Review article: time to revisit Child-Pugh score as the basis for predicting drug clearance in hepatic impairment

Eman El-Khateeb¹,² | Adam S. Darwich³ | Brahim Achour¹ | Varinder Athwal⁴,⁵ | Amin Rostami-Hodjegan¹,⁶

¹Centre for Applied Pharmacokinetic Research, University of Manchester, Manchester, UK
²Clinical Pharmacy Department, Faculty of Pharmacy, Tanta University, Tanta, Egypt
³Logistics and Informatics in Health Care, School of Engineering Sciences in Chemistry, Biotechnology and Health (CBH), KTH Royal Institute of Technology, Stockholm, Sweden
⁴Wellcome Centre for Cell-Matrix Research, Division of Diabetes, Endocrinology and Gastroenterology, University of Manchester, Manchester, UK
⁵Research and Innovation Division, Central Manchester University Hospitals NHS Foundation Trust, Manchester, UK
⁶Certara UK Ltd. (Simcyp Division), Sheffield, UK

Correspondence
Varinder Athwal, Division of Diabetes, Endocrinology and Gastroenterology, University of Manchester, Oxford Road Manchester, M13 9PL UK.
Email: varinder.athwal@manchester.ac.uk
Amin Rostami-Hodjegan, CAPKR, University of Manchester, Stopford Building, Oxford Road Manchester, M13 9PT UK.
Email: amin.rostami@manchester.ac.uk

Summary

Background: Prescription information for many drugs entering the market lacks dosage guidance for hepatic impairment. Dedicated studies for assessing the fate of drugs in hepatic impairment commonly stratify patients using Child-Pugh score. Child-Pugh is a prognostic clinical score with limitations in reflecting the liver’s metabolic capacity.

Aims: To demonstrate the need for better drug dosing approaches in hepatic impairment, summarise the current status, identify knowledge gaps related to drug kinetic parameters in hepatic impairment, propose solutions for predicting the liver disease impact on drug exposure and discuss barriers to dosing guidance in those patients.

Methods: Relevant reports on dosage adjustment in hepatic impairment were analysed concerning the prediction of the impairment impact on drug kinetics using physiologically-based pharmacokinetic (PBPK) modelling.

Results: PBPK models are suggested as a potential framework to understand drug clearance changes in hepatic impairment. Quantifying changes in abundance and activity of drug-metabolising enzymes and transporters, understanding the impact of shunting, and accounting for interindividual variations in drug absorption could help in extending the success of these models in hepatically-impaired populations. These variables might not correlate with Child-Pugh score as a whole. Therefore, new metabolic activity markers, imaging techniques and other scoring systems are proposed to either support or substitute Child-Pugh score.

Conclusions: Many physiological changes in hepatic impairment determining the fate of drugs do not necessarily correlate with Child-Pugh score. Quantifying these changes in individual patients is essential in future hepatic impairment studies. Further studies assessing Child-Pugh alternatives are recommended to allow better prediction of drug exposure.
Liver metabolism is responsible for the elimination for many drugs. The liver has impressive functional hepatic reserve, and consequently, significant hepatic impairment (HI) has to occur before changes in drug metabolism occur. Unlike renal impairment (RI), there is currently no surrogate markers to estimate HI and limited evidence to guide drug dose adjustment. HI can be defined as any acute or chronic liver injury that affects liver functional capacity. Dose adjustment in HI population is challenging as the impact of the disease on drugs clearance varies depending on the drug characteristics as well as individual patient factors. Cirrhosis is a significant and increasing burden of disease worldwide. It is the common end-point of most chronic fibrotic liver diseases and the point at which hepatic reserve has been exhausted. Consequently, decline in hepatic function is evident with progressive cirrhosis. Multiple interacting factors determine the behaviour of drugs in cirrhosis, making drug dose adjustment a challenge. Under or over dosing could have significant clinical consequences. Therefore, given the prevalence of disease and the importance of optimal drug dosing, it is essential to predict drug metabolism. In this review, we focus on strategies for drug dosing in liver cirrhosis.

In cirrhosis, the absorption and disposition kinetics of most drugs are affected. It changes not only the metabolic function of the liver, but it also has an impact on parameters such as liver blood flow, binding to plasma proteins and biliary and renal excretion. These all potentially influence drug pharmacokinetics (PKs) at different degrees depending on the drug and the severity of the disease in the patient. This in turns may lead to significant alterations in the exposure to many drugs, necessitating dosage adjustment to avoid drug toxicity.

Dedicated PK studies for HI patients are part of many drug development programmes, and there is a regulatory guidance on the conduct of such studies and interpretation of the results. This is with a view to providing information to prescribers in the drug label. However, many drug regulatory authorities may approve drugs prior to availability of complete dosage guidance in subgroups of patients, such as those with HI. This raises the need for evidence-based approaches to guide clinicians to the best course of action regarding any dose adjustment of drugs in HI until clinical evidence is established. Physiologically based pharmacokinetic (PBPK) modelling and simulations have been used for this purpose. However optimisation is still required to increase the predictive performance of these models. This review summarises key requirements for developing PBPK models for HI populations, the current scoring systems implemented into these models, their limitations and potential to enhance model predictability.

**3 | CIRRHOSIS EPIDEMIOLOGY, CAUSES AND CLASSIFICATION**

Cirrhosis is a global health burden, accounting for over 1 million deaths per annum, and 4.9%-9.5% of the global population are believed to have some level of cirrhosis. Alcohol, hepatitis C, hepatitis B and nonalcoholic steatohepatitis (NASH) are amongst the most common causes of cirrhosis worldwide. Different classification systems have been used for categorisation of cirrhosis, amongst which Child-Pugh (CP) classification is the most common.

