

Research Article

Prediction of Drug Clearance in Subjects with Varying Degrees of Hepatic Impairment Using Albumin or Bilirubin or Albumin-Bilirubin Score

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Abstract

Hepatic impairment is classified as mild, moderate, and severe based on either Child-Pugh or National Cancer Institute (NCI) classification system. Another classification system based on bilirubin and albumin levels known as albumin-bilirubin (ALBI) scoring system has been proposed mainly for the patients with cancer with hepatic impairment. The objective of this study was to predict drug clearance in subjects with varying degrees of hepatic impairment using albumin or bilirubin or albumin-bilirubin (ALBI) score. There were thirty-five drugs with 64 observations (different degrees of hepatic impairment) in this study. The methods used to predict drug Clearance (CL) in subjects with hepatic impairment were bilirubin or albumin or ALBI score. Prediction fold-errors of 0.5-2, 0.5-1.5, and 0.7-1.3 were used for the assessment of the predictive performance of the proposed three methods. More than 90% observations were within 0.5-2-fold prediction error by all three methods. Based on albumin, bilirubin, and ALBI, 75.0%, 79.7%, and 89.1% observations were within 0.5-1.5-fold prediction error, respectively. ALBI particularly provided a good prediction in subjects with severe liver impairment (93.8% within 0.5-1.5 and 68.8% within 0.7-1.3-fold prediction error). All three approaches are simple. ALBI is suitable for the prediction of drug clearance in patients with hepatic impairment with or without cancer and is simple and accurate.

Keywords: albumin; bilirubin; albumin-bilirubin scoring system; child-pugh scoring system; hepatic impairment; national cancer institute classification system

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Introduction

The liver is the main site of metabolism for many drugs resulting in the clearance of these drugs through a variety of oxidative and conjugative metabolic pathways (phase I and II reactions) [1-2]. Liver impairment may lead to changes in the pharmacokinetics (PK) of drugs which are mainly metabolized due to the reduced capacity of the liver to metabolize drugs. As a result, drugs or active metabolites can be accumulated in the body and may reach to toxic levels. Furthermore, pro-drugs are needed to be converted to active metabolite(s) for therapeutic benefits but liver impairment may lead to reduced formation of active metabolite(s) resulting in the reduced efficacy of such products [1-2].

There can be many liver diseases such as alcoholic liver disease and chronic infections with hepatitis viruses B and C, acute hepatitis D or E, primary biliary cirrhosis, primary sclerosing cholangitis [1-2]. In liver disease, there are changes in the activity of metabolizing enzymes and hepatic transporters [1-2]. Reduced duodenal CYP3A activity has also been noted in liver disease [3]. Liver disease may also alter kidney function resulting in the accumulation of a drug and its active or inactive metabolite(s) even though a drug is not primarily metabolized in the liver [1-2].

Both the United States Food and Drug Administration (FDA) and European Medicinal Agency (EMA) recommend Child-Pugh Score to assess the hepatic impairment to characterize the severity of the disease. Hepatic impairment is classified as mild, moderate, and severe and based on these three categories, enrollments are made in clinical trials and subsequent dosing recommendation. There are 5 parameters which are used to classify Child-Pugh score to assess the hepatic impairment. Three parameters namely albumin, bilirubin, and prothrombin time are laboratory-based whereas ascites and encephalopathy are clinical features. Based on these tests, the FDA has suggested 3 categories of hepatic impairment. Based on Child-Pugh score, these three categories are: Category A or mild liver impairment [score 5-6], Category B or moderate liver impairment [score 7-9], Category C or severe liver impairment (score 10-15). Child-Pugh classification system to assess hepatic impairment is widely used in patients with or without cancer.

Another system to assess hepatic impairment was developed by the National Cancer Institute (NCI) Organ Dysfunction Working Group to guide dosing for anticancer drugs in patients with cancer and hepatic impairment [4]. The NCI classification system uses only two laboratory-based parameters namely total bilirubin and aspartate aminotransferase activity. NCI classification system is much simpler than the Child-Pugh classification system and is easy to implement in routine clinical practice for dosing. NCI classification system has been advocated for patients with cancer and hepatic impairment. Another hepatic impairment classification system which has been found to be suitable in patients with cancer and hepatic impairment is the use of bilirubin and albumin values together and is known as albumin-bilirubin (ALBI) scoring system [5-8].

