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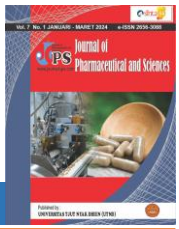

Potential Drug Interactions in Liver Cirrhosis: Patterns and Sociodemographic Factors

Interaksi Obat Potensial pada Sirosis Hati: Tinjauan Pola dan Faktor Sosiodemografi

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Abstract

Liver cirrhosis is a chronic condition characterised by the formation of regenerative nodules and fibrotic tissue resulting from prolonged liver damage. This condition is frequently accompanied by comorbidities and complications, often leading to the use of multiple medications (polypharmacy). Polypharmacy increases the risk of potential drug interactions, which may worsen clinical outcomes. This study aimed to describe the patterns of possible drug interactions and the sociodemographic characteristics of hospitalised patients with cirrhosis at Dr M. Djamil Central General Hospital in Padang. A cross-sectional study was conducted using prospectively collected data from patient medical records. A total of 579 medications used by 50 patients were classified into three categories: cirrhosis-specific drugs (48.9%), symptomatic treatments (43.2%), and medications for comorbid conditions (7.95%). Analysis with drugs.com showed potential drug interactions in 96% of patients, most commonly moderate–to–minor combinations (48%), followed by major, moderate, and minor interactions (22%). In comparison, moderate interactions only and major moderate combinations occurred in 18% and 9% of patients, respectively. In terms of sociodemographic characteristics, most patients were male (58%), under 65 years old (64%), had more than one comorbidity (52%), had a basic education level (32%), were still employed (56%), and did not engage in high-risk social behaviors such as smoking or alcohol consumption (48%).

Keywords*: *Liver cirrhosis, Drug interactions, Polypharmacy, Sociodemographic factors, Pharmacovigilance.

Abstrak

Sirosis hati merupakan kondisi kronis yang ditandai dengan terbentuknya nodul regeneratif dan jaringan fibrotik akibat kerusakan pada hati dalam jangka waktu yang panjang. Kondisi ini sering disertai oleh penyakit penyerta dan komplikasi sehingga menyebabkan pasien menerima banyak obat (polifarmasi). Polifarmasi dapat meningkatkan risiko terjadinya interaksi obat potensial dalam tubuh sehingga menyebabkan perburukan luaran klinis. Penelitian ini bertujuan untuk mendeskripsikan interaksi obat potensial yang terjadi dan polanya serta karakteristik sosiodemografi pasien sirosis hati yang menjalani rawat inap di RSUP Dr. M. Djamil Padang. Penelitian ini menggunakan desain penelitian potong lintang dengan pengumpulan data secara prospektif dari data rekam medis pasien. Sebanyak 579 obat yang digunakan oleh 50 pasien dibagi ke dalam tiga kelompok obat: obat terkait sirosis langsung (48.9 %), obat untuk simptomatik (43,2 %), dan obat untuk mengatasi komorbid (7.95 %). Hasil analisis dengan drugs.com menunjukkan bahwa potensi interaksi obat terdapat pada 96% pasien. Pola interaksi yang paling dominan adalah kombinasi interaksi sedang–ringan (48%), diikuti oleh kombinasi interaksi berat, sedang, dan ringan (22%). Selain itu, interaksi sedang saja ditemukan pada 18% pasien, sedangkan kombinasi berat–sedang tercatat pada 9% pasien. Berdasarkan karakteristik sosiodemografi, mayoritas pasien adalah laki-laki (58 %), berusia di bawah 65 tahun (64 %), memiliki lebih dari satu komorbid (52 %), berpendidikan dasar (32 %), masih bekerja (56 %), dan tidak memiliki kebiasaan sosial berisiko, seperti merokok dan mengonsumsi alkohol (48 %).

Kata Kunci: *Sirosis hati, Interaksi obat, Polifarmasi, Faktor sosiodemografi, Farmakovigilans.*

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Introduction

Liver cirrhosis is a chronic and progressive condition characterised by the formation of nodules and scar tissue in response to long-term injury to normal liver tissue. These structural changes in the liver lead to impaired liver function and the development of serious complications such as oesophageal varices, portal hypertension, ascites, gastrointestinal bleeding, hepatic encephalopathy, kidney failure, and liver cancer [1].