**3.1 | CP system**

Liver cirrhosis is routinely classified based on disease progression into CP grades, CPA (mild), CPB (moderate) and CPC (severe). Although this classification is widely used clinically and can give an indication of the severity of liver disease, it does not express quantitative changes in hepatic metabolic function responsible for drug clearance. Scores in this classification are calculated based on encephalopathy, ascites degree (absent, moderate/controlled or severe/refractory), serum bilirubin and albumin levels, as well as prothrombin time or the international normalised ratio (INR).

**3.2 | Other classification systems**

Apart from CP score, several models exist for grading the severity of liver disease. The Model for End Stage Liver Disease (MELD) score depends on three readily available laboratory variables: serum creatinine, serum bilirubin and INR.
The MELD score was developed and validated to predict mortality in patients with portal hypertension undergoing placement of transjugular intrahepatic portosystemic shunts, but it is now more commonly used to predict survival in cirrhosis and for prioritisation of patients for liver transplant.\(^{13,14}\)

Another system to assess HI specifically in oncology patients was developed by the National Cancer Institute (NCI) Organ Dysfunction Working Group (ODWG) to guide dosing for chemotherapeutics.\(^{15}\) The NCI classification system (NCIc) uses two biochemical parameters to grade hepatic dysfunction: total bilirubin and aspartate aminotransferase.\(^{16}\)

Other classification systems for cirrhosis are available but are not frequently used. Most of these correlate with the CP classification, including Maddrey’s discriminant function (df)\(^{17}\) (using prothrombin time and total serum bilirubin) and the Mayo Survival Model for primary biliary cirrhosis.\(^{18}\)

Using specific markers of metabolic activity is an alternative approach. Monoethylglycinexylidide (MEGX) is a lidocaine metabolite (via cytochrome P450 (CYP) 3A) and a biomarker for the assessment of oxidative enzymes activity.\(^{19}\) Indocyanine green clearance has been validated as a tool for pre-operative assessment of liver function and also gives indication of hepatic blood flow.\(^{20}\) Consequently, it has been assessed as a tool for measuring hepatic function for drug metabolism.\(^{21}\) Galactose single point (GSP) is a simple test that can be used to define clearance of both highly metabolised drugs and drugs which are eliminated without undergoing metabolism in the liver.\(^{22}\) GSP was originally reported in 1995, and further validation studies are awaited.\(^{23}\) Overall, despite promising results, the lack of routine availability limits clinical utility of all these tests.

### 3.3 Limitations of the CP scoring system for drug dosing

Although the CP score is the most commonly used classification system for patients with cirrhosis, it has some limitations that can be explained as follows:

1. **Subjective scoring**: Two elements in CP classification are clinical parameters. These are ascites and encephalopathy scores. They are subjective according to clinical judgement and can also be confused with other disorders.\(^{24}\) For example, a patient with liver cirrhosis and diabetes can experience diabetic coma that can be mistakenly diagnosed as hepatic encephalopathy. Similarly, a patient with a brain tumour along with cirrhosis can show symptoms that may be confused with hepatic dysfunction or disorder. Metabolic encephalopathy can also be precipitated by sepsis or renal insufficiency.\(^{25}\) Ascites severity is also a subjective assessment and may be exacerbated by noncirrhotic factors, including heart failure, cancer and infectious diseases.\(^{26}\) Careful clinical diagnosis is required to rule out other causes and reduce the subjective nature of these parameters. Other scoring systems such as MELD and NCI scores include only biochemical laboratory tests to overcome this subjectivity in CP scoring.

2. **Not accounting for renal function**: Although RI is common with cirrhosis, this scoring system does not consider changes in renal function. For drugs that are mainly eliminated by the kidney, CP classification does not help in clinical predictions or correlate with drug kinetics. Other scoring systems, such as MELD score, were developed to overcome this limitation by including creatinine levels as one of its components.

3. **Not distinguishing between the different causes of cirrhotic liver disease**: Several reports have indicated discrepancies between different causes of cirrhosis in relation to enzyme and transporter expression, inflammatory mediators, speed of progression and control by certain drugs, such as ursodeoxycholic acid (UDCA). Scoring systems (ie, MELD) consider cholestatic and alcoholic cirrhosis as lower risk than other underlying causes in the formula score, but it is uncertain if these aetiologies have better hepatic function compared to other disease aetiologies for the same biochemistry.\(^{27}\)

4. **Wide interindividual variability amongst patients assigned the same score**: As CP scoring stratifies patients into only three categories, wide variations in disease prognosis exist amongst patients within the same group. A study involving over 1000 patients showed that overall survival associated with CP6 class was significantly higher than CPA6.\(^{28}\) This variability becomes more obvious in patients with portal hypertension than those without portal hypertension.\(^{29}\)

5. **Correlation with liver metabolic capacity is not well established**: CP classification was not created to assess liver metabolic function, and it utilises assays attributable to synthetic state, function and clinical status. However, it is not possible to separate the main contributor to CP grade from these three elements. For example, a patient with normal metabolic and synthetic liver function that has refractory ascites or encephalopathy might be scored in the same class as a patient with deteriorated functions and normal clinical measures. Those two patients may require completely different treatment options and drug doses as the metabolic capacity of their livers is widely different. Therefore, the use of markers like serum albumin, prothrombin time, and bilirubin is encouraged and abnormalities in these parameters may be better related to drug elimination capacity than other components of the CP classification, for example, encephalopathy and ascites as recommended by the European Medicine Agency (EMA).\(^{30}\)