The objective of this study was to develop a simple method which can be implemented both in clinical settings and in clinical drug development for the prediction of CL (Dose/area under the curve (AUC)) and subsequently for dose selection in subjects with varying degrees of hepatic impairment. Serum bilirubin or serum albumin or the combination of the two (ALBI) was used to predict CL of drugs in subjects with mild, moderate, and severe hepatic impairment and compare the predicted CL values with the observed CL values (obtained from clinical trials).

Methods

Thirty-five drugs were used in this study to predict the CL of drugs in subjects with varying degrees of hepatic impairment (S1-S34). The following three methods were used to predict drug CL in subjects with hepatic impairment.

Method I: In this method, serum albumin (SA) concentration (g/L) was used to develop equation 1 to predict drug CL in subjects with hepatic impairment.

Predicted CL = Adult CL in healthy subjects X (SA concentration in the subjects with hepatic impairment/SA in healthy subjects) (1)

Method II: In this method, bilirubin concentration ($\mu\text{mol/L}$) was used to develop equation 2 to predict drug CL in subjects with hepatic impairment.

Predicted CL = Adult CL in healthy subjects/(log₁₀ bilirubin concentration in subjects with hepatic impairment/ log₁₀ bilirubin in healthy subjects) (2)

Bilirubin concentrations widely vary across individuals (healthy as well as hepatic impairment) therefore, log₁₀ of bilirubin concentration was used in equation 2. Bilirubin concentrations mg/dL (where reported) were converted to $\mu\text{mol/L}$ by multiplying mg/dL by a factor of 17.1.

Method III: In this method both serum albumin and bilirubin concentrations were used to predict the CL of drugs in subjects with hepatic impairment. In the first step, albumin-bilirubin score (ALBI) was calculated by the following formula [7, 8].

ALBI Score = $-0.085 \times (\text{albumin g/L}) + 0.66 \times \log_{10} (\text{bilirubin } \mu\text{mol/L})$ (3)

In the next step, the CL of a drug was predicted using equation 4.

Predicted CL = Adult CL in healthy subjects X (score in the subject with hepatic impairment/ score in healthy subjects). (4)

Statistical Analysis

Prediction fold-error of 0.5-2, 0.5-1.5 (a 50% prediction error on either side of 1) and a more stringent criteria in terms of 0.7-1.3 (a 30% prediction error on either side of 1) were used for the assessment of the predictive performance of the proposed methods. Prediction fold-error of 0.5-2 is widely used for the predictive power of the method(s) in clinical pharmacology studies but this author thinks that 0.5-2-fold prediction error is too high for clinical purpose therefore, a much narrower range of prediction error such as 0.5-1.5 and 0.7-1.3 was also used in this study. Considering a high variability in the CL in liver impairment, a 50% (0.5-1.5) prediction error was considered accurate and acceptable from clinical perspective. The prediction fold-error was calculated as follows:

$$\text{Prediction fold-error} = (\text{predicted CL}/\text{observed CL}) \quad (5)$$

Results

There were 35 drugs in this study with varying degrees of hepatic impairment. There were 22, 26, and 16 drugs with mild, moderate, and severe hepatic impairment with a total number of 64 observations (data points). The range of albumin and bilirubin levels in healthy subjects and subjects with different degrees of hepatic impairment is shown in Table 1.

Table 1: Range, mean and standard deviation for albumin and bilirubin levels

Healthy (n = 64)	Mild (n = 22)	Moderate (n = 26)	Severe (n = 16)
Albumin (g/L)			
31-55 (43.2 ± 4.3)	33-49 (40.9 ± 4.5)	22-44 (34.7 ± 5.4)	19-40 (28.9 ± 4.1)
Bilirubin ($\mu\text{mol/L}$)			
5-25 (10.8 ± 3.7)	8-22 (14.4 ± 3.8)	15-50 (27.9 ± 9.2)	26-212 (79.6 ± 43.8)*
ALBI			
-2.33 to -3.99	-2.03 to -3.38	-0.93 to -2.85	-0.43 to -2.47
(-3.22 ± 0.33)	(-2.72 ± 0.38)	(-2.01 ± 0.49)	(-1.23 ± 0.43)

Albumin and bilirubin levels are based on the clinical data from this study. The numbers in parenthesis are mean ± standard deviation.

* The highest bilirubin value was 212 $\mu\text{mol/L}$. The next highest bilirubin value was 120 $\mu\text{mol/L}$ leading to a mean and a standard deviation of 70.7 ± 26.9 $\mu\text{mol/L}$.