The health burden caused by cirrhosis is significant at both individual and global levels. Worldwide, liver diseases—including cirrhosis, hepatitis, and liver cancer—account for 4% of all deaths, rank 15th among the leading causes of disease burden measured by Disability-Adjusted Life Years (DALYs), and are the ninth leading cause of death in Southeast Asia [2]. In Indonesia specifically, around 20 million people were living with hepatitis in 2022, with the highest prevalence attributed to the hepatitis B virus. Among those affected, 2,159 patients were reported to have died due to complications from cirrhosis and liver cancer [3]. Complications can increase the risk of death by five to ten times [2].

Due to the complexity of cirrhosis management, the use of multiple medications simultaneously, or polypharmacy, is often unavoidable—both for treating complications and managing comorbid conditions. Polypharmacy also increases the risk of potential drug interactions, which can lead to adverse side effects, worsened clinical outcomes, and prolonged hospital stays [4]. Drug-drug interactions can occur when one medication affects the action of another, leading to reduced effectiveness or increased toxicity. The likelihood of such interactions rises in proportion to the number of drugs a patient is taking. [5]. In cases of liver failure or cirrhosis, metabolic processes are impaired, allowing more of the drug to reach systemic circulation, which results in increased drug bioavailability [6].

Micromedex classifies drug interactions based on two main criteria: severity and documentation strength. In terms of seriousness, interactions are categorised as major (life-threatening and requiring medical intervention), moderate (requiring medical intervention), and minor (not requiring intervention). Based on documentation strength, interactions are classified as excellent (supported by controlled clinical trials), good (supported by non-randomised studies), fair (limited evidence), and unlikely (lacking strong pharmacological evidence)[7].

A study by Muti and Anindya in 2021 reported that 88% of cirrhosis patients experienced potential drug interactions, with the most common combinations involving diuretics (furosemide, spironolactone), non-selective beta-blockers (carvedilol, propranolol), proton pump inhibitors (PPIs), lactulose, psychoactive drugs (benzodiazepines, antidepressants), and cardiovascular medications. The most frequently reported combination was furosemide–propranolol, accounting for 45.7% of cases. Serious adverse effects resulting from potential drug interactions included hypoglycemia, hyperkalemia, gastrointestinal bleeding, acute kidney injury, and respiratory system depression. Although not all possible drug interactions lead to severe side effects, they warrant careful attention, especially in patients with advanced-stage cirrhosis. [8].

In addition to clinical factors, sociodemographic characteristics also play an essential role in determining the risk and patterns of medication use in patients. Usman et al., in their 2021 study of cirrhosis patients at RSUP Dr. M. Djamil Padang, found that the majority were male (69%), early elderly age group (40.8%), employed as housewives (23.9%), and had a high school education as their highest level of schooling (63.4%). This sociodemographic information is crucial for guiding individualised therapy approaches and developing more targeted health policies [9].

The high prevalence of potential drug interactions, the burden they cause, and the risk of complications associated with cirrhosis highlight the need to evaluate and review these interactions and

their patterns. This is crucial for enhancing clinical outcomes and improving the overall quality of life for patients with cirrhosis.

Methods

This study employed an observational, cross-sectional design with prospective data collection conducted in the internal medicine inpatient ward at RSUP Dr M. Djamil, Padang, from January to April 2025. Data were obtained through manual and electronic medical record reviews as well as direct interviews with patients who met the inclusion and exclusion criteria.

The inclusion criteria consisted of inpatients in the internal medicine ward diagnosed with liver cirrhosis (with or without comorbidities) who were over 20 years old. Meanwhile, the exclusion criteria included patients who declined to participate, obstetric patients, and those with mental disorders.

