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Drug-Related Problems in Patients with Liver Failure: An Analysis of Pharmacokinetic Interactions and Dosing Inappropriateness A Literature Review

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Abstract

Drug-related problems represent a major challenge in the pharmacotherapeutic management of patients with liver failure due to significant pharmacokinetic alterations, polypharmacy, and inappropriate dosing. Hepatic dysfunction affects drug absorption, distribution, metabolism, and elimination, thereby increasing the risk of adverse drug reactions, clinically significant drug–drug interactions, and therapeutic failure. This review aimed to summarize current evidence on the determinants of DRPs in patients with liver failure, focusing on pharmacokinetic changes, dose individualization, polypharmacy, and medication safety. A comprehensive literature review was conducted using PubMed, Embase, and the Cochrane Library to identify peer-reviewed studies published between 2015-2026. Keywords included liver failure, liver cirrhosis, drug-related problems, pharmacokinetics, dose adjustment, polypharmacy, and hepatic impairment. Eligible studies evaluated pharmacokinetic alterations, prescribing practices, medication safety, or clinical outcomes in adults with chronic liver disease. The findings consistently showed a high prevalence of DRPs in this population. Approximately one-quarter of commonly used medications required dose adjustment due to altered systemic exposure, while polypharmacy affected nearly one-third of patients and exceeded 50% in several cohorts. Inappropriate prescribing, inadequate dose individualization, and limited use of pharmacokinetic modeling were identified as major contributors to adverse drug reactions, hepatotoxicity, and clinically relevant drug–drug interactions. Additionally, reliance on conventional liver disease classification systems without integrating dynamic hepatic function markers often resulted in suboptimal therapy. Overall, pharmacokinetic alterations, polypharmacy, and inappropriate prescribing are key determinants of DRPs in patients with liver failure, underscoring the importance of individualized dosing, comprehensive medication review, pharmacokinetic modeling, and multidisciplinary pharmaceutical care to improve medication safety.

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Introduction

Current evidence on pharmaceutical interventions for individuals with liver cirrhosis and those undergoing liver transplantation is still relatively scarce. Most published studies have concentrated on administrative aspects of pharmaceutical services, particularly patient medication education and the monitoring of immunosuppressive therapy. In contrast, broader pharmaceutical care interventions aimed at identifying and resolving a wide range of medication-related problems have been insufficiently explored. This gap underscores the necessity for further investigations to strengthen medication management across various therapeutic classes in patients with hepatic disorders (Jibai, et al., 2023; Alobeidi & Jamal, 2023). Moreover, the frequent use of multiple medications, combined with the physiological changes caused by liver failure, substantially increases the occurrence of drug-related problems, which in turn elevates the likelihood of adverse drug reactions and may negatively affect therapeutic outcomes (Khazal & Jamal, 2023; Twinkle, et al., 2024).

Hepatic dysfunction can substantially alter the pharmacokinetics of many medications, making dose individualization a critical component of pharmacotherapy to minimize medication-related risks and maintain therapeutic effectiveness (Golla, et al., 2023). Patients with chronic liver disease are frequently exposed to complex medication regimens, in which the use of potentially inappropriate medications may further compromise clinical outcomes. These challenges are compounded by disease-related changes in hepatic drug handling, including impaired metabolism and clearance, which increase the susceptibility to drug-related problems, adverse drug events, and the accumulation of toxic drug concentrations (Rodríguez, et al., 2025; Farooq, et al., 2023).