The results of the study are summarized in Table 2 and individual data analysis is provided in supplementary Table 1. The results of the study indicate that when all 64 observations were taken into account, the predictive performance of all three methods provided almost similar results (slightly better with ALBI) (Table 2). More than 90% observations were within 0.5-2-fold prediction error by all three methods. Based on albumin, bilirubin, and ALBI, 75.0%, 79.7%, and 89.1% observations were within 0.5-1.5-fold prediction error, respectively. A more stringent criteria of 0.7-1.3-fold prediction error ranged from 64.1% (albumin or bilirubin) to 70.3% (ALBI). The results of the study in subjects with mild, moderate, and severe hepatic impairment by all three methods are described below.

Mild hepatic impairment: There were 22 drugs (22 data points or observations) with mild hepatic impairment. More than 90% observations were within 2-fold and 0.5-1.5-fold prediction error by all three methods (Table 2). More than 86% observations were noted within 0.7-1.3-fold prediction error (Table 2). Overall, all three methods provided excellent prediction of drug CL in subjects with mild hepatic impairment.

Moderate hepatic impairment: There were 26 drugs (26 data points or observations) with moderate hepatic impairment. More than 90% subjects were within 2-fold prediction error by all three methods (Table 2). There were 76.9%, 84.6%, and 84.6% observations within 0.5-1.5-fold prediction error by albumin, bilirubin and ALBI methods, respectively. Prediction error within 0.7-1.3-fold ranged from 65.4 to 69.2% observations by all three methods (Table 2).

Table 2: Comparison between the three methods for the prediction of clearance in subjects with liver impairment

Range (fold-error)	Albumin	Bilirubin	ALBI
All (n = 64)			
0.5-2	61 (95.3)	60 (93.8)	63 (98.4)
0.5-1.5	48 (75.0)	51 (79.7)	57 (89.1)
0.7-1.3	41 (64.1)	41 (64.1)	45 (70.3)
>2	3 (4.7)	4 (6.3)	0 (0)
<0.5	0 (0)	0	1 (1.6)
Mild (n = 22)			
0.5-2	21 (95.5)	21 (95.5)	21 (95.5)
0.5-1.5	20 (90.9)	20 (90.9)	20 (90.9)
0.7-1.3	19 (86.4)	18 (81.8)	17 (77.3)
>2	1 (4.5)	1 (4.5)	1 (4.5)
<0.5	0 (0)	0 (0)	0 (0)
Moderate (n = 26)			
0.5-2	25 (96.2)	25 (96.2)	25 (96.2)
0.5-1.5	20 (76.9)	22 (84.6)	22 (84.6)
0.7-1.3	18 (69.2)	18 (69.2)	17 (65.4)
>2	1 (3.8)	1 (3.8)	1 (3.8)
<0.5	0 (0)	0 (0)	0 (0)
Severe (n = 26)			
0.5-2	15 (93.8)	14 (87.4)	15 (93.8)
0.5-1.5	8 (50.0)	9(56.3)	15 (93.8)
0.7-1.3	4 (25.0)	5 (31.3)	11 (68.8)
>2	2 (12.5)	2 (12.5)	0 (0)
<0.5	0 (0)	0 (0)	1 (6.3)

Number in parenthesis is % of observation

Severe hepatic impairment: There were 16 drugs (16 data points or observations) with severe hepatic impairment. More than 90% observations were within 2-fold prediction error by albumin or ALBI method and 87.4% by bilirubin. The prediction error within 0.5-1.5-fold and 0.7-1.3-fold was poor by albumin or bilirubin (Table 2). On the other hand, the prediction error within 0.5-1.5-fold and 0.7-1.3-fold by ALBI was 93.8% and 68.8%, respectively (Table 2).

Overall, the predictive power of the three methods for the prediction of CL was excellent in subjects with all three categories of hepatic impairment in terms of 0.5-2-fold prediction error (>90% observations). However, the predictive performance of the methods declined in terms of 0.5-1.5-fold and 0.7-1.3-fold prediction error with the severity of hepatic impairment. From the current study, it appears that for subjects with mild or moderate hepatic impairment either of the three methods can provide a reasonable prediction of drug clearance which may help in dose adjustment in this population. However, in subjects with severe hepatic impairment, when the acceptance criteria are narrowed to within 50% or 30% prediction error, the albumin or bilirubin method performed poorly. In this case, the best approach was ALBI where almost 90% and 70% observations were within 50% or 30% prediction error, respectively.