A total of 50 patients participated as respondents in this study, with sampling conducted using the total sampling method. The variables examined included sociodemographic data (age, gender, comorbidities, highest level of education, occupation, and social habits), as well as medication use during the treatment period. Potential drug interactions were then identified using the website *drugs.com*.

This study received ethical approval from the Ethics Committee of RSUP Dr. M. Djamil Padang with approval number DP.04.03/D.XVI.XI/530/2024. All patients who agreed to participate were required to provide informed consent before data collection. The collected data were then analysed descriptively using SPSS version 25.

Results and Discussion

A total of 50 patients with liver cirrhosis who met the inclusion and exclusion criteria were selected. Overall, the hospitalized cirrhosis patients at RSUP Dr. M. Djamil Padang were predominantly male (58%), under 65 years of age (64%), had more than one comorbidity (52%), had a basic education level (32%), were still employed (56%), and did not engage in high-risk social habits such as smoking or alcohol consumption (48%)

Table 1. Sociodemographic Characteristics of Liver Cirrhosis Patients

Sociodemographic Characteristics	Number of respondents	Percentage (%)
Gender		
a. Male	29	58
b. Female	21	42
Age		
a. < 65 years old	32	64
b. ≥ 65 years old	18	36
Comorbidity		
a. No comorbidity	9	18
b. One comorbidity	15	30
c. More than one comorbidity	26	52
Education		
a. No formal education	2	4
b. Elementary school (SD)	16	32
c. Junior high school (SMP)	12	25
d. Senior high school (SMA)	15	30
e. Diploma/ Bachelor's degree (D3/S1)	5	10
Occupation		
a. Employed	28	56
b. Unemployed	22	44
Social habits		
a. None	24	48
b. Smoker	17	34
c. Alcohol user	2	14
d. Smoker and alcohol user	7	4

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Table 1 shows that the majority of the study sample consisted of males, totalling 29 individuals (58%), while females accounted for 21 individuals (42%). This finding is consistent with a study on the profile of cirrhosis patients at RSUP Dr. M. Djamil Padang by Usman et al. in 2021, which reported a higher proportion of male patients at 69%. A similar study by Jessica et al. in 2021 found that 61% of the patients were male. This difference is attributed to the varying progression of cirrhosis between men and women. Women have a lower risk of developing cirrhosis due to the protective effects of sex hormones and a lower incidence of factors that promote fibrosis progression. These hormones increase the likelihood of spontaneous clearance of the hepatitis C virus in women and reduce the risk of hepatitis B reactivation. Additionally, the incidence of hepatocellular carcinoma is significantly lower in women compared to men [9,10].

Furthermore, the results of this study showed that the majority of patients were under 65 years old, with 32 out of 50 patients (64%) in this age group, while 18 patients (36%) were aged 65 or older. A similar finding was reported by Fadilah et al. in 2023, which also showed a higher number of patients under 65 years old. According to a 2019 study by Carrier et al., compared to other organs, both the size and function of the liver decline with age. The number of pores in the liver endothelial cells tends to decrease, accompanied by damage to the sinusoidal vascular system and reduced bile acid secretion. Additionally, gluconeogenesis in the metabolic system decreases, while physiological fat accumulation increases, worsening the condition of steatosis [11]. The progression of cirrhosis is slow and typically takes a long time. Severe symptoms usually appear during the decompensated stage, meaning cirrhosis often remains undetected for 10 years or more if regular examinations are not performed. Additionally, the transition from compensated to decompensated cirrhosis generally takes about six years, which contributes to the lengthy time required for diagnosis. Furthermore, a 2022 study by Ames et al. reported an increasing incidence of cirrhosis among younger individuals, consistent with the findings of this study and previous research conducted in other countries [9,12].