Polypharmacy is highly prevalent among patients with chronic liver disease and represents one of the major factors contributing to drug-related problems (DRPs) and clinically significant drug–drug interactions, thereby increasing the complexity of pharmacotherapy (Szkultecka-Dębek, Bułaś, Skowron, & Drozd, 2025) This challenge is particularly pronounced in patients with decompensated cirrhosis, whose impaired hepatic function complicates medication management and underscores the need for safe, individualized, and evidence-based prescribing practices (Esquíroz A. , et al., 2026) Pharmacological treatment in this population often involves multiple medications to manage complications such as ascites, hepatic encephalopathy, and concurrent chronic comorbidities. Although these therapies are essential for disease management, increasing treatment complexity places patients at greater risk of clinical deterioration and other adverse health outcomes (Mir, Pawar, & Panda, 2022; Rivera-Huizar, Carrillo-Rojas, & Martínez-Silva, 2025). These risks are further exacerbated when pharmaceutical care is suboptimal or regular medication review is lacking, which may result in inappropriate prescribing, prolonged hospitalization, higher healthcare costs, and less favorable clinical outcomes (Casterman, et al., 2026; Karahan, Durmuş, Çakır, GÜN, & Yılmaz, 2026).

The extensive use of multiple medications in patients with chronic liver disease substantially increases the risk of adverse drug reactions (ADRs) and other drug-related problems (DRPs), creating additional challenges for safe and effective pharmacotherapy in individuals with hepatic impairment (Zeleke, Bazezew, & Abebe, 2023). Medication safety is further jeopardized by the frequent prescribing of potentially inappropriate medications, including inappropriate dose selection and excessive treatment duration, both of which contribute to avoidable medication-related harm (Al–Share, Tahrawi, Khasawneh, Alshare, &

Alkhasawneh, 2025). Consistent with these concerns, approximately one-third of hospitalized patients with cirrhosis experience at least one adverse drug reaction, most of which are considered preventable through appropriate prescribing and systematic medication review (Dafonte, et al., 2023).

The management of cirrhosis is further complicated by the growing burden of comorbidities, particularly type 2 diabetes mellitus and heart failure, which often require additional pharmacological therapy and increase the complexity of medication reconciliation and treatment optimization (Hayward, et al., 2023). This complexity is compounded by the high prevalence of potential drug–drug interactions associated with polypharmacy, representing a persistent threat to medication safety in this patient population (Amni, Fitria, & Sari, 2025). Moreover, the frequent use of high-risk medications, such as opioids, benzodiazepines, and nonsteroidal anti-inflammatory drugs, further heightens the risk of serious medication-related complications (Neuschwander-Tetri, et al., 2025). In addition to pharmacotherapeutic complexity, disease-related physiological changes substantially influence drug safety in patients with cirrhosis. Impaired hepatic blood flow, reduced metabolic and synthetic capacity, and other pathophysiological alterations modify drug disposition and increase vulnerability to drug-induced liver injury and the development or exacerbation of hepatic encephalopathy (Meunier et al., 2025; Zoratti et al., 2021; Hayward et al., 2021).

Methodology

A systematic search of the literature was performed using the PubMed, Embase, and Cochrane Library databases. The search employed a combination of keywords related to *liver injury*, *drug-related problems*, *drug interaction*, *dose adjustment*, and *hepatic impairment*. Studies were considered eligible if they were peer-reviewed, published within the last ten years, and evaluated clinical outcomes, pharmacokinetic alterations, or medication prescribing practices in adult individuals with chronic liver disease.

Results

The available evidence consistently indicates that drug-related problems (DRPs) are highly prevalent among patients with hepatic impairment, with inappropriate dose adjustment and preventable adverse drug events representing the most frequently reported medication-related issues (Fernandez, et al., 2026). Studies evaluating drug use in hepatic impairment further suggest that nearly one-quarter of commonly prescribed therapeutic agents require clinically relevant dose modifications because impaired liver function substantially alters systemic drug exposure (Haertter, Lobmeyer, Ferslew, Mitra, & Arnhold, 2025).

These prescribing challenges are particularly apparent for medications with a narrow therapeutic index, where conventional dosing strategies often fail to account for the marked increase in systemic exposure observed in patients with severe hepatic dysfunction (Lin, et al., 2022). Although pharmacokinetic modeling, especially for drugs with high hepatic extraction ratios, has demonstrated considerable potential for guiding individualized dose optimization, its integration into routine clinical practice remains limited (Ozbey, et al., 2023; Ladumor, et al., 2022). This limitation is further reinforced by the continued reliance on traditional liver disease classification systems, which inadequately capture the dynamic physiological changes associated with hepatic impairment, including fluctuations in serum albumin concentrations, progressive reductions in functional liver mass, and declining hepatic metabolic capacity. Consequently, these conventional approaches may not accurately predict alterations in drug

disposition or adequately support individualized dosing decisions (Schneider, Baier, Schlender, & Kuepfer, 2026; Qayyum, et al., 2024).