Discussion

The adjustment of dose of a drug in patients with hepatic impairment is necessary especially, in subjects with moderate to severe hepatic impairment. The Child-Pugh or NCI classification system is widely used for the evaluation of hepatic impairment and for the subsequent dose selection in this population. For patients with hepatic impairment without cancer, Child-Pugh is a popular classification system whereas, oncologists use NCI classification system for patients with cancer. Child Pugh classification system uses 5 parameters of which three parameters are laboratory-based (albumin, bilirubin, and prothrombin time) and two parameters are clinically oriented. On the other hand, NCI classification system uses only two laboratory-based parameters (bilirubin and aminotransferase) and is much simpler than Child-Pugh classification system to implement. The range of laboratory-based parameters in Child-Pugh and NCI classification systems are somewhat arbitrary [4, 5]. In the NCI classification system, the upper limit of normal (ULN) remains undefined and the range of bilirubin levels appear arbitrary [4, 5].

There appears to be some discordance between the Child-Pugh and NCI classification systems [9]. Elmeliegy et al. [9]. evaluated the discordance between the two systems and the impact on dosing recommendations in patients with hepatic impairment. Out of 82 studies evaluated by the authors, 50 studies in patients without cancer used Child-Pugh classification system for hepatic impairment. In patients with cancer (32 studies), 22 studies used NCI classification system and 9 used Child-Pugh classification system. One study followed World Health Organization classification system. The discordance between Child-Pugh and NCI classification systems was evaluated for 5 FDA approved anticancer drugs.

According to the authors [9], NCI classification system tended to classify subjects as less impaired than Child-Pugh. NCI classification system showed less impact of hepatic impairment than Child Pugh for one drug (bosutinib) whereas, an opposite trend was noted for another one drug (axiininib). According to the author, the discordance between the two-classification system for dosing requires attention.

According to Feng et al [5], Child-Pugh scoring system has some shortcomings especially, it is not suitable for hepatocellular carcinoma (HCC) [5]. Furthermore, Child-Pugh scoring system cut off values for the laboratory-based parameters are arbitrary and the assessment of ascites and hepatic encephalopathy is subjective. An alternative to Child-Pugh scoring system is albumin-bilirubin (ALBI) grade. The predictive value provided for HCC patients by the ALBI grade was comparable to that of the Child-Pugh grade [5].

The application of ALBI in place of Child-Pugh has been advocated in patients with HCC because Child-Pugh provides prognosis in patients with cirrhosis whereas, patients with HCC do not have cirrhosis but suffer from other liver pathologies and the degree of liver function is more likely related to the size and tumor stage [5-7]. From a practical perspective, the ALBI approach is simple and can be used not only in routine clinical practice but can also be used in clinical drug development.

The main objective of this study was to use only one or two laboratory-based parameters namely albumin or bilirubin or the combination of the two to predict drug clearance and subsequently dose selection. It was noted that in ALBI classification system, within a single grade (mild, moderate, or severe), there was a wide variation in hepatic function [5]. The Child-Pugh classification system lacks this variability as a result it is probably less accurate than ALBI for dosing purpose [5].

In supplementary Table 1, the values of albumin and bilirubin levels as different categories of hepatic impairment are presented. Overall, data suggest that both albumin and bilirubin levels, in most instances, accurately identify the hepatic impairment grades classified as mild, moderate, and severe.

In this study, the use of albumin or bilirubin levels provided a good prediction of drug CL in patients with mild and moderate hepatic impairment (within 0.5-2 or 0.5-1.5-fold prediction error) but in patients with severe hepatic impairment the prediction of clearance was poor within 0.5-1.5 or 0.7-1.3-fold error prediction error. A better prediction of CL in subjects with severe hepatic impairment was noted with ALBI (approximately 69% within 0.7-1.3-fold prediction error).

Since ALBI is considered more appropriate for patients with cancer than Child-Pugh, the current study indicates that ALBI can also be used for patients without cancer. There is no reason for not using ALBI in place of Child-Pugh and NCI classification system. Both albumin and bilirubin are powerful indicators for hepatic impairment and based on these two parameters and using equations 3 and 4 one can predict CL or exposure (AUC) of a drug with reasonable accuracy in patients with all three degrees of hepatic impairment.

Since dosing of a drug in patients with hepatic impairment is based on PK study and the parameter which is generally used for dose adjustment is either AUC or CL. In this study, the CL of drugs was predicted to evaluate the accuracy of CL prediction and ultimately dose recommendation. It should be noted that all these prediction methods are for the initiation of a dedicated clinical trial(s) including PK. Such predictions will help to start the clinical trial with a more reliable starting dose rather than randomly selected dose. All three methods especially (or preferably), ALBI can also be used in clinical settings.