More than half of the patients (52%) were found to have more than one comorbidity, while the remaining 48% had one or no comorbid conditions. In this study, cirrhosis was often observed alongside other diseases such as cardiovascular disease, diabetes mellitus, and chronic kidney failure. This is because the same risk factors contribute to the development of all these conditions in a single patient. A study published in the *World Journal of Gastroenterology* by Peter Jepsen noted that comorbidities in patients with cirrhosis do not arise directly as causes or consequences of cirrhosis, but rather significantly impact patient mortality and clinical outcomes. Furthermore, the liver plays a central role in detoxification and metabolism, so impairment of this organ can lead to widespread systemic effects. Reduced liver function may result in complications such as kidney dysfunction, coagulation disorders, and metabolic imbalances [13,14].

In this study, the majority of patients had a primary school education, totalling 16 individuals (32%). This differs from the survey by Usman et al., where high school was the most common education level, followed by primary education. However, both studies showed that patients were predominantly of low educational attainment. Florian et al. explained in their research that individuals with lower education levels are at higher risk of experiencing various health problems due to unhealthy lifestyle habits and limited access to adequate healthcare services. Therefore, this study emphasises the importance of targeted interventions for cirrhosis among vulnerable populations [15].

Similarly, a study by Stroffolini et al. in 2019 found a correlation between low education levels and the severity of chronic liver disease. All these studies share common findings and further strengthen the evidence that education influences a patient's economic status, mindset, and behaviour in managing their health condition [9,16].

The following finding of the study concerns the employment status of patients with cirrhosis, with the majority (56%) still actively working. This contrasts with several other studies on the same topic. Usman et al. reported that a higher percentage of patients with cirrhosis were unemployed, including homemakers. On the other hand, a study by Vaz et al. in Sweden in 2020 found that patients with higher socioeconomic status tended to consume more alcohol compared to those with lower socioeconomic status. This suggests that cirrhosis may be more prevalent among individuals who are actively working or have a higher socioeconomic status. However, this situation is difficult to generalise due to cultural and religious differences between Indonesia and other countries [9,17].Lastly, it was recorded that 24 individuals did not have the habits of smoking or alcohol consumption, while 26 had one or both of these habits. Alcohol is a significant risk factor in the development of liver diseases in general, and cirrhosis in particular. Half of the global burden of mortality and morbidity could be eliminated without alcohol, especially in the United

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States and Europe. When a person consumes alcohol, liver enzymes ADH and CYP2E1 break down the alcohol into acetaldehyde, a toxic substance to the body. The body then efficiently converts acetaldehyde into acetate with the help of the enzyme aldehyde dehydrogenase 2 (ALDH2). However, when alcohol is consumed excessively, the level of CYP2E1 increases, producing more harmful substances such as free radicals. These free radicals trigger oxidative stress, leading to inflammation [18,19].

Growing research indicates that smoking is associated with increased severity of liver conditions, particularly fibrosis and liver cancer. This is due to the carcinogenic (cancer-causing) and profibrogenic (scar tissue-promoting) substances found in cigarettes, which affect the body's systems. The toxins in tobacco can alter enzymatic pathways and cause inflammation in the liver. Additionally, smoking can worsen the damaging effects of alcohol on the liver, leading to a higher risk of complications in patients. [20].

Table 2. Medication Use in Hospitalised Liver Cirrhosis Patients

Drug category	Frequency	Percentage (%)
Drugs directly related to cirrhosis	283	48.9
Symptomatic or supportive drugs	250	43.2
Drugs for comorbid conditions	46	7.95

Out of a total of 579 medications used by 50 patients, drugs directly related to cirrhosis were the most commonly used (48.9%), followed by symptomatic treatments (43.2%), and medications for comorbid conditions (7.95%).

Table 3. Drug Categories in Liver Cirrhosis Patients

Drug Category	Frequency	Percentage (%)
Drugs directly related to cirrhosis		
Octreotide acetate	21	42
Phytomenadione	31	62
Tranexamic acid	27	54
N-acetylcysteine	28	56
Spironolactone	42	84
Lactulose	43	86
Ursodeoxycholic acid	18	36
Furosemide	29	58
Propranolol	38	76
Other drugs		
Symptomatic or supportive drugs		
Domperidone	10	20
Sucralfate	35	70
Ampicillin–sulbactam	24	48
Lidocaine	12	24
Omeprazole	31	62
Azithromycin	9	18
Paracetamol	27	54
Potassium chloride	11	22
Levofloxacin	7	14
Lansoprazole	7	14
Benserazide + Levodopa combination	13	26
Other drugs		
Drugs for comorbid conditions		
Rapid-acting insulin analogue	7	14
Dobutamine	10	20
Norepinephrine	7	14
Other drugs		