In spite of all the limitations discussed above, CP scoring system is still the most widely used in drug development. This scoring system is recommended by the US FDA and the EMA owing to its reproducibility, low cost, classification of cirrhosis into only three main categories (simplicity of interpretation) and incorporation of routinely measured parameters for hepatically impaired patients. Ninety five percent of PK studies dedicated for HI populations in drug development use CP classification to categorise patients at...
different stages of disease severities by contrast less than 2% use NCI or MELD score exclusively.31

4 | MOVING BEYOND CP SCORING SYSTEM

Several attempts have been made to correlate CP score with NCI, MELD and other scoring systems15 or to use other noninvasive metabolic scoring systems. One or a combination of these methods is proposed to overcome the limitations of the CP system. The following have been proposed:

Disease severity index (DSI): This test uses metabolism of oral and intravenous radioactive cholates that account for the changes in first-pass metabolism and the effect of shunting.32 This score showed good correlation with CP score but not with the MELD score. Although it seems to be a promising noninvasive method, its applicability in routine clinical practice and in clinical trials has yet to be investigated.

Refining the CP scoring system: The current cut-off points for several factors in the CP scoring system (shown in Table S1) were not previously validated. Therefore, this scoring system has shown some shortcomings in predicting the 5-year survival of patients with different aetiologies. A retrospective study was performed to refine these cut-off levels for bilirubin, albumin and INR and to introduce creatinine levels into the classification system.33 Although these changes reflected better predictive performance for intermediate and long-term survival, they have not yet been investigated against the metabolic capacity of the liver for different drugs.

Moreover, the objective biochemical components of CP score (albumin, bilirubin and prothrombin time) need further validation against exposure to a broad range of drugs, in order to confirm utility. In order to progress the field, clinical PK studies should provide individual components of a given CP for every patient. Further modifications may include separation of CPA category into A5 and A6 subclasses for HI studies, and the presence of portal hypertension may provide added benefit. Assessment of these can be done retrospectively and on historical studies as long as the records for various components making the CP scores were available for re-analysis.

Imaging techniques: Liver stiffness measurements such as transient elastography correlate with the deposition of hepatic fibrosis and can be used to identify patients with cirrhosis and predict progression to decompensated disease.31 Computed tomography has also been used as a tool to scale-up enzyme abundance and activity data by measuring the functional hepatocyte volume as a direct reflection of the functional reserve of the organ and correlating these values with changes in the CP score.34,35 The simulation outputs for different drugs were in agreement with the biologically determined scalars using microsomal and cytosolic protein contents.36 These technologies offer promise, but more studies are required to investigate the change in the activities of different DMET against image-related measures.

5 | REGULATORY PERSPECTIVE ON DRUG DEVELOPMENT IN HI

With drug dosing moving from a "one size fits all" approach to more "personalised" dosing, individualised tailoring of drug dose to optimise efficacy and minimise harm has become a key focus of investigation. The US FDA guidance recommends PK studies in patients with impaired hepatic function if the hepatic metabolism and/or excretion accounts for a substantial portion of the elimination of the parent drug or its active metabolite(s) (>20% of absorbed dose is eliminated by the liver). The guidance also recommends a HI study even if the drug and/or its active metabolite are eliminated to a lesser extent by the liver when the drug/metabolite has a narrow therapeutic index. In the case of drugs that are intended only for single-dose administration, a HI study will generally not be necessary unless clinical concerns suggest otherwise.37

These PK studies determine the plasma concentrations of the parent drug and sufficiently important active metabolites and calculate PK parameters, such as the area under the concentration-time curve (AUC), terminal half-life (t1/2), maximum plasma concentration (Cmax) and apparent clearance for the parent compound (CL/F). For multiple dose studies, trough concentration (Cmin) and fluctuation should be taken into account. When possible, both unbound and total concentrations are used to express these parameters. Generally, dose reduction is required if the change in the AUC in HI exceeds a twofold increase relative to healthy volunteers.37 Usually, doses are reduced if the liver disease has resulted in a clinically significant impairment in the clearance of the drug except for prodrugs, in which doses may be increased or the frequency of administration may be decreased. In some cases, the drug may be classified as contraindicated in severe liver impairment, depending on the drug's therapeutic window and the impact on the clearance of the drug. In the case of lack of data supporting drug labelling, the drug may be classified as "used with extreme caution".38 To ensure equitable access to patients with cirrhosis to potentially safe and efficacious medication, it is critical that drugs are appropriately scrutinised in HI.

6 | THE NEED FOR DOSE ADJUSTMENT IN HI

Around 50%-80% of NMEs approved in the United States between the years 2013 and 2014 did not include clinical studies that inform dosage recommendations in RI and HI, irrespective of whether these clinical trials were required.5 The percentage of drugs which did not have dosing recommendations for mild and moderate HI at initial approval was ~30% and 50%, respectively, in both of the years 2013 and 2014. However, for severe HI, this proportion was close to 80% in 2013 and ~60% in 2014, as shown by the left part of Figure 1 derived from data published by Jadhav et al.5

We followed the same strategy and found that a similar trend persisted in subsequent years in the period 2015-2019 (Table S2). Biologics were not included in this survey. In 2015, about 36%, 33%
and 72% of the NMEs lacked study-based label guidance for mild (CPA), moderate (CPB) and severe (CPC) cirrhosis, respectively. In the following 4 years (2016-2019), the situation remained similar with a gradual rise in the percentage of drugs without label guidance, mainly in the severe stage of cirrhosis, as shown in Figure 1. These drugs are now available in the market without any labelling guidance regarding their dose levels in this special patient population.