Another key observation emerging from the reviewed literature is the limited implementation of real-time clinical decision-support systems to assist medication management in patients with hepatic impairment. As a result, potentially inappropriate medications, particularly nephrotoxic and sedative agents that should either be avoided or prescribed with close monitoring, continue to be incorporated into therapeutic regimens despite reduced hepatic synthetic function (Ravenstijn, et al., 2022).

Polypharmacy was consistently recognized as a major determinant of medication-related complications in patients with chronic liver disease. Several studies demonstrated that the concurrent use of multiple medications substantially increases the risk of iatrogenic harm, including drug-induced hepatotoxicity and other drug-related problems (Danjuma, et al., 2022; Babu, Sadanandan, Patel, & Uttangi, 2021). Supporting these findings, a recent systematic review and meta-analysis estimated that approximately 31% of patients with chronic liver disease experience polypharmacy, underscoring the considerable medication burden within this population (Danjuma, et al., 2023). Moreover, findings from several clinical cohort studies reported prevalence rates exceeding 50%, indicating that extensive polypharmacy remains common in routine clinical practice and is associated with a greater risk of preventable drug-related problems and clinically significant drug–drug interactions (Szkultecka-Dębek, Bułaś, Skowron, & Drozd, 2025).

The reviewed studies also suggest that inappropriate prescribing frequently involves medications known to present substantial safety concerns in patients with hepatic dysfunction. Nonsteroidal anti-inflammatory drugs (NSAIDs) and sedative–hypnotic agents were among the most frequently prescribed high-risk medications despite their well-established association with hepatic encephalopathy, renal dysfunction, and progression of liver decompensation (Kareliya, Kamejaliya, & Pillai, 2022). In addition, inadequate surveillance for drug-induced liver injury remains an ongoing concern, particularly among older adults receiving multiple medications with known hepatotoxic potential, thereby further increasing the risk of preventable medication-related harm (Szkultecka-Dębek, Bułaś, Skowron, & Drozd, 2025).

Table 1. Synthesis of Evidence on Drug Related Problems in Patients with Chronic Liver Disease

Study	Study Design	Main Findings	Clinical Implications
Fernandez et al. (2026)	Model-informed evidence study	Drug-related problems (DRPs) were highly prevalent, with inappropriate dose titration contributing substantially to preventable adverse drug events.	Individualized dose optimization is essential to improve medication safety.
Haertter et al. (2025)	Hepatic impairment trials	Approximately 25% of investigated drugs required dose adjustment because hepatic impairment significantly altered systemic drug exposure.	Standard dosing recommendations may not be appropriate for patients with hepatic dysfunction.

Study	Study Design	Main Findings	Clinical Implications
Lin et al. (2022)	Pharmacokinetic analysis	Drugs with narrow therapeutic indices exhibited marked increases in systemic exposure in severe hepatic impairment.	Therapeutic drug monitoring and dose modification are recommended for high-risk medications.
Ozbey et al. (2023); Ladumor et al. (2022)	Pharmacokinetic modeling	PBPK modeling accurately predicted dosage requirements for drugs with high hepatic extraction.	Pharmacokinetic modeling may improve individualized dosing strategies.
Schneider et al. (2026); Qayyum et al. (2024)	PBPK modeling	Static liver severity classifications inadequately capture dynamic physiological changes affecting drug disposition.	Dynamic biomarkers should complement conventional disease staging.
Ravenstijn et al. (2022)	Clinical guidance	Limited implementation of clinical decision support systems contributes to inappropriate continuation of contraindicated medications.	Decision-support tools may reduce prescribing errors.
Danjuma et al. (2022); Babu et al. (2021)	Observational studies	Polypharmacy is a major contributor to drug-related problems and hepatotoxicity.	Comprehensive medication review should be routinely implemented.
Danjuma et al. (2023)	Systematic review and meta-analysis	The pooled prevalence of polypharmacy among chronic liver disease patients was approximately 31%.	Polypharmacy represents a major medication safety concern.
Szkultecka-Dębek et al. (2025)	Narrative review	Polypharmacy prevalence exceeded 50% in several cohorts and was strongly associated with DRPs and drug-drug interactions.	Deprescribing strategies should be considered when clinically appropriate.
Kareliya et al. (2022)	Drug utilization study	NSAIDs and sedative-hypnotics were frequently prescribed despite substantial safety concerns.	High-risk medications should be prescribed cautiously in cirrhotic patients.

