General introduction

Liver cirrhosis is a progressive disease developing from chronic liver inflammation due to a variety of underlying causes [1]. These causes comprise alcohol abuse, viral hepatitis, non-alcoholic fatty liver disease (NAFLD), autoimmune diseases, and others [2]. Liver cirrhosis is accompanied by a variety of severe complications that drastically reduce patients' quality of life and life expectancy. With 1.2 million deaths per year [3], liver cirrhosis was the 11th leading cause of death and the 15th leading cause of morbidity worldwide in 2016 [4]. To date, there is no cure for liver cirrhosis except for liver transplantation [5]. Treatment options comprise the treatment of the underlying cause as well as symptomatic treatment. However, pharmacological interventions in liver cirrhosis patients must generally be conducted with caution as these patients are at higher risk of adverse drug reactions (ADRs) [6].

The disease progression of liver cirrhosis can be classified into two clinical stages. The first stage is the compensated stage in which the human organism compensates for the reduced functionality of parts of the system, thus, presenting itself as asymptomatic. When the pathophysiological changes overwhelm the compensation capacity of the organism, a phase transition into the decompensated state occurs [7]. This decompensation is characterized by the presence of variceal bleeding, encephalopathy, ascites, hepato-renal syndrome (HRS), and/or jaundice [8]. Once the first decompensation event occurs, the patient's life expectancy drastically drops from 12 to 2-4 years [7]. Therefore, the determination of a patient's decompensation risk is of high clinical relevance for adapting surveillance and treatment to delay or even prevent decompensation. However, most prognostic cirrhosis scores used in clinical practice, such as the Child-Pugh score or the MELD score, focus on patient survival prognosis rather than disease progression [9-12]. Nevertheless, several studies investigated markers of decompensation. The hepatic venous pressure gradient (HVPG) seems to have prognostic power, but the invasive measurement procedure is difficult to justify in patients with compensated cirrhosis [13; 14]. Other investigated predictors of decompensation are anemia, vitamin D levels [15], or markers of systemic inflammation such as interleukin-6 (IL-6) levels [16]. However, there is no simple, routinely performed serum marker-based score to predict decompensation in cirrhotic patients. Therefore, one aim of the presented work was the development and validation of a score that predicts the decompensation risk in compensated liver cirrhosis patients and, thereby, enables the identification of patients at high risk.

Although liver cirrhosis is divided into two clinical stages, the underlying pathophysiology progresses continuously. Resulting from chronic liver damage, formerly healthy tissue gradually turns fibrotic. Consequently, the liver's functional capacity is reduced, leading to a decrease in detoxification enzymes and the synthesis of proteins such as albumin. Furthermore, the changed liver architecture results in increased resistance to the portal vein flow, initiating portal hypertension. Portal hypertension, in turn, triggers changes in the systemic blood flow along with various potential complications of liver cirrhosis, such as HRS and ascites. Additionally, the increased portal pressure induces the formation of new and re-opening of existing collaterals, creating varices and portosystemic shunts. Shunted portal blood bypasses the liver, further contributing to the reduction of hepatic detoxification capacity [1; 2].

Not only the impaired detoxification capacity but many of the pathophysiological changes involve relevant processes that influence the pharmacokinetics (PK) of a drug. The PK of a drug is defined as "what the body does to the drug" and is determined by the so-called ADME processes, where ADME stands for absorption, distribution, metabolism, and excretion. Absorption is the uptake of a drug from its location of application into the systemic blood circulation. Upon reaching the systemic circulation,

the drug distributes throughout the body. In the blood, the drug can bind to albumin or other plasma proteins. It is assumed that only the proportion of the drug that is unbound can leave the blood and distribute into organs and tissues. Metabolism of drugs takes place in different tissues and organs, with the liver being the major site of this process. In general, metabolism increases the hydrophilicity of compounds to facilitate excretion into the urine by the kidneys or into the bile by the liver. After oral administration, the so-called first-pass metabolism in the intestine and the liver takes place before the distribution. Already during the absorption phase, drugs can be metabolized in the intestine. Upon absorption, the drug does not directly enter the systemic circulation but instead is taken up into the portal vein. The portal vein drowns into the liver, where again metabolization of the drug can take place before entering the systemic circulation [17].

In liver cirrhosis, all ADME processes are potentially influenced by pathophysiological changes. Increased intestinal permeability as a result of portal hypertension [18; 19] and changes in the intestines, such as changes in gastric residence or colon transit time, may affect oral absorption [20]. Diminished plasma protein levels such as albumin lead to an increased unbound fraction of drugs in the blood, thus facilitating tissue penetration. Changes in body composition may simultaneously alter the distribution pattern of a drug [6; 21]. Changes in intestinal enzyme expression together with shunting decrease the first-pass metabolism [22; 23]. The loss of healthy liver tissues, as well as expressional changes in detoxification enzymes, decreases the metabolization capacity further, and the HRS contributes to a reduction of excretion due to renal malfunction [6; 21].

The interplay of all these described and many more changes can result in pronounced drug PK changes. However, the complexity of this interplay together with the dependency on drug properties makes a simple prediction of the quality and especially the quantity of these changes difficult. For most drugs, liver cirrhosis increases the exposure. Therefore, liver cirrhosis patients are at higher risk of ADRs [6]. Regulatory authorities, including the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA), recommend performing PK studies in patients with hepatic impairment for all drugs under clinical development (1) for which the probability of the drug being administered to these patients is high, (2) for which at least 20% of the absorbed drug is metabolized by the liver and, thus, hepatic impairment is expected to have a significant effect on the PK of the drugs and potential active metabolites, or (3) for drugs that have a narrow therapeutic window [24; 25]. However, patient recruitment and high costs make these studies challenging, calling for other methods to replace or at least supplement clinical studies by guiding the study design and patient stratification [26].