Table 1 indicates that there is a wide variability in albumin and bilirubin values not only in healthy subjects but in subjects with hepatic impairment. The mean albumin values decrease with the severity of the hepatic impairment and the mean

bilirubin values increase with the severity of the hepatic impairment. In both groups, in terms of mean, there is a clear distinction across the groups.

There is high variability in the observed PK parameters in subjects with hepatic impairment especially, in severe liver impairment. Therefore, the dose adjustment will require a correct estimate of change in the magnitude of exposure of a drug especially, in severe hepatic impairment. A 2-fold (0.5-2) prediction error may not be acceptable for the selection of the 'right dose' in subjects with severe hepatic impairment. A dedicated clinical PK study will provide accurate information regarding the impact of hepatic impairment of a drug. PK study should be conducted in all three categories of hepatic impairment because PK can be different across three groups especially, in subjects with moderate or severe hepatic impairment than the healthy subjects. It should be also recognized, that the recommended dose of a drug in subjects with varying degrees of hepatic impairment in the package insert is an average value in a given population. In an individual subject, the recommended dose in package insert may not be optimum and will require adjustment. This adjustment can be done using albumin or bilirubin levels of an individual patient rather than going through any classification system of hepatic impairment.

For many drugs, mild hepatic impairment may not be of concern but moderate and severe especially, severe can be of serious concern. While going over the studies, the author noted that almost in all hepatic impairment studies, the patients irrespective of the degree of hepatic impairment received the same dose as healthy subjects. This may be acceptable for patients with mild or moderate hepatic impairment but not patients with severe hepatic impairment. This is not a good practice and in clinical trials the patients with severe hepatic impairment should receive lower dose than the patients with mild or moderate hepatic impairment. This can be easily done by predicting CL of a drug as described in this manuscript and then adjusting the dose for dedicated clinical trials in subjects with hepatic impairment particularly, in subjects with severe hepatic impairment.

Conclusions

This study demonstrates that the levels of albumin or bilirubin or the combination of the two can be used to predict CL of a drug with reasonable accuracy in subjects with varying degrees of hepatic impairment. In this study, most of the drugs used for analysis were for patients without cancer. Based on the literature and the current study, ALBI is suitable for the classification of hepatic impairment in patients with or without cancer. Particularly, in patients with severe hepatic impairment, the prediction accuracy of ALBI is more accurate than using only albumin or bilirubin.

In short, one can use bilirubin or albumin levels using equations 3 and 4 for the prediction of CL in patients with varying degrees of hepatic impairment and subsequently dose recommendation. It is also possible that the dose of a drug in subjects with hepatic impairment can be directly predicted without predicting the CL by using the proposed methods. This will however, require a separate analysis.

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Availability of data and material: Data were taken from the literature and references are provided in the manuscript. All the data that support the findings of this study are available Supplementary Table.

Author contribution: This is a single author article. IM conceived the research project, collected and analyzed the data, and wrote the manuscript.

Ethical statement: The author declares that no clinical trials were conducted for this study.

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Appendix

Table S1: Observed and predicted clearance of drugs by three methods in patients with varying degrees of hepatic impairment

	Albumin	Bilirubin	Observed	Predicted CL (L/hr)			Ratio (predicted/observed)		
	g/L	µmol/L	CL (L/hr)	Albumin	Bilirubin	ALBI	Albumin	Bilirubin	ALBI
Voclosporin Ref S1									
Healthy	42 (37-47)	14 (7-29)	77.5 ± 25.8						
Mild	46 (43-50)	16 (4-30)	48.0 ± 28.8	84.9	75.2	86.1	1.77	1.57	1.79
Moderate	35 (28-40)	33 (9-50)	34.3 ± 17.2	64.6	59.5	54.5	1.88	1.73	1.59
Midazolam Ref S2									
Healthy	45 ± 4	10.6 ± 4.9	24.8 ± 8.1						
Mild	40 ± 5	22.2 ± 13.8	25.5 ± 8.2	19.7	19.0	18.6	0.77	0.74	0.73
Moderate	34 ± 5	29.8 ± 18.6	9.8 ± 6.6	16.8	17.3	13.2	1.71	1.77	1.35
Severe	28 ± 3	79.5 ± 45.6	8.4 ± 2.1	13.8	13.4	7.8	1.64	1.60	0.92
Tigecycline Ref S3									
Healthy	37-52	5-17	29.8 ± 11.3						
Mild	35-55	8-31	31.2 ± 13.9	28.2	23.1	26.5	0.90	0.74	0.85
Moderate	29-46	17-66	22.1 ± 9.3	23.4	17.0	18.4	1.06	0.77	0.83
Severe	28-33	34-157	13.5 ± 2.7	22.6	13.6	15.2	1.67	1.01	1.13
Voxelotor Ref S4									
Healthy	43 ± 2.9	12 ± 4.0	7.5 ± 26.0						
Mild	44 ± 2.3	10 ± 5.0	6.7 ± 24.4	7.7	7.9	8.2	1.15	1.18	1.23
Moderate	42 ± 2.6	17 ± 6.0	6.1 ± 28.7	7.3	6.5	7.4	1.20	1.07	1.21
Severe	31 ± 5.1	52 ± 29	3.8 ± 25.5	5.4	4.7	4.0	1.42	1.23	1.06
Sirolimus Ref S5									
Healthy	35.8 ± 3.9	12.0 ± 5.4	21.3 ± 4.2						
Severe	19.3 ± 2.0	67.4 ± 60.0	6.9 ± 3.1	11.3	12.4	3.9	1.64	1.80	0.57