Discussion

Drug–drug interactions represent a major clinical concern in patients with liver disease because they can alter hepatic metabolism and biliary drug elimination, thereby accelerating progression to acute-on-chronic liver failure (Huang, Wang, Chen, Yu, & Zhang, 2025). This risk is further amplified by polypharmacy, which markedly increases the likelihood of clinically significant interactions. When these interactions are not recognized and managed appropriately, they may lead to serious clinical consequences, including emergency

hospitalization, admission to intensive care units, and increased mortality (Danjuma, et al., 2025; Farooq, et al., 2023).

The safe use of medications in this population is further complicated by substantial interindividual variability in hepatic enzyme activity, as well as drug–nutrient interactions that can alter drug disposition and potentiate toxicity beyond that expected from individual medications alone (Datta, et al., 2021; Ngcobo, 2025). Pharmacotherapeutic management is particularly challenging in patients with decompensated cirrhosis, who frequently require medications with recognized hepatotoxic potential, including antibiotics and neuromodulatory agents. Consequently, continuous assessment of liver function throughout treatment is essential to minimize medication-related harm (Dorelo, et al., 2021; Dorelo, et al., 2021).

Regular monitoring of biochemical markers, especially serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin levels, remains a cornerstone of early detection of drug-induced hepatotoxicity, particularly among patients receiving extensive polypharmacy involving ten or more concomitant medications (Izhar, et al., 2025). Given these challenges, pharmacotherapy should be optimized through structured medication review and deprescribing strategies targeting medications with limited long-term clinical benefit, particularly in patients with decompensated cirrhosis whose treatment priorities may progressively shift toward supportive or palliative care (Johnson & Hayward, 2021).

Improving medication safety in patients with hepatic impairment will ultimately require greater integration of real-time clinical decision-support systems into routine clinical practice. By combining patient-specific measures of hepatic function with the pharmacokinetic and pharmacodynamic characteristics of individual medications, these systems have the potential to support more accurate and individualized prescribing decisions than approaches based solely on generalized estimates of hepatic drug clearance.

Conclusion

This review highlights that drug-related problems (DRPs) remain a major challenge in the pharmacotherapeutic management of patients with liver failure. These problems primarily arise from disease-related pharmacokinetic alterations, extensive polypharmacy, and inappropriate dose selection. Impaired hepatic function affects drug absorption, distribution, metabolism, and excretion, often rendering standard dosing strategies unsuitable and increasing the risk of preventable adverse drug events, particularly for medications with narrow therapeutic indices and extensive hepatic metabolism.

The reviewed evidence also identifies polypharmacy as a major contributor to clinically significant drug–drug interactions, hepatotoxicity, hepatic encephalopathy, and acute-on-chronic liver failure. Persistent medication-related risks are further exacerbated by the limited use of pharmacokinetic modeling, inadequate incorporation of patient-specific hepatic function into prescribing decisions, and the absence of standardized evidence-based dosing recommendations. Optimizing pharmacotherapy in patients with liver failure therefore requires individualized dosing strategies, comprehensive medication review, and greater integration of clinical decision-support systems to improve medication safety and therapeutic outcomes.

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