During the different phases of clinical trials, patients are recruited and treated by the investigational drug to test its safety and efficacy. Many special patient populations are excluded during these phases to avoid subjecting those individuals to any risks of unexpected side effects due to inappropriate dosing. However, extensive narrowing of the inclusion criteria or expansion of the exclusion criteria without an obvious aim may influence the inference and usefulness of clinical trials with respect to different issues. First, a large number of patients may miss the opportunity to participate in such trials that may be clinically beneficial. Second, trial results will be less likely to capture the diversity in patient populations that might be exposed to this therapy after being released onto the market. The study population may in fact only represent a small fraction of the market population. Third, extensive time wastage in the recruitment of patients can occur with "restricted" criteria in all phases of clinical studies.

Ironically, when we examine the exclusion criteria related to organ dysfunction, one can find that these exclusions are based on liver function tests (LFTs) and CP scores, in the case of hepatic dysfunction. Unlike renal dysfunction, where creatinine clearance can be a reliable measure of renal clearance, neither LFTs nor CP score accurately reflects the drug-metabolising efficiency of the liver. The upper limits of normal (ULN) range for LFTs, such as aspartate transaminase (AST) and alanine transaminase (ALT), is around 40 IU/L. These can vary between populations according to sex, age and weight of the patient as well as between laboratories. Some patients with mild and moderate HI may have LFTs between 5 and 20 folds the ULN; however, they can still tolerate the approved doses without any symptoms or complications. Thus, for drugs metabolised by the liver, a total exclusion of patients with liver enzymes above twofold to threefold ULN does not necessarily correlate to liver dysfunction and the lack of more metabolic-reflective measures is an urgent issue.

Due to the aforementioned reasons, the American Society of Clinical Oncology (ASCO) adopted a suggestion to modify the eligibility criteria in cancer research clinical trials to be more inclusive of patients with organ dysfunction as long as the dose is suitably adjusted based on evidence-based data. After this recommendation, the FDA published a guidance document for broadening eligibility criteria to increase diversity in enrolment and to include more patients from underrepresented populations.

7 | CAN PBPK MODELLING HELP IN FILLING THE GAP IN DEDICATED CLINICAL TRIALS?

Although PBPK modelling may inform regulatory approval for many drugs and in different situations with more confidence in relation to drug-drug interactions and paediatric applications, only a small number of FDA submissions use PBPK for predicting drug exposure in HI. Different physiological changes in cirrhosis with disease progression were reported to have an impact on drug exposure, such as changes in blood flow to the gut, liver, kidneys and other organs, plasma protein levels, haematocrit level, liver size, DMET expression and activity both in the liver and the gut, renal function and liver circulation, including shunting.

As described in Section 2, articles that assessed PBPK models for different drugs in HI populations were collected irrespective of the software tool used for model development. This search resulted in 60 different publications that match the search criteria, of which only 14 were relevant to the purpose of this review (Table S3). Application of the above mentioned changes in the models produced good predictions (predicted outcomes within twofold of observed data). However, poor predictive performance of these models has been reported in other scenarios, which have shown underprediction of clearance of the modelled drugs, especially in moderate and severe stages of cirrhosis (Figure 2 and Table S3). No single factor can be the source of these biases, as they are not related to common features of the drugs. For example, some models for CYP2D6 substrates showed good performance with moderate HI populations as in the case of eliglustat, whilst others such as atomoxetine did not. However, some of these studies used different software tools and different model structures. The IQ consortium has recently conducted a comprehensive PBPK modelling and simulation research with fixed physiological parameters on nearly 60 drugs and concluded that about 70% of the predicted performance was within twofold.

Similar to previous studies, most of the 30% outliers were observed in moderate and severe HI populations. Improved understanding of these pathophysiologlcal processes in advanced disease and an appropriate classification system of HI are needed. Stratifying
patients based on liver metabolic capacity and availability of clinical
data for model’s validation would improve predictive performance,
reliability and utility of these models.

The use of PBPK modelling in drug development has grown over the
years to inform dosing, optimise clinical study design, shorten the dura-
tion of clinical studies and simulate untested scenarios (such as steady
state exposure, drug-drug interactions or different doses and/or for-
mulations). This approach is thought to be valid for noncirrhotic liver
diseases, such as earlier hepatic steatosis or fatty liver disease,
as long as the degree of change in physiological (system) parameters related to
drug PKs (as mentioned above) is well known. For oncology drug expo-
sure in patients with hepatocellular carcinoma, other classification sys-
tems such as the albumin- bilirubin (ALBI) grade were recommended.50,51

8.1 | The heterogeneous nature of the disease and
the scoring system

As pointed out earlier, chronic liver disease is progressive and dif-
ferent grades and classifications are available with different scoring
systems. The mild grade of CP classification is variable with widely
different survival rates depending on whether the disease is asso-
ciated with portal hypertension or not.52 Other scoring systems do
not correlate well with CP score making the use of these systems
interchangeably very difficult. Moreover, the level of change in the
expression and activity of different DMET is not the same across
scores and is also affected by the aetiology of the disease and its sur-
rounding environment.53 This can be partly attributed to the fact
that the liver is actually not “well-stirred” as usually assumed in differ-
ent models. The well-stirred model assumes that the liver is a single
well-stirred compartment and that the unbound drug concentration in the emer-
gent blood is in equilibrium with the unbound drug within the liver.54 Some preclinical evidence has shown that interzonal and interlobar differences in the distribution of enzymes and transporters
as well as the location and degree of liver disease can have a key role
in predicting the PK outcome.55-57 Therefore, designing a dedicated study using the most common scoring system, such as CP scoring, with all its limitations with regard to assessment of hepatic metabolic
capacity, makes dosage adjustment for those patients and extrapola-
tion of PBPK models for liver disease more challenging.