Table S1 Continued

	Albumin	Bilirubin	Observed	Predicted CL (L/hr)			Ratio (predicted/observed)		
	g/L	µmol/L	CL (L/hr)	Albumin	Bilirubin	ALBI	Albumin	Bilirubin	ALBI
Clazosentan Ref S6									
	Mean (range)								
Healthy	55 ± 4	10.8 ± 1.3	34 (28-42)						
Mild	49 ± 8	16.8 ± 9.1	25 (17-36)	31	29	29	1.23	1.16	1.16
Moderate	43 ± 7	35.1 ± 16.0	15 (12-18)	27	23	23	1.80	1.53	1.52

Severe	28 ± 7	67.5 ± 61.1	9 (6-13)	18	19	10	1.96	2.16	1.12
Vilaprisan	Ref S7		Mean (%CV)						
Healthy	43.1 ± 2.3	9.1 ± 6.7	12.4 ± 48.8						
Mild	41.7 ± 3.0	10.3 ± 8.4	10.7 ± 74.4	12.0	11.8	11.8	1.12	1.10	1.10
Healthy	43.3 ± 2.3	7.0 ± 2.2	14.1 ± 41.1						
Moderate	38.8 ± 5.2	14.9 ± 12.5	10.2 ± 66.8	12.6	10.2	11.4	1.24	1.00	1.12
Mifamurtide	Mean (range)		Mean (%CV)		Ref S8				
Healthy	43 (41-48)	12 (7-31)	33 (16)						
Mild	42 (36-37)	14 (9-31)	31 (29)	32	31	31	1.03	1.00	1.01
Healthy	44 (41-49)	13 (9-17)	37 (18)						
Moderate	36 (22-42)	27 (22-48)	31 (38)	30	29	26	0.98	0.94	0.85
Rivaroxaban	Ref S9		Mean (%CV)						
Healthy	44 ± 2	12.0 ± 6.8	6.6 (33.4)						
Mild	44 ± 4	10.3 ± 3.4	5.7 (42.4)	6.6	7.0	6.7	1.16	1.23	1.17
Moderate	34 ± 4	32.7 ± 17.1	2.8 (59.1)	5.1	4.7	4.1	1.82	1.39	1.43
Ornidazole	Ref S10								
Healthy	45 ± 4	17 ± 6	3.1 ± 0.1						
Severe	27.9 ± 2.2	212 ± 125	2.1 ± 0.3	1.9	1.6	0.8	0.90	0.77	0.40

