Hussien Ahmed Hussien and Khaled Abdelkawy drafted and revised the manuscript. All authors reviewed the results and approved the final version of the manuscript.

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