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Medications related to cirrhosis are used directly to manage complications arising from the disease, such as hepatic encephalopathy, ascites, oesophageal varices, and as hepatoprotective agents. This group is predominantly comprised of drugs such as spironolactone (84%) and furosemide (58%) as diuretics, lactulose (86%) for the treatment of hepatic encephalopathy, and propranolol (76%) for the prophylaxis of oesophageal varices caused by portal hypertension (MIMS, 2025). Additionally, octreotide (42%) is used to control variceal bleeding; phytonadione (62%) and tranexamic acid (54%) serve as anticoagulant and antifibrinolytic agents; ursodeoxycholic acid (36%) and N-acetylcysteine (56%) are used for primary biliary cirrhosis therapy and as antioxidants; tenofovir (2%) functions as an antiviral for cirrhosis patients with hepatitis; vasopressin (2%) is used in the initial management of esophageal bleeding; and lastly, carvedilol (8%) is administered as primary prophylaxis for portal hypertension. The high overall frequency of medication use in this group highlights that the primary focus of treatment is managing the complications of liver disease. [21–23].

Next, the symptomatic drug group includes antibiotics, antiemetics, and pain relievers, which serve to alleviate symptoms or provide temporary relief until clinical parameters improve. This group consists of a wide variety of medications, predominantly ampicillin-sulbactam as an antibiotic (48%), paracetamol as an antipyretic and analgesic (54%), and omeprazole (62%) and sucralfate (70%) for patients with indications such as ulcers or GERD. [21,23].

Following that, medications such as ondansetron (2%), metoclopramide (10%), and domperidone (20%) were used as antiemetics and prokinetic agents. The antibiotic group included a variety of agents such as levofloxacin (14%), cefoperazone (2%), cefixime (2%), cefepime (8%), amikacin (2%), ampicillin (2%), ciprofloxacin (2%), cefotaxime (2%), ceftazidime (2%), azithromycin (18%), and meropenem (2%). Additionally, medications used to correct electrolyte imbalances in patients included calcium lactate (2%), calcium polystyrene sulfonate (2%), calcium gluconate (6%), potassium chloride 7.46% (10%), sodium bicarbonate (6%), and potassium chloride (22%) [23].

Lidocaine (24%) was administered as a local anaesthetic before paracentesis procedures. Pain management included the use of ketorolac (4%) and ketoprofen (10%) as analgesics. Anaemia was treated with ferrous sulfate (2%) and folic acid (8%). Dexamethasone (6%) and hydrocortisone (8%) were used as anti-inflammatory agents for cirrhotic patients experiencing inflammation or autoimmune conditions. Gastrointestinal symptoms were addressed with lansoprazole (14%), bisacodyl (2%), antacids (2%), loperamide (4%), ranitidine (2%), and attapulgite (10%)—medications commonly used to treat ulcers, diarrhoea, and constipation. Gastrointestinal disturbances are frequent in cirrhosis due to disease-related complications. Additionally, cetirizine (4%) and diphenhydramine (2%) were used to manage allergic reactions. The relatively high usage of symptomatic medications reflects the frequent occurrence of secondary conditions and symptoms in cirrhotic patients that require supportive treatment. [21,23,24].