8.2 | Information on abundance and
activity of DMET

8.2.1 | Drug-metabolising enzymes

Xenobiotic detoxification process in the liver relies on the presence of
metabolic enzymes. Within the hepatocyte, transforming enzymes are
primarily located in the microsomes (small vesicles) of the endoplasmic
reticulum and the soluble fraction of the cytoplasm (cytosol). The im-
pact of impairment on drug clearance varies depending on the meta-
bolic reaction involved to clear this drug and the functional reserve of
these enzymes in the liver. Phase I metabolism is usually known to be
significantly affected by the severity of hepatic dysfunction to a higher
degree than phase II conjugation reactions. The difference between
phase I and phase II biotransformation in response to HI supports the
oxygen limitation theory.58 This theory is based on the assumption of
reduced oxygen transfer from blood to hepatocytes by capillarisation
of sinusoids and cirrhotic tissue development. It relies on the obser-
vation that oxidative Phase I reactions are substantially reduced in liver
disease, whilst Phase II (conjugative) metabolic reactions are preserved
until end-stage liver disease is reached.59 For example, theophylline
clearance, which depends mainly on CYP450 oxidative metabolism,
was shown to be reduced by 37% in cirrhotic rats and activity was
restored to normal values by oxygen supplementation.60

Some clinical studies showed that glucuronidation does not appear to be altered except when hepatic cell mass is reduced
abruptly,61,62 whilst others found that some patients with severe he-
patic disease exhibited an increase in enzyme activities.62,63 Debinski
et al64 demonstrated upregulation of UDP-glucuronosyltransferase
(UGT) enzymes in the remaining viable human hepatocytes of dis-
edased livers, as observed using immunohistochemical staining
(Table S5). Impaired glucuronidation is observed for drugs, such as
morphine, lamotrigine, lomepazepam, zidovudine and mycopheno-
late mofetil, especially in advanced stages of cirrhosis.62

Clinical studies have also shown that the biotransformation of
CYP3A4 substrates, such as midazolam or erythromycin, is
significantly reduced in severe HI, whilst for CYP2C, the situation is different as the expression trends of these enzymes are highly variable (ranging from no change in liver disease to about 34%-72% of that in healthy control subjects). Murray et al recently concluded that CYP2C protein expression is not impaired in cirrhotic livers by studying selective drug substrates. 

Studies using immunochemical quantification reported variability in the microsomal levels of different CYP isoforms with different sensitivities toward disease progression as shown in Figure 3 and Table S4.65–68 This wide variation in the response of enzymes to hepatic injury is most probably linked to the disease stage and its severity as proposed by Frye et al who suggested a "sequential progressive model of hepatic dysfunction," leading finally to a decrease in the activity of most CYP450 enzymes in end-stage liver disease.69 Moreover, a doubling in CYP2E1 activity and depletion in glutathione levels were revealed in chronic alcohol ingestion, leading to lower protection against paracetamol, isoniazid, methotrexate and other substrates of this enzyme.62

There are several methods for assessing metabolic enzyme activity and expression in cirrhotic patients and comparing them to healthy control subjects. One of these methods is the measurement of tissue-specific mRNA expression either through reverse transcription (RT)-quantitative polymerase chain reaction (PCR) or microarrays.70,71 In spite of the utility of this approach, many limitations have been reported, including the following:

- Providing a relative quantification between tissues.
- mRNA does not always correlate with protein abundances such as the weak correlation for most CYP450s57 and UGTs.72

Another commonly used approach is the use of selective probe drugs for a limited number of enzymes (Table 1). These probes should have a high degree of enzyme selectivity either in vitro or in vivo.65,73,74 However, this technique has the limitation of small sample size (limited number of patients) in addition to the interference of other factors that may affect the study results, such as other elimination pathways (eg, renal elimination), inaccuracy in metabolic ratio calculations for complex pathways75 and the effect of genotype differences.76

Apart from relative quantification, absolute quantification of protein abundances is relatively recent with limited studies available (Tables S3 and S4). It provides the possibility of measuring absolute and direct protein amounts for incorporation into PBPK models and bridging between studies without the necessity of correlation to a reference sample. Different techniques have been used for protein quantification, such as immunoblotting as well as label-free and isotope-labelling proteomic techniques. The choice of suitable methodology depends on the sample under study, the number and nature of the target proteins being quantified, whether discrimination of isoforms of the same subfamily is required and the overall cost.70,77

According to Prasad et al,76 the changes in abundance of CYPs, UGTs and other drug-metabolising enzymes in cirrhotic livers are dependent not only on the enzyme but also on the origin or cause of cirrhosis. For example, there is an evidence of more extensive reduction in drug-metabolising enzyme abundance in alcoholic cirrhosis than hepatitis C-induced cirrhosis.76 However, this study did not assess changes in enzyme abundances for mild and moderate cirrhosis.
patients or zonal differences in these abundances across the liver. Moreover, some of the enzymes, such as CYP2B6, CYP3A5, UGT2B17 and UGT1A1, were below the detection limit of the analytical method.