Physiologically based pharmacokinetic (PBPK) models are a promising computational modeling technique to predict the changes in PK in liver cirrhosis patients. These mechanistic models aim to include all PK-relevant anatomical and physiological organism properties as well as drug-specific properties to predict drug PK. A mechanistic representation of physiological properties together with a clear distinction between organism and drug properties make PBPK modeling a great tool for the extrapolation from healthy individuals to individuals with pathophysiological changes, e.g., liver cirrhosis patients [27]. To date, several approaches to using PBPK modeling for the prediction of PK in liver cirrhosis patients have been published. They all quantified the mean changes for several physiological parameters for the three Child-Pugh classes [22; 28-30]. The categorization of patients into these three classes is based on the Child-Pugh score, which is a clinical score calculated from three blood parameters and two qualitative assessments. The three classes are associated with survival prognoses. [9; 10]. It is routinely used in clinics and has been applied for patient classification in the majority of published studies on PK in liver cirrhosis patients. However, the Child-Pugh score was not designed to estimate the impact of liver cirrhosis on drug PK, and its performance toward PK predictions is limited [31]. This might be one reason why the predictive power of these modeling approaches that all use Child-Pugh classes for disease progression classification is mixed [29].

Furthermore, the published approaches miss the implementation of some important pathophysiological changes, including ascites and changes in body composition [32]. Therefore, the second aim of the presented work was to implement these changes and to develop a database, henceforward called repository, that describes the pathophysiological changes in liver cirrhosis patients considering continuous disease progression by using the more granular Child-Pugh score instead of the classes. Additionally, this repository should include interpatient variability and changes that have been left out before. Subsequently, this repository was tested in a PBPK framework to evaluate its performance toward PK prediction in liver cirrhosis patients.

The structure of the presented work comprises the following sections:

- General Introduction
- Part I: Background (chapters 1-5)
- Part II: Materials and Methods (chapters 6-9)
- Part III: Results (chapters 10-12)
- General Conclusion and Outlook
- Part IV: Appendices containing additional and supportive information

After this general introduction, which presents the overall motivation, gives an overview of the current scientific context, and outlines the thesis, the background provides relevant base information for the topics covered in the research chapters (chapters 10-12). Firstly, liver cirrhosis with a special focus on the pathophysiology is elucidated. Next, the term real-world data (RWD) is defined, followed by an explanation of the statistical methodology of survival analysis, which together represent the basis for the first research chapter (chapter 10). Subsequently, the basics of PK and PK modeling approaches, especially PBPK modeling, are explained. A good understanding of these topics is needed to predict drug PK changes in liver cirrhosis as this was worked on in chapters 11 and 12. Lastly, the Markov Chain Monte Carlo (MCMC) approach, a parameter estimation method from the field of Bayesian statistics used to analyze pathophysiological changes over the course of liver cirrhosis in chapter 11, is described.

The first research chapter (chapter 10) focuses on the prediction of progression from compensated to decompensated liver cirrhosis. Predictors of decompensation were identified via survival analysis using RWD from 6,049 patients. From the predictors, a risk score was built to predict a patient's risk to decompensate within the next three years. The resulting *Early Prediction Of Decompensation* (EPOD) score comprised the three routinely measured serum parameters platelet count, albumin, and bilirubin concentration. This score was then validated in three real-world cohorts, comprising 19,305 patients. To make the score easily available for further research, an online tool for score calculation was provided (epod-score.com). The results of chapter 10 were published as an original article in *Liver International* [33].

In the second research chapter (chapter 11), pathophysiological changes in liver cirrhosis that can affect drug PK were quantified depending on the Child-Pugh score. For this purpose, data on 30 parameters was collected from literature and RWD, resulting in 216,609 data points. The data was processed using MCMC, quantifying the dependence on the Child-Pugh score in a continuous fashion and, furthermore, capturing not only mean trends but also the population variability. The chapter resulted in a comprehensive repository of quantified trends and variability of pathophysiological changes in liver cirrhosis patients.

In the third research chapter (chapter 12), the pathophysiology repository that was generated in chapter 11 was used to generate virtual populations of liver cirrhosis patients. These populations were then integrated into a PBPK framework, simulating the PK changes for seven drugs, and comparing

those to observed data from five studies. The simulation results were analyzed with respect to different processes and properties of liver cirrhosis to assess the quality of various aspects of the repository. The simulations revealed good agreement with observed plasma concentration data and 96% of all data points for predicted AUC ratios, c_{max} ratios, and t_{half} ratios were within a twofold prediction range. Furthermore, when comparing these results to previously published approaches, the presented repository adds information on variability, allowing proper population predictions, as well as changes in body composition, the integration of ascites, and the integration of shunting. This study thereby advances the field of PK modeling in liver cirrhosis patients, which can facilitate dosing decisions as well as the planning and analysis of clinical studies in these patients.

Lastly, the results of the thesis are summarized and discussed in the general conclusion and outlook, followed by the listed references and the appendix providing supplementary information on the research chapters and the curriculum vitae (Part IV: Appendices).