Table S1 Continued

	Albumin	Bilirubin	Observed	Predicted CL (L/hr)			Ratio (predicted/observed)		
	g/L	µm/L	CL (L/hr)	Albumin	Bilirubin	ALBI	Albumin	Bilirubin	ALBI
E5564	Ref S11		mL/hr						
Healthy	42 ± 3	10.3 ± 5.1	83 ± 27						
Mild	41 ± 3	13.7 ± 5.1	80 ± 27	81	81	78	1.01	1.01	0.98
Healthy	41 ± 3	8.6 ± 3.4	74 ± 19						
Moderate	38 ± 5	34.2 ± 34.2	73 ± 16	69	45	57	0.94	0.62	0.78
Cabotegravir	Ref S12								
Healthy	43.3 ± 5.1	9.4 ± 2.9	0.25 ± 0.08						
Moderate	36.0 ± 6.5	24.4 ± 10.6	0.31 ± 0.11	0.21	0.17	0.18	0.68	0.56	0.58
FTY720	Ref S13								
Healthy	43 ± 2	10.3 ± 3.4	11.9 ± 3.6						
Mild	43 ± 3	15.4 ± 5.1	10.6 ± 3.4	11.9	10.1	11.4	1.12	0.95	1.08
Moderate	36 ± 4	41 ± 22.1	8.5 ± 3.4	9.4	7.5	7.3	1.11	0.88	0.85
Lidocaine	Ref S14								
Healthy	42 ± 5	12 ± 6	54 ± 15						
Mild	40 ± 4	21 ± 13	46 ± 19	51.4	43.9	47.8	1.12	0.95	1.04
Severe	29 ± 7	120 ± 102	19 ± 7	36.4	27.9	19.7	1.89	1.45	1.02
Opicapone	Ref S15								
Healthy	44.6 ± 1.7	9.1 ± 4.0	29 ± 22						
Moderate	44.1 ± 5.6	22.7 ± 14.5	16 ± 40	29	21	26	1.79	1.28	1.64
Conivaptan	Ref S16								
Healthy	43.8 ± 3.5	8.7 ± 2.6	15.5 ± 4.2						
Severe	28.0 ± 6.6	68.8 ± 46.6	9.4 ± 1.8	9.9	7.9	5.8	1.05	0.84	0.62

Table S1 Continued

	Albumin	Bilirubin	Observed	Predicted CL (L/hr)			Ratio (predicted/observed)		
	g/L	µm/L	CL (L/hr)	Albumin	Bilirubin	ALBI	Albumin	Bilirubin	ALBI
Teneligliptin	Ref S17								
Healthy	40 (36-43)	7 (4-12)	13.1 ± 1.7						
Mild	42 (37-45)	9 (4-21)	9.8 ± 2.5	13.7	11.4	13.4	1.39	1.17	1.37
Moderate	35 (29-36)	19 (5-34)	8.6 ± 1.7	11.5	8.7	9.9	1.33	1.2	1.06
Levosimendan	Ref S18								
Healthy	44 ± 0.4	10 ± 1	20.0 ± 1.6						
Moderate	38 ± 1.5	31 ± 4	16.8 ± 2.4	17.3	13.4	14.6	1.03	0.80	0.87
Cabozantinib	Ref S19								

Healthy	41.4 ± 3.3	8.7 ± 2.7	2.0 ± 0.6						
Mild	35.4 ± 3.3	14.9 ± 2.7	1.2 ± 0.7	1.7	1.6	1.5	1.43	1.34	1.28
Moderate	28.3 ± 6.4	33.5 ± 12.5	1.5 ± 1.4	1.4	1.2	1.0	0.91	0.82	0.67
Edoxaban	Ref S20								
Healthy	38.5 ± 1.6	13.7 ± 5.3	31.2 ± 8.0						
Mild	35.8 ± 4.1	12 ± 12	32.9 ± 9.1	29.1	31.5	28.3	0.88	0.96	0.86
Healthy	39.1 ± 2.0	12 ± 3.2	31.8 ± 7.2						
Moderate	35.5 ± 4.6	25.7 ± 20.5	33.8 ± 9.5	28.8	24.1	25.4	0.85	0.71	0.75
Levetiracetam	Ref S21		mL/min/1.73 m ²						
Healthy	47.3 ± 2.9	7.9 ± 3.1	63.4 ± 9.7						
Mild	43.6 ± 3.4	18 ± 11	62.5 ± 8.7	58.4	63.6	63.3	0.94	1.02	1.01
Moderate	33.7 ± 5.3	40.5 ± 21.5	55.4 ± 10.5	45.2	49.7	39.7	0.82	0.90	0.72
Severe	29.6 ± 4.9	120 ± 67	29.2 ± 13.5	39.7	38.4	25.2	1.36	1.32	0.86