8.2.2 | Transporters

Drug transporters are membrane-bound proteins present in organs, such as the intestine, liver and kidneys, and they play a key role in the absorption and elimination of drugs and their metabolites. Figure 4 shows the most important transporters in drug disposition within the liver. Drug transporters are categorised either functionally into two superfamilies: uptake transporters or phase 0 proteins and efflux transporters or phase III proteins or structurally mainly into solute carriers (SLC) and ATP-binding cassette (ABC) transporters. Relative transporter mRNA levels have previously been measured by quantitative PCR at different stages of HCV liver disease. NTCP and OCT1 showed a significant rise in mild F1 fibrosis relative to normal control (~75% and 38%, respectively), whilst later stages showed a nonsignificant difference in NTCP expression relative to healthy subjects and a significant reduction, by 38%, in OCT1 levels in severe cirrhosis. On the other hand, OATP-C transporters showed a gradual reduction of 16%, 20% and 60% with F1, F2, to F3 fibrosis scores, respectively.

### TABLE 1

Activity studies for different CYP450 isoforms at different degrees of disease severity with the applied indices and probes

<table>
<thead>
<tr>
<th>Study</th>
<th>Stage of liver disease</th>
<th>CYP isoform</th>
<th>Probe</th>
<th>Cause of cirrhosis (number of patients)</th>
<th>Measure/index for activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sotaniemi73</td>
<td>Mild, moderate, and severe</td>
<td>CYP3A4, CYP2A6</td>
<td>Lignocaine (iv) Coumarine (P.O)</td>
<td>All are alcoholic (26)</td>
<td>- Plasma concentration of MEGX metabolite in the 15-min postinjection</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Urine recovery of the hydroxyl metabolite after 2, 4 and 24 h from the oral dose</td>
</tr>
<tr>
<td>Frye69</td>
<td>Mild and Moderate-to-severe</td>
<td>CYP1A2, CYP2C19, CYP2D6, CYP2E1</td>
<td>- Caffeine - Mephenytoin - Debrisoquin - Chlorzoxazone</td>
<td>HCV (14), HBV (1), chemical (1), alcoholic (2), PSC (1), cryptogenic (1)</td>
<td>- Cp of Paraxanthine in the 8−h postdose sample</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Urinary recovery of hydroxyl metabolite/urine recovery of parent (mephenytoin)+metabolite</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Urinary recovery of hydroxyl metabolite/urine recovery of parent (debrisoquin)+metabolite</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Cp of hydroxydebrisoquin in the 4−h postdose sample</td>
</tr>
<tr>
<td>Adedoyin74</td>
<td>Mild and moderate</td>
<td>CYP2C19, CYP2D6</td>
<td>S-mephenytoin - Debrisoquin</td>
<td>Not specified</td>
<td>Urine was collected over 192 h</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Urinary recovery of 4-hydroxymephenytoin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Urinary excretion ratio of the hydroxydebrisoquin relative to (debrisoquin-hydroxydebrisoquin urine recoveries)</td>
</tr>
</tbody>
</table>

Abbreviations: Cp, plasma concentration; HBV, hepatitis B virus infections; HBV, hepatitis C virus infections; iv, intravenous dosing; P.O, Per oral dosing, MEGX, monoethylglycinexylidide (lignocaine metabolite).

**FIGURE 4** Location of clinically relevant drug transporters expressed in human hepatocytes. Uptake transporters located in the basolateral membrane include members of the SLC superfamily, such as OCT1, OCT3, OAT2, OAT7, OATP1B1, OATP1B3, OATP2B1 and NTCP. Efflux transporters located in the basolateral membrane include members of the ABC transporters superfamily, such as MRP3, MRP4 and MRP6. Efflux transporters are also located in the canalicular membrane and include BCRP, BSEP, MATE 1, MDR3, MRP2 and P-gp.
Ogasawara et al also investigated the effect of HCV-related cirrhosis on 17 different hepatic drug transporters and observed that the expression of most of these transporters (OCT1, OATP1B1, OATP1B3, MATE1, MRP4, MRP5 and BCRP) decreased by approximately 50% in cirrhosis. This does not only affect the hepatic uptake of drugs via these transporters but also biliary excretion was also noticeably reduced.

More and co-workers studied transporter mRNA (using QuantiGene Plex 2.0 assay) as well as relative transporters protein expression (using Western blotting) in human liver tissues with steatosis (with no cirrhosis), alcoholic cirrhosis or diabetic alcoholic cirrhosis compared to normal livers. A summary of the results of the study is shown in Table 2. This study did not assess the activity at different stages of disease severity and did not measure OATP1B1/1B3 because of lack of commercially available high-quality specific antibodies for these transporters at the time of the study. Moreover, the results are not scalable to liver tissue levels, which limit their usefulness in modelling. Recent studies assessed changes in transporter abundances per unit mass of tissue using LC-MS proteomic techniques in samples with different causes of cirrhosis and reported progressive reduction of most key transporters with disease progression.

### 8.3 Small sample size in dedicated clinical studies

In clinical studies dedicated to HI, which are designed to developing dosage recommendations, subjects are stratified based on CP score with at least six subjects per arm. Although the guidance states that for pathways known to exhibit genetic polymorphism (such as CYP2D6 and CYP2C19) the number increases and should include no less than eight subjects per arm, this still might not be enough to represent the whole population and allow accurate prediction of drug exposure changes in HI. Other causes of differences can be age, weight, smoking, concomitantly administered drugs and other disease states that are not completely reported for every patient. Moreover, most of these dedicated studies do not enrol all classes of liver impairment (Figure 1). In some situations, reduced (in terms of the acceptable number of enrolled patients) clinical trials are accepted when the oral clearance of