Comorbid conditions such as diabetes, hypertension, chronic obstructive pulmonary disease (COPD), and heart failure in cirrhotic patients were managed using medications including levodopa-benserazide combination (26%), insulin analogues (14%), dobutamine (20%), and antihypertensive agents like candesartan (4%) and amlodipine (2%). The levodopa-benserazide combination was used to treat asterixis, or fine tremors, resulting from toxin accumulation in the brain associated with hepatic encephalopathy. Levodopa, a dopamine precursor, is paired with carbidopa or benserazide to prevent peripheral conversion of levodopa into dopamine, thereby reducing tremors by ensuring more levodopa reaches the brain. Additionally, a combination of levodopa, carbidopa, and entacapone (2%) was prescribed. Carbidopa serves the same function as benserazide, while entacapone inhibits the catechol-O-methyltransferase (COMT) enzyme, which breaks down levodopa in peripheral tissues. This classification pattern reflects the presence of multiple disease burdens (comorbidities) that require targeted therapy beyond liver disease management alone. [23,25,26].

Several cirrhotic patients in this study also presented with comorbid conditions such as chronic obstructive pulmonary disease (COPD) or bronchospasm, for which they were prescribed a combination of ipratropium bromide and salbutamol (8%). This combination of β2-adrenergic agonists and anticholinergic agents provides rapid bronchodilation and prolonged therapeutic effects. Budesonide (4%) was also administered as an anti-inflammatory agent targeting pulmonary inflammation in COPD patients. Additionally, norepinephrine (14%) and dopamine (2%) were used as vasopressors in cases of shock, particularly in patients with septic shock. Heparin (2%) was prescribed as an anticoagulant; atorvastatin (4%) was used for managing dyslipidemia; and allopurinol (2%) served as maintenance therapy for patients

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with gout. Cyclosporine (2%) was administered as an immunosuppressant, and betahistine (2%) was given to manage vertigo or dizziness [21,23,27].

Table 4. Patterns of Drug Interactions in Patients with Liver Cirrhosis

Interaction Pattern	Frequency	Percentage (%)
Moderate	9	18
Moderate + Minor	24	48
Mayor + Moderate + Minor	11	22
Mayor + Moderate	4	8
No Interaction	2	4

Table 3 illustrates the patterns of drug interactions in patients with liver cirrhosis, categorised into three groups: moderate-only, a combination of moderate and minor interactions, and a combination of major, moderate, and minor interactions. The most prevalent interaction pattern was the combination of moderate and minor interactions, observed in 24 patients (48%). This was followed by a combination of major, moderate, and minor interactions, accounting for 22% of the total patients. The least common pattern involved patients who were potentially exposed to significant and moderate interactions—reported in only four respondents (8%). Additionally, there are two patients with no reported interactions.

A study conducted at RSPAD Gatot Soebroto reported that 88% of patients experienced potential drug interactions. Among the 35 total interactions identified, the majority were classified as minor (82.86%), followed by moderate (8.57%) and major (8.57%) interactions. Similarly, Farooq et al. stated in their article that moderate interactions were the most prevalent during hospitalisation, at 77.6%, with minor and major interactions accounting for 15.7% and 6.7%, respectively. The current study revealed a comparable pattern to that of Farooq et al., with moderate interactions being the most frequently observed among all types of drug interactions [4,8].

Using Drugs.com as the only source for identifying potential drug interactions is a key limitation, as it lacks consistency, transparency, and detailed clinical evidence. More established tools such as Micromedex and Lexicomp provide broader, more reliable, and better-documented information. [28–30].

Conclusions

The findings from this study, which involved 50 patients with liver cirrhosis, revealed that the majority were male (58%), under the age of 65 (64%), had more than one comorbidity (52%), had completed only elementary education (32%), were still employed (56%), and did not engage in high-risk social behaviors such as alcohol consumption or smoking (48%). A total of 579 medications were recorded, with the most significant proportion belonging to drugs directly related to cirrhosis management (48.9%), followed by symptomatic treatments (43.2%), and medications for comorbid conditions (7.95%). Furthermore, analysis of potential drug interactions showed that while most patients experienced interactions categorised as minor or moderate, greater attention is needed regarding the risk of serious or major interactions. This is essential for minimising harmful side effects and achieving better clinical outcomes.

Conflict of Interest

The author declares that there are no conflicts of interest in the design, implementation, analysis, or reporting of this study. All processes were carried out objectively and independently, without any interference from external parties.

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