Table S1 Continued

	Albumin g/L	Bilirubin µm/L	Observed CL (L/hr)	Predicted CL (L/hr)			Ratio (predicted/observed)		
				Albumin	Bilirubin	ALBI	Albumin	Bilirubin	ALBI
Axitinib	Ref S22								
Healthy	39 ± 5.9	9.9 ± 10.4	32.1 ± 20.2						
Mild	35 ± 9.0	14.6 ± 15.2	40.9 ± 68.3	28.8	27.6	26.7	0.70	0.68	0.65
Moderate	22 ± 8.7	27 ± 26	16.4 ± 7.2	18.1	22.4	11.2	1.10	1.37	0.68
Propofol	Ref S23		L/min						
Healthy	40 ± 6	17 ± 5	1.75 ± 0.32						
Mild	36 ± 4	21 ± 7	1.74 ± 0.37	1.58	1.63	1.49	0.91	0.94	0.86
Moderate	31 ± 7	50 ± 16	1.38 ± 0.39	1.34	1.27	1.00	0.97	0.92	0.72
Maribavir	Ref S24								
Healthy	44 ± NA	10.3 ± NA	3.3 ± 0.97						
Moderate	43 ± NA	17.1 ± NA	2.9 ± 1.4	3.2	2.7	3.1	1.11	0.93	1.05
Zidovudine	Ref S25								
Healthy	40 ± 5	10 ± 5	154 ± 49						
Mild	33 ± 3	15 ± 13	55 ± 20	113	131	99	2.05	2.38	1.79
Moderate	31 ± 9	23 ± 19	49 ± 21	106	113	84	2.17	2.31	1.72
Severe	28 ± 4	84 ± 49	38 ± 13	96	80	54	2.52	2.11	1.42
Semaglutide	Ref S26		mL/hour						
Healthy	42 (38-46)	11.5 (4-24)	40 ± 13						
Mild	42 (39-45)	15.5 (7-29)	43 ± 12	40	36	39	0.93	0.83	0.91
Moderate	40 (35-46)	18.9 (7-37)	37 ± 7	37	33	35	1.01	0.90	0.94
Severe	33 (29-39)	53.4 (32-95)	43 ± 4	31	25	23	0.72	0.57	0.53

NA = The authors did not provide standard deviation or range.

Table S1 Continued

	Albumin g/L	Bilirubin µm/L	Observed CL (L/hr)	Predicted CL (L/hr)			Ratio (predicted/observed)		
				Albumin	Bilirubin	ALBI	Albumin	Bilirubin	ALBI
Acetaminophen	Ref S27								
Healthy	32 ± 6	21.4 ± 15.0	22.1 ± 3.8						
Severe	25 ± 5	60.4 ± 30.6	13.9 ± 3.6	17.3	16.5	11.3	1.24	1.19	0.82
Morphine	Ref S28								
Healthy	40 ± NA	25 ± NA	118 ± 10						
Severe	27 ± 6	98 ± 50	48 ± 13	80	85	47	1.66	1.76	0.97
Amprenavir	Ref S29								
Healthy	49 (45-53)	7 (8-12)	17 (11-62)						
Cirrhosis	32 (30-40)	21 (2-51)	12 (7-18)	11	11	9	0.92	0.92	0.75
Ritonavir	Ref S29								
Healthy	49 (45-53)	7 (8-12)	17 (7-56)						
Cirrhosis	32 (30-40)	21 (2-51)	9 (4-43)	11	11	8.8	1.22	1.22	0.98
Theophylline	Ref S30								

Healthy	43.7 ± 4.1	9.4 ± 2.7	3.7 ± 0.6						
Mild	42.5 ± 2.3	13.8 ± 3.9	3.1 ± 0.8	3.6	3.1	3.4	1.16	1.0	1.10
Severe	28.2 ± 5.0	64.0 ± 47.4	1.3 ± 0.4	2.4	2.0	1.4	1.85	1.54	1.08
Zomepirac	Ref S31								
Healthy	52 ± NA	17.1 ± NA	15.5 ± 5.2						
Mild	49 ± 5	15.4 ± 10.3	12.6 ± 3.3	14.6	16.1	14.5	1.16	1.27	1.15
Severe	40 ± 6	25.6 ± 11.9	8.3 ± 2.7	11.9	13.5	10.6	1.44	1.63	1.28

Table S1 Continued

	Albumin	Bilirubin	Observed	Predicted CL (L/hr)			Ratio (predicted/observed)		
	g/L	µm/L	CL (L/hr)	Albumin	Bilirubin	ALBI	Albumin	Bilirubin	ALBI
Niraparib	Ref S32								
Healthy	41 (35-46)	7 (5-14)	15.2 ± NA						
Moderate	29 (22-38)	42 (29-51)	9.7 ± NA	10.8	7.8	7.2	1.11	0.80	0.74
Meperidine	Ref S33								
Healthy	46 ± 3	12 ± 5.1	54 ± 13						
Severe	29 ± 5	67 ± 82	24 ± 6	34	32	21	1.42	1.33	0.89
Olaparib	Ref S34								
Healthy	41 (34-46)	6 (4-19)	6.6 ± 3.2						
Mild	37 (30-46)	13 (3-15)	5.4 ± 2.1	6.0	4.7	5.4	1.10	0.87	1.00
Moderate	27 (2-37)	25 (10-45)	5.3 ± 3.8	4.3	3.7	3.1	0.82	0.70	0.58