### TABLE 2 Transporter mRNA and protein expression in cirrhotic livers with different aetiologies

<table>
<thead>
<tr>
<th>Cause of cirrhosis</th>
<th>No change from control (↔)</th>
<th>Decreased compared to control (↓ %)</th>
<th>Increased compared to control (↑ %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transporter mRNA expression</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>SLCO1B1, ABCC2, ABCC3, ABCC6</td>
<td>SLCO1B3 (78%)</td>
<td>SLCO2B1 (51%), ABCC1 (38.44%), ABCC4 (58%), ABCC5 (34%), ABCG2 (194%)</td>
</tr>
<tr>
<td>Alcohol and diabetes mellitus</td>
<td>SLCO1B1, SLCO1B3, SLCO2B1, ABCG2, ABCC1, ABCC2, ABCC4, ABCC5, ABCC6</td>
<td>ABCC3 (88%)</td>
<td></td>
</tr>
<tr>
<td>Transports protein expression</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol and diabetes mellitus</td>
<td>ABCC2</td>
<td>ABCC6 (~30%-40%)</td>
<td>ABCB1 (1.5-2 folds), ABCB3 (2-3 folds)</td>
</tr>
<tr>
<td>Alcohol</td>
<td>SLC47A1, ABCC2, ABCB1, SLCO2B1</td>
<td>SLC10A1 (35%), SLCO1B1 (55%), SLCO1B3 (87%), SLC22A1 (73%), ABCG2 (50%), ABCB11 (36%)</td>
<td>ABCB1 (2.5 folds)</td>
</tr>
<tr>
<td>Alcohol</td>
<td>—</td>
<td>SLC10A1 (24%), SLCO1B1 (39%), SLCO1B3 (21%), SLC22A7 (74%), ABCB2 (70%), and OATPB2B1 (27%)</td>
<td>—</td>
</tr>
<tr>
<td>Chronic hepatitis C</td>
<td>ABCG2, ABCC3, SLCO1B1</td>
<td>ABCB11, ABCB2, SLCO10A1, SLCO1B3, SLC22A1, ABCB1 (32%-56%)</td>
<td>SLC47A1 (46%)</td>
</tr>
<tr>
<td>Chronic hepatitis C</td>
<td>—</td>
<td>ABCB11 (53%), SLCO2B1 (26%)</td>
<td>ABCB1 (~3.5 folds), ABCB4 (~3 folds)</td>
</tr>
<tr>
<td>Cholestatic liver disease</td>
<td>—</td>
<td>—</td>
<td>ABCB1 (~4 folds), ABCB4 (~2.5 folds)</td>
</tr>
<tr>
<td>Autoimmune hepatitis</td>
<td>—</td>
<td>ABCC2 (82%)</td>
<td></td>
</tr>
</tbody>
</table>

*Data derived from Ref. 81
*Data derived from Ref. 82
*Data derived from Ref. 83
the drug shows a negative correlation with the progression of the disease. In that case, the findings in the moderate category would be applied to patients with a mild CP category, and dosing in the severe category would generally be contraindicated. However, dosage adjustment in moderate HI cannot be generalised or extrapolated to mild or less severe conditions and the drug can be still useful in severe stages with appropriate dosage adjustment.

8.4 | Accounting for the change in plasma protein binding in HI patients

Plasma protein concentrations mainly albumin and α1 acid glycoprotein are known to decline with progress of HI severity. The fraction unbound of a drug is the proportion that is responsible for therapeutic effect and available for systemic metabolism and elimination which can be calculated in HI from Equation 1. Scaling with this equation was shown to have high predictive performance especially for albumin bound drugs.

$$f_{u,HI} = \frac{1}{1 + \frac{[P]_{u,HI}}{[P]_{u,normal}} \times f_{u,normal}}$$  

(1)

where $f_{u,normal}$ and $f_{u,HI}$ denote free drug fraction in plasma in normal and HI subjects, respectively, $[P]_{u,normal}$ and $[P]_{u,HI}$ the plasma protein concentrations in normal and hepatic disease, respectively. Although the prediction of the absolute value of $f_u$ was good, the authors did not assess the predictive performance based on the relative changes of $f_u$ (by comparing the observed and predicted changes of different drugs in various HI populations).

When doses are intended to be adjusted in cirrhotic patients, CL/Funbound and AUCunbound are the parameters that should be taken into account rather than the total parameters; CL/Ftotal and AUCtotal (bound and unbound) as the latter are deceiving. For instance, the AUCtotal may not change or, on the contrary, may decrease, whilst the unbound value, which is more clinically relevant, increases. This conclusion has been recommended by many studies and was observed for different drugs, such as naproxen, carvedilol, and quinine. The decrease in CL/Funbound is obscured by the increase in the unbound fraction of the drug in the blood $f_{ub}$ as can be deduced from the following equation:

$$\frac{\text{CL/F}_{\text{unbound}}}{\text{CL/F}_{\text{total}}} = \frac{\text{CL/F}_{\text{total}}}{f_{ub}}$$  

(2)

Therefore, the net result may be unchanged total CL/Ftotal as in the case of naproxen in cirrhotic patients compared to that in healthy controls or a worse result as in the case of quinine, which showed an increase in CL/Ftotal for cirrhotic patients relative to healthy individuals. This may lead to a major error in dose adjustment. This factor will mainly affect the systemic clearance of low clearance or low extraction ratio drugs.

It is also important to note that differences in protein binding obtained from in vitro experiments and in vivo situations can be observed, and this can contribute to the poor predictive performance for some drugs in HI populations.

8.5 | The shunting effect

Due to the progressively developing portal hypertension with increasing cirrhosis severity, spontaneous porto-systemic shunts (SPSS) are formed to vent the increased portal pressure. Unfortunately, although this mechanism seems to be compensating for deterioration during cirrhosis, complications such as hepatic encephalopathy, variceal bleeding, portal vein thrombosis and deterioration of liver function start to appear. Concerning PKs of administered drugs, these SPSS as well as surgically implemented TIPS constitute a challenge to the predictive performance of different models. TIPS can lead to a reduction in gut CYP3A4 levels as well as levels of hepatic enzymes. Therefore, changes in the mesenteric blood flow and CYP3A4 should be accounted for in the models based on the presence or absence of these shunts, their severities and the stage of cirrhosis. Computed tomography images can help in visualisation and identification of SPSS. It should be highlighted that the MELD score fails to capture severity of portal hypertension, whilst CP does reflect this to an extent, but neither of these scoring systems addresses the presence or severity of spontaneous portosystemic shunting.

8.6 | Impact of HI on drug absorption is not well understood

As pointed out earlier, the degree of shunting and the corresponding changes in mesenteric blood flow and intestinal enzyme abundances and activities in HI can affect oral drug bioavailability. The bioavailability of drugs such as morphine, meperidine, verapamil, metoprolol, clomethiazole, labetalol, carvedilol and midazolam may increase to double their values in cirrhosis because they escape extensive first-pass metabolism.

One of the changes that may occur in severe HI is the change in the gastric emptying time. In a PBPK modelling and simulation study that compared the residence times of metformin in the elderly and young populations with and without HI, a 40%-50% increase in gastric emptying time was suggested in patients with CP-C compared to their healthy control counterparts. Although these findings have not been validated by clinical data, this change may not only cause a slight delay in $T_{max}$ (time to $C_{max}$) or the rate of absorption but may also play a role, to some degree, in alteration of the extent of absorption in these populations.

9 | FUTURE DIRECTIONS

Given the limitations in the classification systems of HI, it is clear that there is no magic number that can be applied to all drugs in all patients with HI. Strategies using CP score or other tests
of disease severity and interindividual variation cannot reliably predict differences in exposure to therapeutic drugs. Genotyping is one of the key methods that have previously been used to individualise patient’s therapy; however, there are still variabilities amongst patients with the same genotype. Liver biopsy is an invasive and impractical approach to the characterization of individual patients by direct measurement of the expression of metabolising enzymes and transporters or their activities. Therefore, newly developed liquid biopsy and multi-omic techniques are proposed as a minimally invasive alternative to tissue biopsies by measuring plasma biomarkers that reflect the liver’s metabolic capacity. The link between liquid biopsy and tissue is predicated on accounting for the continuous shedding into the bloodstream of exosomes that contain a sample from the intracellular bimolecular pool of liver tissue. This technology has recently been applied to the characterisation of various hepatic enzymes and transporters at baseline and after drug treatment in healthy controls and liver cancer patients. The technique has the potential of monitoring not only markers of hepatic elimination of drugs but also biomarkers of disease severity and progression. However, the use of this technique for the highlighted application requires further assessment in liver disease to demonstrate its applicability in clinical practice.

10 | CONCLUSION

There is an unmet clinical need for dose adjustment in HI, especially for drugs that have been released to the market and are lacking appropriate guidance in patients with liver disease. PBPK modelling and simulations tool was proposed to address this gap. Dedicated PK clinical studies required for dosage adjustment in HI and for the validation of PBPK models use CP system for patients’ stratification which has significant limitations. Other scoring systems, DSI, and imaging techniques and the emerging liquid biopsy technology can be introduced to overcome some of CP pitfalls. It is unlikely that CP score will be replaced in the near future by an alternative stratification system for dose adjustment in HI. Nonetheless, efforts to improve stratification of hepatic drug clearance should be encouraged, especially given the poor performance of current methodology to capture exposure changes for some drugs.

ACKNOWLEDGEMENTS

E.E-K was funded by the Egyptian Missions Sector. Authors also acknowledge Eleanor Savill of Certara for assistance in preparing the manuscript for submission.

Declaration of personal interests: All authors declare that there is no conflict of interest.

AUTHORSHIP

Guarantor of the article: E.E-K.

Author contributions: E.E-K wrote and edited the article. A.R-H, V.A and E.E-K designed the structure of the article. AS.D, B.A, V.A and A.R-H edited the article and provided expert opinion. All authors approved the final version of the article.

DATA AVAILABILITY STATEMENT

Data sharing not applicable - no new data generated.

ORCID

Eman El-Khateeb https://orcid.org/0000-0002-8365-6528
Adam S. Darwich https://orcid.org/0000-0001-8218-4306
Brahim Achour https://orcid.org/0000-0002-2595-5626
Varinder Athwal https://orcid.org/0000-0002-1684-721X
Amin Rostami-Hodjegan https://orcid.org/0000-0003-3917-844X

REFERENCES

15. Patel H, Egorin MJ, Remick SC, et al. Comparison of Child-Pugh (CP) criteria and NCI organ dysfunction working group (NCI-ODWG) criteria for hepatic dysfunction (HD): implications for...


61. Larson AM, Kaplan MM, Bonis PAL. Drugs and the liver: metabolism and mechanisms of injury. UpToDate, Waltham, MA. Published online 2009.


65. Larson AM, Kaplan MM, Bonis PAL. Drugs and the liver: metabolism and mechanisms of injury. UpToDate, Waltham, MA. Published online 2009.


SUPPORTING INFORMATION
Additional supporting information will be found online in the Supporting Information section.

How to cite this article: El-Khateeb E, Darwich AS, Achour B, Athwal V, Rostami-Hodjegan A. Review article: time to revisit Child-Pugh score as the basis for predicting drug clearance in hepatic impairment. Aliment Pharmacol Ther. 2021;00:1-14. https://doi.org/10.1111/apt.16489